Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Indacaterol maleate/ Glycopyrronium bromide

Proprietary Product Name: Ultibro Breezhaler

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

First round report January 2017

Second round report May 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
AEs	Adverse events
AUC	Area under the curve
CER	Clinical evaluation report
CI	Confidence Interval
CCV	Cerebro cardiovascular
EU	European Union
FEV1	Forced expiratory volume in 1 second
FDC	Fixed dose combination
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
MACE	Major adverse cardiovascular event
SAEs	Serious adverse event
SGRG-C	St George's respiratory questionnaire

1. Introduction

1.1. Submission type

This is an application for extension of indications for Ultibro/Xoterna Breezhaler 110/50 µg (indacaterol maleate/glycopyrronium bromide) powder for inhalation in hard capsule

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

The bold phrase is the proposed new indication.

1.2. Drug class and therapeutic indication

Ultibro Breezhaler is a fixed dose combination of indacaterol maleate and glycopyrronium bromide for inhaled use. Indacaterol is a long acting beta agonist (LABA) and glycopyrronium is an anti-cholinergic, long acting M1-5 muscarinic receptor antagonist (LAMA). Both act in a complementary manner to reverse airway obstruction in COPD. Both compounds are approved for symptomatic relief in patients with COPD but not in patients with asthma or mixed airways disease.

2. Clinical rationale

Reference is made to the clinical evaluation report for Submission PM-2012-4395-1-5.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

One study (FLAME) has been submitted to support this application.

3.2. Paediatric data

Not applicable.

3.3. Good clinical practice

The study has been conducted in full compliance with GCP.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

Not submitted.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

Not submitted.

6. Dosage selection for the pivotal studies

Not submitted.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

One study has been submitted to support the extension of indication and the inclusion of the trial in the clinical trials section of the PI.

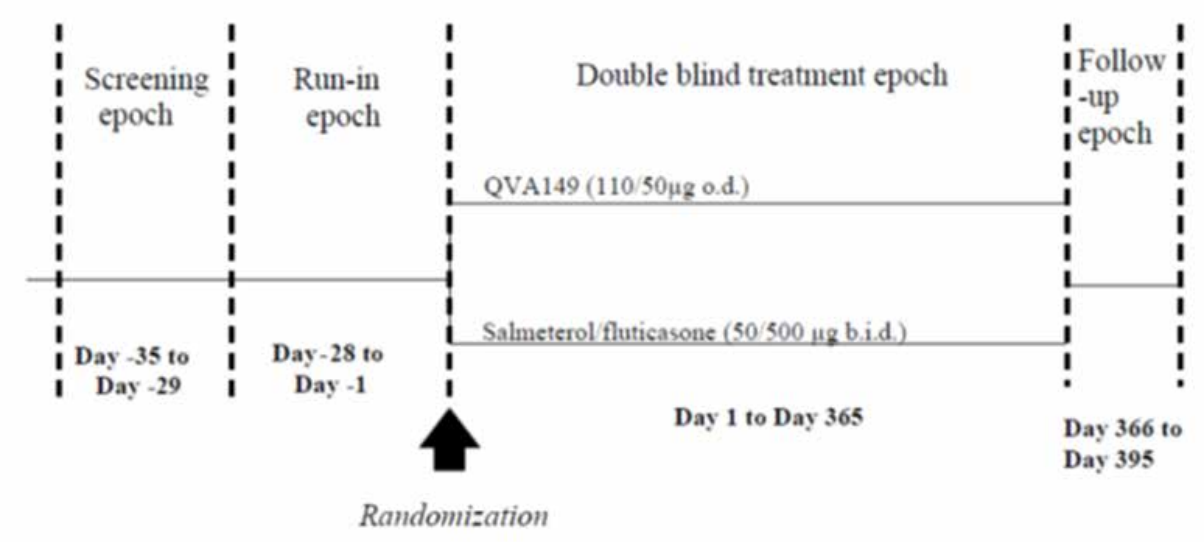
7.2. Pivotal or main efficacy studies

7.2.1. Study QVA149A2318

7.2.1.1. Study design, objectives, locations and dates

Study QVA149A2318: A 52 week treatment, multi-centre, randomised, double blind, double dummy, parallel-group, active controlled study to compare the effect of QVA149 (indacaterol maleate /glycopyrronium bromide) with salmeterol/fluticasone on the rate of exacerbations in subjects with moderate to very severe COPD. See flow chart below in Figure 1.

Figure 1: Study QVA149A2318; study design



7.2.1.1. Inclusion and exclusion criteria

The study population consisted of male and female adults age 40 years and older, with a clinical diagnosis of COPD according to Global Initiative for Chronic Lung Disease (GOLD 2011), a smoking history of at least 10 pack years and a documented history of at least 1 COPD exacerbation requiring systemic glucocorticosteroid and/or antibiotics in the previous 12 months. Patients were also required to have post-bronchodilator FEV1 ≥ 25% and < 60% of

the predicted normal value, and post-bronchodilator FEV1/FVC < 0.70 and a Modified Medical Research Council (mMRC) grade of at least 2 at the visit at the start of the run-in period.

Exclusion criteria:

1. Pregnant or nursing (lactating) women
2. Women of child bearing potential.
3. Patients with Type I or uncontrolled Type II diabetes.
4. Patients with a history of long QT syndrome or whose QTc measured at start of the run-in epoch was prolonged (> 450 ms for males and females) and confirmed by a central assessor. These patients were not re-screened.
5. Patients who had a clinically significant ECG abnormality at the start of the run-in period or double blind treatment.
6. Patients who had a clinically significant laboratory abnormality at the start of the run-in period.
7. Patients who had a clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction), arrhythmia, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or haematological abnormalities which could interfere with the assessment of the efficacy and safety of the study treatment.
8. Patients with paroxysmal (for example intermittent) atrial fibrillation were excluded.
9. Patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof: anticholinergic agents; LABA and SABA; sympathomimetic amines; lactose or any of the other excipients of trial medication.
10. Patients with a history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there was evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
11. Patients with narrow angle glaucoma, symptomatic benign prostatic hyperplasia or bladder neck obstruction or moderate to severe renal impairment or urinary retention.
12. 12. Patients who had not achieved an acceptable spirometry results at the start of the run-in period in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for acceptability (one retest could be performed for patients that did not meet the acceptability criteria).
13. Patients who had a COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the 6 weeks prior to Visit 1.
14. Patients who developed a COPD exacerbation of any severity (mild/moderate/severe) between screening (Visit 1) and treatment epoch (Visit 201) were not eligible but were permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.
15. Patients who had a respiratory tract infection within 4 weeks prior to screening (Visit 1).
16. Patients who developed a respiratory tract infection between screening and prior to treatment were not eligible, but were permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection.
17. Patients requiring long term oxygen therapy prescribed for > 12 hours per day.
18. Patients with any history of asthma.

19. Patients with an onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years.
20. Patients with a blood eosinophil count > 600/mm^3 at the start of the run-in period.
21. Patients with allergic rhinitis who used a H1 antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose or regimen was permitted).
22. Patients with concomitant pulmonary disease (for example lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension).
23. Patients with clinically significant bronchiectasis.
24. Patients with a diagnosis of α-1 anti-trypsin deficiency.
25. Patients with active pulmonary tuberculosis, unless confirmed by imaging to be no longer active.
26. Patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation.
27. Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study. (Maintenance program was permitted.)
28. Use of other investigational drugs/devices (approved or unapproved) at the time of enrolment, or within 30 days or 5 half-lives of the screening visit (Visit 1), whichever was longer.
29. Patients unable to use an electronic patient diary and EXACT-PRO diary.
30. Patients unable to use a dry powder inhaler device, Metered Dose Inhaler (MDI) or a pressurized MDI (rescue medication) or comply with the study regimen.

7.2.1.2. Study treatments

QVA149 110/50 µg capsules for inhalation were supplied in blisters delivered via Novartis single dose dry powder inhaler (SDDPI) and salmeterol/fluticasone dry inhalation powder was delivered via Accuhaler device.

The formulation and batch details are given below in Table 1.

Table 1: Study QVA149A2318 study medication formulation and batch numbers

Study medication formulation and batch numbers

Study drug and strength	Formulation control number	Batch number
QVA149 110/50 mcg	6002585	X105E1, X124DK
QVA149 Placebo	6001727	X090DI, X087BK, X343KK, X124CH
Salmeterol/fluticasone 50/500 mcg	X3610913, X1170314, 4541, X1680614	7006953, 8004100
Salmeterol/fluticasone Placebo	7006738	X3170813, X1020313, X1970513, X2370513, X3180913, X2681212, X0210213, X0800213, X0810213, X1960513, X3190913, X3200913

Additional study treatments:

- SABA (salbutamol or albuterol) inhaler could be used as rescue medication on an 'as needed' basis throughout the study.
- Tiotropium was also to be used in the run-in period. Patients received ipratropium bromide 20 µg for use instead of tiotropium during the 3 days prior to the start of the run-in period (if required) and in the 24 hours prior to randomization (if required) to allow washout of

tiotropium. Patients discontinued both tiotropium (at least 24 hours) and ipratropium (at least 8 hours) prior to randomisation.

7.2.1.1. Efficacy variables and outcomes

The primary analysis variable was the rate of all COPD exacerbations during the treatment period, (the period between the first day of the study drug administration to one day after the last day of the study drug administration).

Other (secondary) efficacy endpoints were:

- time to first COPD exacerbation (mild/moderate/severe)
- rate and time of moderate/severe exacerbation
- change from baseline in pre-dose FEV1 and FVC after 4, 12, 26, 38, and 52 weeks of treatment
- FEV1 $AUC_{0\text{-}12h}$ after 4, 12, 26, 38, 52 weeks of treatment in a subset of approximately 600 patients (the serial spirometry set)
- Symptoms and rescue medication used (number of puffs) as reported by the patients using the patient e-Diary
- SGRQ-C after 4, 12, 26, 38, and 52 weeks of treatment and percentage of patients with a clinically important improvement of at least 4 or 8 in the total SGRQ-C score after 52 weeks of treatment.

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

- dyspnoea
- sputum volume
- sputum purulence

or;

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

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

It is stated in the CSR that, 'for the purposes of this study, the type of treatment provided for a COPD exacerbation determined the severity of the exacerbation. A worsening of symptoms that met the above symptom definition that was not treated with systemic corticosteroids and/or antibiotics was considered a mild COPD exacerbation. A COPD exacerbation was considered of moderate severity if treatment with systemic corticosteroids or antibiotics or both was required and severe, if hospitalisation was required (in addition to treatment with systemic corticosteroids and/or antibiotics). An emergency room visit of longer than 24 hours was considered a hospitalisation. A COPD exacerbation that required an emergency room visit for less than 24 hours was of moderate severity, providing the exacerbation was treated with systemic corticosteroids or antibiotics or both'.

7.2.1.2. Randomisation and blinding methods

All eligible patients were randomised via Interactive Response Technology (IRT) to one of the treatment arms. Randomisation was stratified by smoking status, severity of airflow limitation and ICS use. Patients, investigator staff, persons performing the assessments, and data analysts remained blind to the identity of the treatment from the time of randomisation until database lock. A double-dummy design was used because the identity of the study drugs could not be disguised due to their different forms. Unblinding only occurred in the case of patient emergencies (and at the conclusion of the study).

7.2.1.3. Analysis populations

The randomised set (RAN) comprised all randomised patients. Patients in RAN were analysed according to the treatment to which they were randomised.

The full analysis set (FAS) included all randomised patients who received at least one dose of study drug. Following the intent-to-treat principle, patients were analysed according to the treatment they were assigned to at randomisation.

The per-protocol set (PPS) included all patients in the FAS without any major protocol deviations.

Major protocol deviations were defined prior to database lock and the unblinding of the study. Patients were analysed according to the treatment they were randomised to.

The safety set included all patients who received at least one dose of study drug. Patients were analysed according to the treatment they received.

7.2.1.4. Statistical methods

The comparison of QVA149 (110/50 µg QD) to salmeterol/fluticasone (500/50 µg BD) was evaluated by testing the following null hypothesis (Ho) versus the alternative hypothesis (Ha) at one-sided significance level of 0.025:

- Ho: There was at least 15% increase in rate of mild/moderate/severe COPD exacerbations for COPD patients at risk of exacerbating treated with QVA149 (110/50 µg QD) compared to salmeterol/fluticasone (50/500 µg BD).
- Ha: Rate ratio of mild/moderate/severe COPD exacerbations for COPD patients at risk of exacerbating treated with QVA149 (110/50 µg QD) compared to salmeterol/fluticasone (50/500 µg BD) was less than 1.15.

The number of exacerbations during the 52 week treatment period was analysed using a generalised linear model assuming a negative binomial distribution. The model included terms for treatment, smoking status at baseline, inhaled corticosteroid (ICS) use at screening, baseline severity of airflow limitation, and region as fixed effects.

An estimate of the ratio of exacerbation rates in the treatment groups (QVA149 versus salmeterol/fluticasone) was presented together with a two-sided 95% confidence interval (CI). If the upper limit of the CI was less than 1.15, non-inferiority of QVA149 compared to salmeterol/fluticasone could be claimed, and the following hypothesis was tested at one-sided significance level of 0.025 using the same CI computed from above:

- Ho2: There was no difference in the rate of mild/moderate/severe COPD exacerbations for COPD patients at risk of exacerbating treated with QVA149 (110/50 µg QD) compared to salmeterol/fluticasone (50/500 µg BD).
- Ha2: For COPD patients at risk of exacerbating, the rate of mild /moderate /severe COPD exacerbations treated with QVA149 (110/50 µg QD) was lower than that of patients treated with salmeterol/fluticasone (50/500 µg BD).

If the upper limit was less than 1, then Ho2 was rejected and superiority QVA149 versus SFC in reducing the rate of COPD exacerbation could be claimed. The overall type I error from the two hypothesis tests described above (that is, the non-inferiority test and the following superiority test) was kept at significance level 0.05 (two-sided).

In relation to the secondary endpoints, it appears that no multiplicity adjustments were performed.

7.2.1.5. Participant flow

The following table is extracted from the dossier (Table 2).

Table 2: Participant flow

Analysis set	QVA149 n (%)	Salm/Flut n (%)	Total n (%)
Randomized set (RAN)	1680 (100)	1682 (100)	3362 (100)
Analysis set	**QVA149 n (%)**	**Salm/Flut n (%)**	**Total n (%)**
Safety set (SAF)	1678 (99.9)	1680 (99.9)[1]	3358 (99.9)
Full analysis set (FAS)	1675 (99.7)	1679 (99.8)	3354 (99.8)
Per-protocol set (PPS)	1528 (91.0)	1556 (92.5)	3084 (91.7)

7.2.1.1. Major protocol violations/deviations

Overall, 8.3% of patients were excluded from the per-protocol analysis, mainly due to protocol deviations (7.7%).

7.2.1.2. Baseline data

COPD history and baseline disease characteristics were well-balanced between the treatment arms, see Table 3. The majority of patients had moderate or severe COPD by airflow limitation at baseline (91.5%), see Tables 3 and 4.

Disease severity was similar between the treatment arms in terms of the GOLD combined assessment and mMRC Dyspnoea Scale. Almost all (99.9%) patients had baseline mMRC ≥ 2 (72% had a score of 2). In the year prior to study entry, 80.6% of patients had experienced one COPD exacerbation, and 19.3% of patients had experienced 2 or more exacerbations.

Table 3: Severity of COPD at baseline

Variable Statistic/Category	QVA149 N=1680	Salm/Flut N=1682	Total N=3362
Severity of COPD (GOLD 2011-2014) - Airflow limitation, n (%)[a]			
Mild (GOLD 1)	0	0	0
Moderate (GOLD 2)	560 (33.3)	563 (33.5)	1123 (33.4)
Severe (GOLD 3)	973 (57.9)	981 (58.3)	1954 (58.1)
Very severe (GOLD 4)	133 (7.9)	124 (7.4)	257 (7.6)
Severity of COPD (GOLD 2015) - Combined assessment of COPD, n (%)[a]			
Low risk and less symptoms (Group A)	2 (0.1)	0	2 (0.1)
Low risk and more symptoms (Group B)	400 (23.8)	422 (25.1)	822 (24.4)
High risk and less symptoms (Group C)	1 (0.1)	2 (0.1)	3 (0.1)
High risk and more symptoms (Group D)	1265 (75.3)	1249 (74.3)	2514 (74.8)
Number of COPD exacerbations in the previous year, n (%)[a]			
0	1 (0.1)	1 (0.1)	2 (0.1)
1	1355 (80.7)	1355 (80.6)	2710 (80.6)
≥2	324 (19.3)	325 (19.3)	649 (19.3)
mMRC Dyspnea Scale, n (%)			
Grade 0	1 (0.1)	0	1 (0.0)
Grade 1	2 (0.1)	2 (0.1)	4 (0.1)
Grade 2	1202 (71.5)	1210 (71.9)	2412 (71.7)
Grade 3	439 (26.1)	432 (25.7)	871 (25.9)
Grade 4	36 (2.1)	38 (2.3)	74 (2.2)
COPD Assessment Test (CAT) score			
n	1674	1677	3351
Mean (SD)	16.9 (7.06)	16.6 (6.97)	16.7 (7.02)
Median (range)	17.0 (0 - 40)	16.0 (1 - 40)	17.0 (0 - 40)
CAT score categorized, n (%)[a]			
0 - 10 (mild)	331 (19.7)	347 (20.6)	678 (20.2)
11 - 20 (moderate)	845 (50.3)	859 (51.1)	1704 (50.7)
21 - 30 (severe)	440 (26.2)	421 (25.0)	861 (25.6)
31 - 40 (very severe)	58 (3.5)	50 (3.0)	108 (3.2)

[a] A few patients had missing information.

Table 4: Duration of COPD

Variable Statistic/Category	QVA149 N=1680	Salm/Flut N=1682	Total N=3362
Duration of COPD (years)			
n	1679	1682	3361
Mean (SD)	7.2 (5.31)	7.3 (5.45)	7.3 (5.38)
Median (range)	5.8 (0.2 - 56.7)	5.9 (0.0 - 37.3)	5.8 (0.0 - 56.7)
Duration of COPD, n (%)[a]			
< 1 year	84 (5.0)	80 (4.8)	164 (4.9)
1 - 5 years	634 (37.7)	616 (36.6)	1250 (37.2)
> 5 - 10 years	545 (32.4)	568 (33.8)	1113 (33.1)
> 10 - 15 years	273 (16.3)	263 (15.6)	536 (15.9)
> 15 - 20 years	97 (5.8)	105 (6.2)	202 (6.0)
> 20 years	46 (2.7)	50 (3.0)	96 (2.9)
ICS use at screening, n (%)			
No	726 (43.2)	743 (44.2)	1469 (43.7)
Yes	954 (56.8)	939 (55.8)	1893 (56.3)
LABA use at screening, n (%)			
No	551 (32.8)	554 (32.9)	1105 (32.9)
Yes	1129 (67.2)	1128 (67.1)	2257 (67.1)
ICS/LABA use at screening, n (%)			
No	896 (53.3)	904 (53.7)	1800 (53.5)
Yes	784 (46.7)	778 (46.3)	1562 (46.5)
LAMA use at screening, n (%)			
No	672 (40.0)	653 (38.8)	1325 (39.4)
Yes	1008 (60.0)	1029 (61.2)	2037 (60.6)
Smoking status at screening, n (%)			
Ex-smoker	1016 (60.5)	1013 (60.2)	2029 (60.4)
Current smoker	664 (39.5)	669 (39.8)	1333 (39.6)
Estimated number of pack years			
n	1680	1682	3362
Mean (SD)	41.6 (21.37)	41.9 (22.27)	41.8 (21.82)
Median	40.0 (10.0 - 180.0)	40.0 (5.0 - 259.3)	40.0 (5.0 - 259.3)

ICS = inhaled corticosteroid, LABA = long-acting beta-2 agonist, LAMA = long-acting muscarinic antagonist, ICS/LABA = fixed dose combination of ICS and LABA.

Duration of COPD was calculated from the date first diagnosed with COPD recorded on the eCRF until Visit 1.

Smoking status at screening is shown.

Pack years = total years of smoking multiplied by cigarette packs smoked per day which was summarized as recorded on the eCRF.

[a] One patient in the QVA149 arm had missing information.

7.2.1.3. Results for the primary efficacy outcome

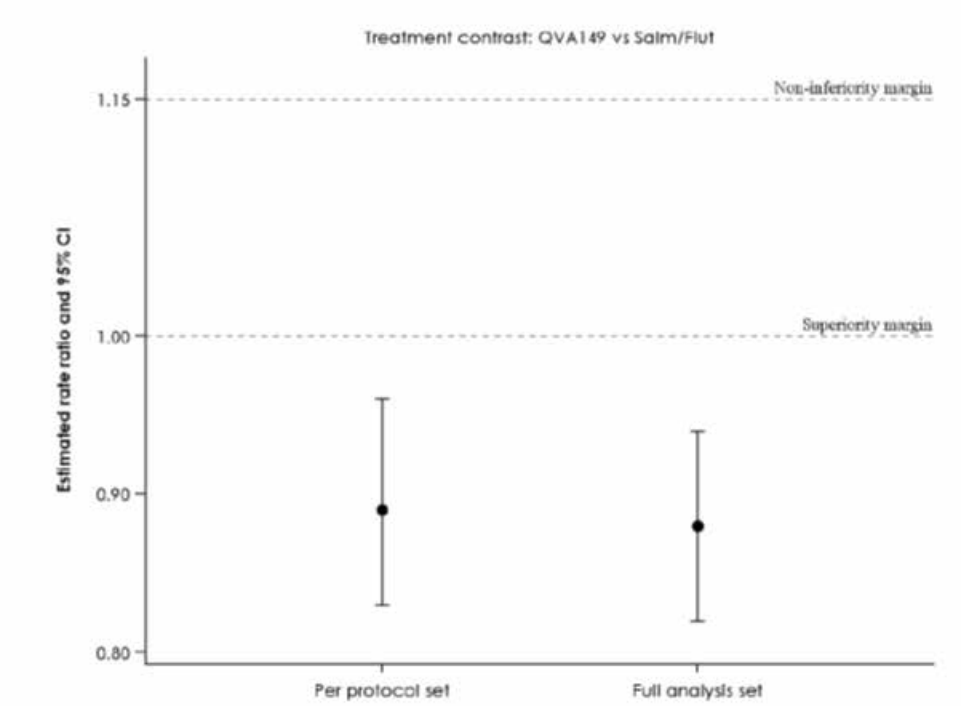
The annualised rate of all COPD exacerbations was statistically significantly lower with QVA149, 3.59 (3.28, 3.94) compared to salmeterol/fluticasone 4.03 (3.68, 4.41). The rate ratio is 0.89 (0.83, 0.96), p = 0.003, see Figure 2 and Table 5.

The estimated rate ratio for all COPD exacerbations (mild, moderate or severe) and associated 95% CI during double blind treatment (PPS and FAS) is shown in the figure below. Details of the model are described in Figure 2.

The study report states that this study, 'met its primary and secondary objectives for this endpoint. The upper bound of the 2-sided 95% CI of the rate ratio was less than 1.15

demonstrating that QVA149 was non-inferior to salmeterol/fluticasone. … the upper bound of 2-sided 95% CI for rate ratio was less than 1, demonstrating the superiority of QVA149 to salmeterol/fluticasone'. See Figure 2 below for further details.

Figure 2: Estimated COPD exacerbation (mild, moderate or severe) rate ratio and associated 95% confidence intervals during double-blind treatment (Per protocol set and Full analysis set) Study QVA149A2318



Generalized linear model assuming a negative binomial distribution with fixed effects of treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region.

As the offset variable log(exposure time in years) was used.

The non-inferiority margin was assumed to be 1.15, and non-inferiority would be demonstrated of QVA149 to Salm/Flut if the upper bound of 2-sided 95% CI for rate ratio was less than 1.15.

Superiority of QVA149 to Salm/Flut would be demonstrated if the upper bound of 2-sided 95% CI for rate ratio was less than 1.

Table 5: Summary and generalised linear model for the rate of COPD exacerbations (mild, moderate or severe) during double blind treatment (per protocol set)

Variable Statistic/Category	QVA149 N=1528	Salm/Flut N=1556
Number of COPD exacerbations		
N	1528	1556
Mean (SD)	3.0 (3.30)	3.2 (3.27)
Median	2.0	2.0
Min – Max	0 - 23	0 - 20
Number of COPD exacerbations categorized - n (%)		
0	343 (22.4)	290 (18.6)
1	336 (22.0)	318 (20.4)
2	209 (13.7)	247 (15.9)
3	173 (11.3)	167 (10.7)
≥4	467 (30.6)	534 (34.3)
Total number of COPD exacerbation episodes	4531	4969
Total number of treatment years	1380.02	1374.22
Occurrence rate in 100 patient years	328.33	361.59
Model based estimates	**QVA149 N = 1518**	**Salm/Flut N = 1556**
Annualized rate (95% CI)	3.59 (3.28, 3.94)	4.03 (3.68, 4.41)
Treatment comparisons (QVA149 vs. salm/flut)		
Rate ratio	0.89	-
95% CI	(0.83, 0.96)	-
p-value	0.003	-

Total number of treatment years = sum of exposure to double-blind drug expressed in years (days / 365.25).

Occurrence rate in 100 patient years = total number of COPD exacerbation episodes / total number of treatment years*100.

7.2.1.4. Results for other efficacy outcomes

Only the secondary efficacy variables stipulated in the protocol are considered here.

Time to first COPD exacerbation

The median time to event in the QVA149 arm was 71.0 days, compared to 51.0 days in the salmeterol/fluticasone arm. The hazard ratio of risk reduction in QVA149 versus salmeterol/fluticasone was 0.84, (95% CI: 0.78, 0.91); p < 0.001, see Table 6.

Table 6: Time to first COPD exacerbation

	QVA149 N=1675	Salm/Flut N=1679
Patients with event, n (%)	1295 (77.3)	1368 (81.5)
Patients without event, n (%)	380 (22.7)	311 (18.5)
Time at risk (days), median (range)	65.0 (1-397)	48.0 (1-382)
Time to event (days), Percentiles		
25% (95% CI)	13.0 (12.0, 16.0)	15.0 (13.0, 17.0)
Median (95% CI)	71.0 (60.0, 82.0)	51.0 (46.0, 57.0)
75% (95% CI)	279.0 (251.0,315.0)	198.0 (178.0,225.0)
Event-free rates, % (95% CI)		
Week 12	46.9 (44.4, 49.3)	39.7 (37.3, 42.0)
Week 26	33.6 (31.3, 35.9)	26.5 (24.3, 28.6)
Week 38	26.0 (23.9, 28.2)	20.4 (18.5, 22.4)
Week 52	20.5 (18.6, 22.5)	16.1 (14.3, 17.9)
Log rank test for treatment difference		

	QVA149 N=1675	Salm/Flut N=1679
p-value vs Salm/Flut	<0.001	
Cox regression analysis		
Hazard ratio QVA149 / (Salm/Flut)	0.84	
95% CI	(0.78, 0.91)	
p-value	<0.001	

Patients who did not experience a COPD exacerbation were censored at the earlier date of last double-blind treatment + 1, death and final visit.

Event-free rates were calculated at the end of the specified weeks by the Kaplan Meier method.

Time at risk = time from treatment start until the first COPD exacerbation or censoring.

Cox regression: Time to first COPD exacerbation = treatment + baseline total symptom score + baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study) + smoking status at screening + ICS use at screening + airflow limitation severity + region.

n.e. = not estimable.

COPD exacerbations starting between first dose and one day after date of last treatment are included.

All analyses are based on data reported on the "COPD Exacerbation Episodes" eCRF.

Rate and time to first moderate or severe COPD exacerbation

The annualised rate of moderate or severe COPD exacerbations was 0.98 with QVA149 compared to 1.19 with salmeterol/fluticasone. The rate ratio of exacerbation rate of moderate or severe exacerbations of QVA 149 versus salmeterol/fluticasone (rate ratio: 0.83, 95% CI 0.75, 0.91, $p < 0.001$, see Table 7.

Table 7: Summary and generalised linear model for the rate of moderate or severe COPD exacerbation

Variable Statistic/Category	QVA149 N=1675	Salm/Flut N=1679
Number of COPD exacerbations		
N	1675	1679
Mean (SD)	0.8 (1.12)	0.9 (1.14)
Median	0.0	1.0
Min – Max	0 - 9	0 - 8
Number of COPD exacerbations categorized - n (%)		
0	938 (56.0)	835 (49.7)
1	426 (25.4)	482 (28.7)
2	185 (11.0)	203 (12.1)
3	71 (4.2)	97 (5.8)
≥4	55 (3.3)	62 (3.7)
Total number of COPD exacerbation episodes	1265	1452
Total number of treatment years	1504.18	1478.67
Occurrence rate in 100 patient years	84.10	98.20
Model estimates	**QVA149 N = 1651**	**Salm/Flut N = 1656**
Annualized rate (95% CI)	0.98 (0.88, 1.10)	1.19 (1.07, 1.32)
Treatment comparisons		
Rate ratio	0.83	-
95% CI	(0.75, 0.91)	-
p-value	<0.001	-

Change from baseline in pre-dose FEV1 and FVC after 4, 12, 26, 38, and 52 weeks of treatment

See Table 8 for details. Improvements over 52 weeks in pre-dose trough FEV1 for QVA149 versus salmeterol/fluticasone ranged from 0.062 on Day 365 to 0.086 L on Day 183. Improvements in QVA149 treated group over the comparator was seen at different time points. FVC changes showed similar trends: Over 52 weeks, improvements in pre-dose trough FVC for QVA149 versus salmeterol/fluticasone ranged from 0.160 L on Day 365 to 0.209 L on Day 183, see Table 9.

Table 8: FEV1 changes; mixed model for repeated measures (MMRM) of change from baseline in pre-dose trough FEV1 (L) by visit (full analysis set)

					---------- Treatment difference ---------		
Visit	Treatment	BL Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value
Pre-dose trough FEV1 (Number of patients included in the analysis - QVA149: n=1597, Salm/Flut: n=1595)							
Baseline	All		1.074				
Day 29 CFB	QVA149	1.064	0.079 (0.0070)	Salm/Flut	0.073 (0.0061)	(0.061, 0.085)	<0.001
	Salm/Flut	1.064	0.006 (0.0070)				
Day 85 CFB	QVA149	1.068	0.070 (0.0072)	Salm/Flut	0.078 (0.0065)	(0.066, 0.091)	<0.001
	Salm/Flut	1.071	-0.008 (0.0072)				

					---------- Treatment difference ---------		
Visit	Treatment	BL Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value
Day 183 CFB	QVA149	1.074	0.049 (0.0073)	Salm/Flut	0.086 (0.0069)	(0.073, 0.100)	<0.001
	Salm/Flut	1.075	-0.037 (0.0074)				
Day 267 CFB	QVA149	1.075	0.034 (0.0074)	Salm/Flut	0.073 (0.0071)	(0.059, 0.087)	<0.001
	Salm/Flut	1.084	-0.039 (0.0075)				
Day 365 CFB	QVA149	1.078	0.015 (0.0075)	Salm/Flut	0.062 (0.0073)	(0.048, 0.077)	<0.001
	Salm/Flut	1.087	-0.048 (0.0076)				

Baseline FEV1 is defined as the average of the -45 min and -15 min FEV1 values taken on Day 1.
Pre-dose trough FEV1 is defined as the mean of FEV1 at -45 min and -15 min before morning dose.

Table 9: FVC changes

					---------- Treatment difference ----------		
Visit	Treatment	BL Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value
Pre-dose trough FVC (Number of patients included in the analysis - QVA149: n=1597, Salm/Flut: n=1595)							
Baseline	All		2.710				
Day 29 CFB	QVA149	2.703	0.146 (0.0127)	Salm/Flut	0.177 (0.0113)	(0.155, 0.199)	<0.001
	Salm/Flut	2.694	-0.032 (0.0128)				
Day 85 CFB	QVA149	2.709	0.134 (0.0131)	Salm/Flut	0.206 (0.0120)	(0.182, 0.229)	<0.001
	Salm/Flut	2.698	-0.071 (0.0131)				
Day 183 CFB	QVA149	2.716	0.088 (0.0135)	Salm/Flut	0.209 (0.0129)	(0.184, 0.235)	<0.001
	Salm/Flut	2.712	-0.121 (0.0136)				
Day 267 CFB	QVA149	2.711	0.071 (0.0137)	Salm/Flut	0.183 (0.0132)	(0.157, 0.209)	<0.001
	Salm/Flut	2.721	-0.111 (0.0137)				
Day 365 CFB	QVA149	2.717	0.022 (0.0139)	Salm/Flut	0.160 (0.0138)	(0.133, 0.187)	<0.001
	Salm/Flut	2.727	-0.138 (0.0140)				

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval, CFB = change from baseline.

FEV1 $AUC_{0\text{-}12h}$ after 4, 12, 26, 38, 52 weeks of treatment in a subset of approximately 600 patients (the serial spirometry set)

QVA149 group was statistically superior to salmeterol/fluticasone group from Day 1 onwards (p = 0.022). The LS mean improvement for QVA149 was 0.027 L greater than for salmeterol/fluticasone at Day 1 and 0.117 L greater at Day 85, see Table 10 for details.

Table 10: MMRM of change from baseline in FEV1 (L) AUC $_{0\text{-}12h}$, by visit (Serial spirometry set)

					---------- Treatment difference -------		
Visit	Treatment	BL Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value
FEV1 AUC(0-12h) (Number of patients included in the analysis - QVA149: n=279, Salm/Flut: n=277)							
Baseline	All		1.109				
Day 1 CFB	QVA149	1.093	0.130 (0.0146)	Salm/Flut	0.027 (0.0118)	(0.004, 0.050)	0.022
	Salm/Flut	1.086	0.103 (0.0146)				
Day 29 CFB	QVA149	1.104	0.134 (0.0161)	Salm/Flut	0.101 (0.0153)	(0.071, 0.131)	<0.001
	Salm/Flut	1.099	0.033 (0.0162)				
Day 85 CFB	QVA149	1.111	0.127 (0.0165)	Salm/Flut	0.117 (0.0162)	(0.085, 0.149)	<0.001
					---------- Treatment difference -------		
Visit	Treatment	BL Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value
	Salm/Flut	1.102	0.010 (0.0166)				
Day 183 CFB	QVA149	1.115	0.113 (0.0166)	Salm/Flut	0.116 (0.0163)	(0.084, 0.148)	<0.001
	Salm/Flut	1.115	-0.002 (0.0167)				
Day 267 CFB	QVA149	1.116	0.094 (0.0169)	Salm/Flut	0.113 (0.0169)	(0.080, 0.146)	<0.001
	Salm/Flut	1.128	-0.019 (0.0170)				
Day 365 CFB	QVA149	1.117	0.078 (0.0174)	Salm/Flut	0.110 (0.0180)	(0.074, 0.145)	<0.001
	Salm/Flut	1.129	-0.032 (0.0176)				

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval, CFB = change from baseline.

All LS Means, SEs, CIs, and p-values are from a MMRM: change from baseline in FEV1 AUC0-12h= treatment + baseline FEV1 + smoking status at screening + ICS use at screening + airflow limitation severity + visit + treatment*visit interaction + baseline FEV1*visit interaction + region.

SGRQ-C after 4, 12, 26, 38, and 52 weeks of treatment

SGRQ-C after 4, 12, 26, 38, and 52 weeks of treatment and percentage of patients with a clinically important improvement of at least 4 or 8 in the total SGRQ-C score after 52 weeks of treatment. Estimated treatment differences and associated 95% confidence intervals of the SGRQ total score starting from Day 85 onwards show results favouring QVA149 over salmeterol/fluticasone, see Table 11. The proportion of patients with a clinically meaningful improvement in the SGRQ total score (≥ 4 point reduction) was higher in the QVA149 arm compared to the salmeterol/fluticasone arm from Day 85 onwards (49.2% versus 43.7%, odds ratio 1.30 (CI: 1.11, 1.51), p< 0.001 on Day 365), respectively.

Symptoms and rescue medication used (number of puffs) as reported by the patients using the patient e-Diary

The reduction in daily rescue medication usage was approximately 0.25 inhalations per day compared to salmeterol/fluticasone, see Table 11.

There was no significant reduction in the daily symptom score with QVA149 compared to salmeterol/fluticasone (LS mean -0.03, p = 0.619), and there was a significant increase in the night time score with QVA149 compared to salmeterol/fluticasone, (LS mean 0.14, p = 0.011).

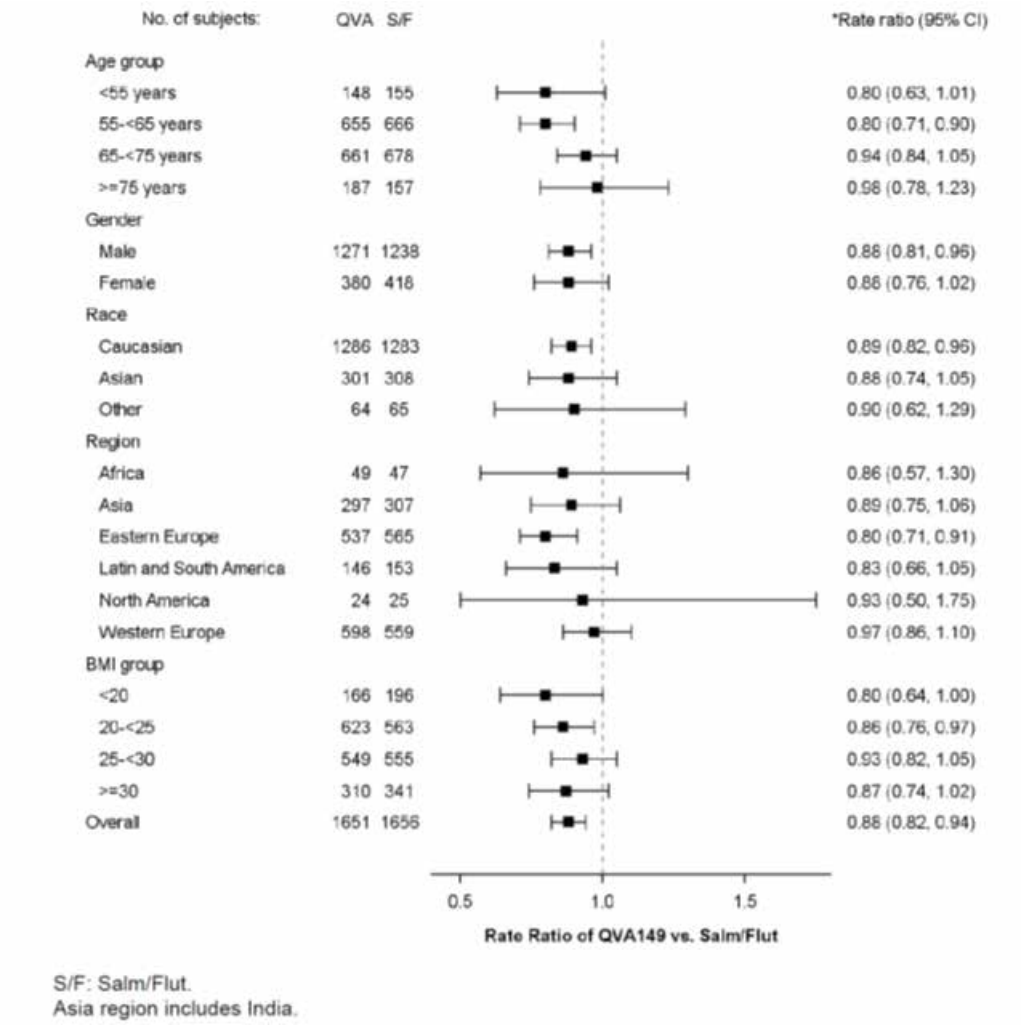
Table 11: Change in St Georges score

					-------- Treatment difference -------		
Visit	Treatment	BL Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value
SGRQ-C total score (Number of patients included in the analysis - QVA149: n=1602, Salm/Flut: n=1593)							
Baseline	All		46.9				
Day 29 CFB	QVA149	47.3	-2.3 (0.36)	Salm/Flut	0.0 (0.32)	(-0.7, 0.6)	0.886
	Salm/Flut	47.0	-2.3 (0.36)				
Day 85 CFB	QVA149	47.1	-3.2 (0.38)	Salm/Flut	-1.3 (0.37)	(-2.0, -0.6)	<0.001
	Salm/Flut	47.0	-1.9 (0.38)				
Day 183 CFB	QVA149	46.9	-3.5 (0.39)	Salm/Flut	-1.2 (0.39)	(-2.0, -0.5)	0.001
	Salm/Flut	47.0	-2.3 (0.39)				
Day 267 CFB	QVA149	46.7	-3.5 (0.40)	Salm/Flut	-1.8 (0.41)	(-2.6, -1.0)	<0.001
	Salm/Flut	46.9	-1.7 (0.40)				
Day 365 CFB	QVA149	46.8	-3.1 (0.41)	Salm/Flut	-1.3 (0.43)	(-2.1, -0.4)	0.003
	Salm/Flut	46.7	-1.9 (0.41)				

The converted SGRQ-C total score is presented.

Subgroup analyses are listed in Figure 3.

Figure 3: Forest plot of estimated COPD exacerbation (mild, moderate or severe) rate ratio and associated 95% confidence intervals during double blind treatment by demographics (full analysis set)



S/F: Salm/Flut.
Asia region includes India.

7.2.1.5. Evaluator commentary

This study is a well design study (double blind comparator controlled) that has used the commonly accepted definition for evaluating and recording COPD exacerbations with the use of a patient's electronic diary; it also complies with the definitions for exacerbation, severity scores recommended in the EU Guideline on Clinical investigation of medicinal products in the treatment of COPD.

The primary efficacy endpoint revealed non-inferiority and then statistical superiority to the comparator treatment.

Some secondary endpoints, showed statistically significant difference favouring the study medication.

7.3. Analyses performed across trials: pooled and meta analyses

Not applicable.

7.4. Evaluator's conclusions on clinical efficacy

The sponsor's clinical summary states that, in relation to COPD, 'approximately 50% of patients, including those with only moderate airflow obstruction, have at least one exacerbation per year. Furthermore, 22% of COPD patients with moderate airflow obstruction and 33% of patients with severe obstruction have at least 2 exacerbations per year (Hurst et al 2010)[1]. Exacerbations impact patients of varying COPD severities. The prevention of only one COPD exacerbation of any severity may have a significant effect on patient outcomes (Wedzicha and Wilkinson 2006)[2]. There is also evidence that exacerbations, particularly more frequent exacerbations, are responsible for accelerating the progression of the disease, leading to earlier development of disability, respiratory failure, and death. Thus, an important goal of COPD management is to prevent exacerbations (GOLD 2016)'.

This study showed that QVA149 was statistically superior to salmeterol/fluticasone in relation to the primary efficacy endpoint that is rate of all COPD exacerbations. This is the basis for the proposed extension of indications, 'prevention of exacerbations'. This is based on the mean (SD) exacerbations of 3.0 (3.30) in the QVA149 group versus 3.2 (3.27) in the salmeterol/fluticasone group. This finding relates to all severities of exacerbations (mild, moderate and severe). Thus, the evaluator questions the clinical relevance of this margin of difference to support the indication of 'prevention of exacerbation'. It is noted that moderate to severe categories of exacerbation were 0.8 (1.12) and 0.9 (1.14) respectively, see Table 7. It would seem that a significant proportion was mild exacerbation. The sponsor should provide, in the Section 31 response, the number of mild exacerbations: mean (SD), number of COPD exacerbations categorised, annualised rate and rate ratio as expressed in Table 7 for moderate to severe exacerbations. If this analysis is already included in the dossier, the sponsor should provide its location.

The secondary efficacy endpoints are presented in Section 7.2.1.4. Some endpoints showed statistical superiority favouring QVA149 over the comparator. However, the evaluator questions the clinical relevance of the magnitude of these findings: for example, time to first COPD exacerbation is expressed in median time and is a crude index. The rate ratio of exacerbation rate of moderate or severe exacerbation of 0.83, 95% CI 0.75, 0.91, $p < 0.001$ is of limited clinical relevance. Similarly, pre dose FEV1 over time (62 to 86 mL) is also of limited clinical relevance indicating that the rate of progression of disease was not significantly different between groups.

In addition, there are multiple secondary endpoints; the study report states that no multiplicity adjustments were performed on any secondary endpoints giving rise to concerns about the statistical validity of these results.

Whilst this study provides some evidence of efficacy, the magnitude of efficacy is inadequate to support the extension of indications to include 'prevention of exacerbation'. In addition, prevention also correlates to reduced progression of disease. This would mean that prevention of exacerbation would indirectly alter the course of COPD. Altering the course needs to be confirmed with studies earlier in the course of the illness, see EU Guideline EMA/CHMP/483572/2012- corr 1 Guidelines on clinical investigation of medical products for the treatment of COPD.

The original report (PM-2012-4395-5) discussed a study where the primary efficacy endpoint was the exacerbation rate (moderate to severe as per the GOLD definition). This study was Study A2304 where the inclusion criterion was severe and very severe COPD, see that report where one of the treatment arms was QVA149. The study duration was 64 weeks where it is

[1] Hurst JR, et al Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*; 2010; 63: 1128-1138.
[2] Wedzicha JA, Wilkinson T (2006) Impact of chronic obstructive pulmonary disease exacerbations on patients and payers. *Proc Thorac Soc* 2006; 3: 218-221.

reported that the mean (SD) number of moderate to severe exacerbations in the QVA149 group was 1.11 (1.3). Whilst cross study comparison has its limitations, especially as the inclusion criterion was a more severe COPD, the results are in line with that reported in the current study. That study was considered (by the evaluator of the original submission), insufficient to support the proposed indication that QVA149 reduces exacerbations.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Pivotal and/or main efficacy studies

The pivotal study provided safety data on QVA149. The details of safety monitoring are similar to those of previously submitted data, (see PM-2012-4395-1-5).

8.2. Patient exposure

Table 12: Patient exposure

	Statistic	QVA149 N=1678	Salm/Flut N=1680
Exposure (days)	n	1678	1680
	Mean (SD)	327.6 (94.63)	321.7 (101.17)
	Median	365.0	365.0
	Min - Max	1 - 418	1 - 426

Compliance was high in both treatment arms, with a mean of approximately 99% of days where drug was taken as per protocol over the treatment period.

8.1. Adverse events

8.1.1. All adverse events (irrespective of relationship to study treatment)

8.1.1.1. Integrated safety analyses

The overall incidence of AEs was similar across the treatment arms. The most commonly (approximately 80%) affected primary SOC was respiratory, thoracic and mediastinal disorders, followed by infections and infestations. The incidence of infection and infestation AEs was 42.3% in the QVA149 arm versus 48% in the salmeterol/fluticasone arm, see Table 13.

Table 13: Incidence of AEs

	QVA149 N=1678 n (%)	Salm/Flut N=1680 n (%)
Patients with at least one AE	1459 (86.9)	1498 (89.2)
Primary system organ class		
Respiratory, thoracic and mediastinal disorders	1328 (79.1)	1403 (83.5)
Infections and infestations	710 (42.3)	807 (48.0)
Gastrointestinal disorders	163 (9.7)	164 (9.8)
Musculoskeletal and connective tissue disorders	137 (8.2)	167 (9.9)
Nervous system disorders	103 (6.1)	103 (6.1)
General disorders and administration site conditions	87 (5.2)	87 (5.2)
Vascular disorders	77 (4.6)	68 (4.0)
Injury, poisoning and procedural complications	76 (4.5)	69 (4.1)
Cardiac disorders	73 (4.4)	84 (5.0)
Skin and subcutaneous tissue disorders	57 (3.4)	43 (2.6)
Metabolism and nutrition disorders	52 (3.1)	69 (4.1)
Investigations	45 (2.7)	56 (3.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	41 (2.4)	35 (2.1)
Psychiatric disorders	31 (1.8)	39 (2.3)
Renal and urinary disorders	30 (1.8)	28 (1.7)
Eye disorders	25 (1.5)	26 (1.5)
Hepatobiliary disorders	17 (1.0)	15 (0.9)

	QVA149 N=1678 n (%)	Salm/Flut N=1680 n (%)
Ear and labyrinth disorders	16 (1.0)	17 (1.0)
Reproductive system and breast disorders	16 (1.0)	19 (1.1)
Blood and lymphatic system disorders	13 (0.8)	19 (1.1)
Endocrine disorders	10 (0.6)	6 (0.4)
Immune system disorders	5 (0.3)	11 (0.7)
Congenital, familial and genetic disorders	4 (0.2)	1 (0.1)
Social circumstances	1 (0.1)	1 (0.1)
Pregnancy, puerperium and perinatal conditions	0	1 (0.1)

Primary system organ classes are sorted in descending order of frequency in the QVA149 group.
All adverse events starting on or after the time of first administration of double-blind drug but not later than 7 days (30 days in case of an SAE) after the last administration are included.

A summary of the most frequently reported AEs (≥ 1% in any treatment arm) by preferred term is presented in Table14. Overall the most frequently reported AE was COPD, which was reported with a similar frequency across both treatment arms (77.4% and 81.8%, in QVA149 and salmeterol/fluticasone, respectively). Other frequently reported AEs (> 5% in both treatment arms) were nasopharyngitis (11.7% versus 11.6%), viral upper respiratory tract infection (7.9% versus 8.2%) and upper respiratory tract infection bacterial (7.4% versus 10.0%), respectively. Overall, there were no meaningful differences in AE frequencies between treatment arms.

Table 14: Most frequent > 1% Adverse events

	QVA149 N=1678 n (%)	Salm/Flut N=1680 n (%)
Patients with at least one AE	1459 (86.9)	1498 (89.2)
Preferred term		
Chronic obstructive pulmonary disease	1299 (77.4)	1374 (81.8)
Nasopharyngitis	197 (11.7)	195 (11.6)
Viral upper respiratory tract infection	132 (7.9)	138 (8.2)
Upper respiratory tract infection bacterial	125 (7.4)	168 (10.0)
Lower respiratory tract infection	82 (4.9)	98 (5.8)
Upper respiratory tract infection	81 (4.8)	83 (4.9)
Pneumonia	53 (3.2)	80 (4.8)
Cough	50 (3.0)	51 (3.0)
Dyspnoea	49 (2.9)	51 (3.0)
Hypertension	46 (2.7)	42 (2.5)
Headache	38 (2.3)	35 (2.1)
Back pain	35 (2.1)	34 (2.0)
Influenza	35 (2.1)	56 (3.3)
Oropharyngeal pain	35 (2.1)	33 (2.0)
Bronchitis	29 (1.7)	44 (2.6)
Rhinitis	27 (1.6)	28 (1.7)
Oedema peripheral	26 (1.5)	14 (0.8)
Non-cardiac chest pain	21 (1.3)	13 (0.8)
Arthralgia	20 (1.2)	24 (1.4)
Constipation	20 (1.2)	17 (1.0)
Diarrhoea	20 (1.2)	24 (1.4)
Oral candidiasis	20 (1.2)	71 (4.2)
Dyspepsia	18 (1.1)	9 (0.5)
Pyrexia	18 (1.1)	29 (1.7)
Musculoskeletal pain	17 (1.0)	13 (0.8)
Respiratory tract infection viral	17 (1.0)	8 (0.5)
Sinusitis	17 (1.0)	21 (1.3)
Dry mouth	16 (1.0)	3 (0.2)
Urinary tract infection	15 (0.9)	22 (1.3)
Gastritis	10 (0.6)	22 (1.3)
Gastroenteritis	10 (0.6)	19 (1.1)
Sputum increased	10 (0.6)	23 (1.4)
Dizziness	7 (0.4)	28 (1.7)
Dysphonia	7 (0.4)	30 (1.8)
Oropharyngeal candidiasis	2 (0.1)	17 (1.0)

Severity

Mild AEs occurred in 30.3% of patients in the QVA149 arm compared to 27.7% in the salmeterol/fluticasone arm; moderate AEs occurred in 39.9% of patients in the QVA149 arm compared to 43.1% of patients in the salmeterol/fluticasone arm. Severe AEs were reported in 16.7% of patients in the QVA149 compared to 18.4% in the salmeterol/fluticasone arm.

Deaths

All deaths (including those reported after 30 days after last treatment, but before end of study period) were adjudicated in a blinded fashion by an external independent panel, see Table 15. Overall, the causes of death by major category were similar between treatment arms. In the

QVA149 treatment arm, respiratory cause was the most frequent cause of death (11 patients, 0.7%), while cardiovascular cause was most frequent cause of death in the salmeterol/fluticasone arm (11 patients, 0.7%). The incidence of overall adjudicated MACE and/or CV deaths was similar and balanced between the treatment arms (1.9% versus 1.8%).

Table 15: Number of deaths by adjudicated primary cause

Primary cause of death category Subcategory	QVA149 N=1678 n (%)	Salm/Flut N=1680 n (%)
Number of deaths	24 (1.4)	24 (1.4)
Cancer	1 (0.1)	2 (0.1)
Other Cancer - Acute Myeloid Leukemia	0	1 (0.1)
Other Cancer - Carcinoma with unknown primary	1 (0.1)	0
Other Cancer - Hypopharyngeal	0	1 (0.1)
Cardiovascular	9 (0.5)	11 (0.7)
Fatal MI	2 (0.1)	2 (0.1)
Fatal stroke - Ischemic with hemorrhagic conversion	0	1 (0.1)
Presumed CV death	0	2 (0.1)
Pump failure	0	1 (0.1)
Presumed Sudden death	0	2 (0.1)
Sudden death - Last seen between 1 and 24 hours	2 (0.1)	1 (0.1)
Sudden death - Witnessed within 1 hour	5 (0.3)	2 (0.1)
Indeterminate	2 (0.1)	1 (0.1)
Indeterminate	2 (0.1)	1 (0.1)
Other	1 (0.1)	2 (0.1)
Accidental	0	1 (0.1)
Other - Non CV procedure (post surgical operation complications)	1 (0.1)	0
Suicide	0	1 (0.1)
Respiratory	11 (0.7)	8 (0.5)
COPD Exacerbation with Pneumonia	5 (0.3)	2 (0.1)
COPD Exacerbation without Pneumonia	4 (0.2)	6 (0.4)
Other respiratory - Pneumothorax	1 (0.1)	0
Pneumonia	1 (0.1)	0

Causes of death were determined by an independent adjudication committee. All deaths were adjudicated.

Only deaths occurring on treatment plus 30 days after end of treatment are included.

SAEs

The proportion of patients experiencing an SAE was similar across the treatment arms (18.4% and 19.9% in QVA149 and salmeterol/fluticasone arms, respectively). SAEs were most frequently reported within the respiratory, thoracic and mediastinal SOC, followed by infections and infestations SOC.

Adjudicated CCV SAEs

A similar percentage of patients experienced at least one adjudicated CCV SAE in both treatment arms (2.4% and 2.7% in QVA149 and salmeterol/fluticasone arms, respectively).

Adverse events of special interest were 31.7% (QV149) and 35.6% (salmeterol/fluticasone). These were events compatible with beta adrenergic or anticholinergic mechanism of action.

8.1.2. Laboratory investigations:

8.1.2.1. Haematology

No clinically significant difference between the two treatment groups was seen in relation to worsening haematology values, see Table 16.

Table 16: Number of patients with newly occurring or worsening clinically notable haematology values at any time post baseline

Parameter	Notable criterion	QVA149 N=1678 n/m (%)	Salm/Flut N=1680 n/m (%)
Hematocrit	Male: < 0.37	32/1190 (2.7)	30/1164 (2.6)
	Female: < 0.32	2/ 351 (0.6)	3/ 372 (0.8)
	Total	34/1541 (2.2)	33/1536 (2.1)
Hemoglobin	Male: < 115 g/L	31/1195 (2.6)	27/1169 (2.3)
	Female: < 95 g/L	2/ 351 (0.6)	4/ 372 (1.1)
	Total	33/1546 (2.1)	31/1541 (2.0)
Platelets	< 75 10E9/L	5/1538 (0.3)	3/1531 (0.2)
	> 700 10E9/L	1/1538 (0.1)	2/1531 (0.1)
	Both: < 75 and > 700 10E9/L	0/1538	0/1531
Leukocytes	< 2.8 10E9/L	2/1546 (0.1)	1/1541 (0.1)
	> 16.0 10E9/L	12/1546 (0.8)	26/1541 (1.7)
	Both: < 2.8 and > 16.0 10E9/L	0/1546	0/1541

n = number of patients meeting the criterion, i.e. who had a newly occurring clinically notable value or had a worsening of a value during treatment which was already notable at baseline. For patients with a missing value at baseline, any post-baseline notable value was considered as newly occurring.

8.1.2.2. Blood chemistry

No significant difference was seen between groups except for a higher percentage of patients in the QVA149 arm (4.3%) reported newly occurring notable blood urea nitrogen levels (> 9.99 mmol/L) compared to the salmeterol/fluticasone arm (2.6%), see Table 17. There were no significant changes in LFTs, urinalysis.

Changes in Vital Signs were not clinically significant and were low.

QTc changes were clinically not significant.

Table 17: Number of patients with newly occurring or worsening clinically notable chemistry values at any time post baseline

Parameter	Notable criterion	QVA149 N=1678 n/m (%)	Salm/Flut N=1680 n/m (%)
Albumin	< 25 g/L	1/1551 (0.1)	0/1549
Alk. phosphatase	> 3 x ULN	1/1551 (0.1)	1/1548 (0.1)
ALT	> 3 x ULN	8/1551 (0.5)	2/1548 (0.1)
AST	> 3 x ULN	9/1551 (0.6)	3/1548 (0.2)
Total bilirubin	> 34.2 umol/L	1/1551 (0.1)	3/1549 (0.2)
Blood urea nitrogen	> 9.99 mmol/L	66/1550 (4.3)	41/1549 (2.6)
Creatinine	> 176.8 umol/L	6/1550 (0.4)	2/1549 (0.1)
Glucose	< 2.78 mmol/L	6/1550 (0.4)	2/1549 (0.1)
	> 9.99 mmol/L	64/1550 (4.1)	69/1549 (4.5)
	Both: < 2.78 and > 9.99 mmol/L	0/1550	0/1549
Gamma GT (U/L)	> 3 x ULN	39/1551 (2.5)	32/1549 (2.1)
Potassium	< 3 mmol/L	1/1549 (0.1)	0/1547
	> 6 mmol/L	13/1549 (0.8)	8/1547 (0.5)
	Both: < 3 and > 6 mmol/L	0/1549	0/1547
Sodium	< 125 mmol/L	2/1550 (0.1)	3/1549 (0.2)
	> 160 mmol/L	0/1550	0/1549
	Both: < 125 and > 160 mmol/L	0/1550	0/1549
Total protein	< 40 g/L	0/1550	0/1549
	> 95 g/L	0/1550	0/1549
	Both: < 40 and > 95 g/L	0/1550	0/1549

n = number of patients meeting the criterion, i.e. who had a newly occurring clinically notable value or had a worsening of a value during treatment which was already notable at baseline. For patients with a missing value at baseline, any post-baseline notable value was considered as newly occurring.
m = total number of patients with a post-baseline value for the specified parameter, considering data from scheduled, unscheduled or premature discontinuation visits up to 7 days after last dose.

8.2. Evaluator's overall conclusions on clinical safety

This 52 week study provides adequate evidence of safety and supports the safety findings obtained in the original submission. No undue safety concerns were identified.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

- This study was designed as a non-inferiority study and then if non-inferiority was shown, as a superiority study in relation to the primary efficacy endpoint which was the rate of exacerbation. This study met these expectations.
- Exacerbations were well defined; the COPD inclusion was moderate to severe.
- The study was well designed and the duration was adequate.
- Safety results were in line with those described in the original submission.
- The Clinical study has adequate efficacy and safety data to include in the Clinical trials section.

9.2. First round assessment of risks

- Though statistical superiority has been shown in this study, the clinical significance of this margin is considered inadequate (and of small magnitude) to support the extension of indication.
- The margin of difference also includes mild exacerbations, the rate of which could not be verified by the evaluator.
- There are multiple secondary endpoints and issues of multiplicity have not been factored into the statistical considerations.
- The incidence of pneumonia (as confirmed by radiographic imaging that is chest x-ray or CT scan) was numerically higher in the salmeterol/fluticasone arm (4.8%) compared to QVA149 arm (3.2%). This also suggests that the difference in exacerbations may be due to increased infections that are biologically plausible in the comparator group.

9.1. First round assessment of benefit-risk balance

The first round assessment is unfavourable to include the extension of indication, prevention of exacerbation. However the inclusion of FLAME study is acceptable in the Clinical Trials section, provided the amendments recommended by the evaluator are made.

10. First round recommendation regarding authorisation

The first round assessment is unfavourable to include the extension of indication, prevention of exacerbation. However the inclusion of FLAME study is acceptable in the Clinical Trials section provided the amendments recommended by the evaluator are made.

11. Clinical questions

11.1. Efficacy

It is noted in the pivotal study, the moderate to severe categories of exacerbation were 0.8 (1.12) and 0.9 (1.14) respectively, see Table 7. It would seem that a significant proportion was mild exacerbation. The sponsor should provide, in the post-first round response, the number of mild exacerbations: mean (SD), number of COPD exacerbations categorised, annualised rate and rate ratio as expressed in Table 7 for moderate to severe exacerbations. If this analysis is already included in the dossier, the sponsor should provide its location.

12. Second round evaluation of clinical data submitted in response to questions

It is noted in the pivotal study, the moderate to severe categories of exacerbation were 0.8 (1.12) and 0.9 (1.14) respectively, see Table 7. It would seem that a significant proportion was mild exacerbation. The sponsor should provide, in the Section 31 response, the number of mild exacerbations: mean (SD), number of COPD exacerbations categorised, annualised rate and rate ratio as expressed in Table 7 for moderate to severe exacerbations. If this analysis is already included in the dossier, the sponsor should provide its location.

Sponsors response:

The sponsor's response is provided in Table 18 below.

Table 18: Summary and generalised linear model for the rate of mild COPD exacerbations during double blind treatment (Full analysis set)

Variable Statistic/Category	QVA149 N=1675	salmeterol/fluticasone N=1679
Number of mild COPD exacerbations		
N	1675	1679
Mean (SD)	2.2 (3.04)	2.4 (3.07)
Median	1.0	1.0
Min – Max	0 - 23	0 - 20
Number of mild COPD exacerbations categorised - n (%)		
0	608 (36.3)	568 (33.8)
1	370 (22.1)	352 (21.0)
2	194 (11.6)	218 (13.0)
3	149 (8.9)	134 (8.0)
≥4	354 (21.1)	407 (24.2)
Total number of mild COPD exacerbation episodes	3678	3986
Total number of treatment years	1504.18	1478.67
Occurrence rate in 100 patient years	244.52	269.57
Model based estimates	**QVA149 N = 1651**	**salmeterol/fluticasone N = 1656**
Annualised rate (95% CI)	2.46 (2.20, 2.74)	2.72 (2.43, 3.03)
Treatment comparisons (QVA149 vs. salmeterol/fluticasone)		
Rate ratio	0.91	-
95% CI	(0.83, 0.99)	-
p-value	0.030	-

Total number of treatment years = sum of exposure to double-blind drug expressed in years (days / 365.25).

Occurrence rate in 100 patient years = total number of COPD exacerbation episodes / total number of treatment years*100.

Estimates are from a generalised linear model assuming a negative binomial distribution with fixed effects of treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region. As the offset variable log(exposure time in years) was used.

COPD exacerbations starting between first dose and one day after last treatment are included. COPD exacerbations that occurred within 7 days of each other are collapsed as one event.

All analyses are based on data reported on the "COPD Exacerbation Episodes" eCRF.

The sponsor states that mild exacerbations also have a negative impact on patient's health status; FLAME demonstrated a significant reduction in all exacerbations as well as in the category of moderate to severe exacerbations.

Evaluation of response:

Table 19 below reveals the mean (SD) and the annualised rate of exacerbations in each treatment group.

Table 19: The mean (SD) and the annualised rate of exacerbations in each treatment group

Severity	Source, CER	Mean (SD)		Annualised rate (95% CI)	
		QVA 149	Salm/Flut	QVA 149	Salm/Flut
Mild, moderate, severe	Table 9	3.0 (3.30)	3.2 (3.27)	3.59 (3.28, 3.94)	4.03 (3.68,4.41)
Moderate, severe	Table 12	0.8 (1.12)	0.9 (1.14)	0.98 (0.88. 1.10)	1.19 (1.07, 1.32)
Mild	Table on page 23	2.2 (3.04)	2.4 (3.07)	2.46 (2.20,2.74)	2.72 (2.43,3.03)

It is evident from the above findings that a significant proportion of the rates of exacerbation have been of mild severity. Mild severity is defined in the study protocol as, 'a worsening of symptoms that either did not meet the above symptom definition but was treated by the investigator with systemic corticosteroids or antibiotics, or that met the symptom definition but did not receive antibiotics and/or systemic corticosteroids, was not considered a moderate or severe COPD exacerbation for the study. However, these events were captured on the COPD exacerbation CRF as mild exacerbations'.

Whilst the evaluator does not dispute the fact that mild exacerbations impact the patient's health, it is the opinion of the evaluator that the clinical significance of these findings are inadequate to support the extension of indication. The inclusion of FLAME in Clinical Trials section of the PI ensures that the findings will assist the prescriber to be informed regarding appropriate treatment.

12.1. Sponsor response to the clinical evaluation report

Comment 1

Though statistical superiority has been shown in this study, the clinical significance of this margin is considered inadequate (and of small magnitude) to support the extension of indication.

Sponsor's response:

The sponsor disagrees with the evaluator's comment pointing to the annualised rate of exacerbations where it states that the differences point to clinically meaningful results. Several relative benefits from large studies relating to other monotherapies are discussed; also relative risk reduction in the current FLAME study are also discussed to support that the magnitude of effect is sufficient to support the indication of 'prevention of exacerbation'.

It also maintains that the 'results of Study A2318 showed a consistent clinically relevant benefit of QVA149 on all exacerbation outcomes compared with salmeterol/fluticasone'.

To support the magnitude of efficacy observed in the FLAME study as clinically significant the sponsor states that, 'it is important to note that the comparator in this trial, salmeterol/fluticasone, demonstrated a 25% annualised rate of exacerbation reduction versus

placebo in TORCH (Calverley et al 2007[3]), and is one of the most commonly prescribed drugs in COPD patients who are at risk of repeated exacerbations. There is no minimal clinically important difference (MCID) in terms of reduction of COPD exacerbations as defined in regulatory Guidelines to support an indication claim for 'prevention of exacerbations.'

Evaluator's comment:

The sponsor's response is noted.

In relation to the magnitude of efficacy noted in the TORCH study, the evaluator observes that the approved indication for Seretide does not include prevention of exacerbation, rather it is approved for, 'the symptomatic treatment of patients with severe COPD (FEV1 < 50% predicted normal) and a history of repeated exacerbations who have significant symptoms despite regular beta-2 agonist bronchodilator therapy. Seretide is not indicated for the initiation of bronchodilator therapy in COPD'.

The sponsor states, that 'the absolute difference in the rate of all COPD exacerbations per year was 0.44'. The evaluator maintains that the clinical significance is considered inadequate to extend indications. However, is acceptable for inclusion of FLAME study in Clinical Trials section.

Comment 2:

The margin of difference also includes mild exacerbations, the rate of which could not be verified by the evaluator.

See above.

Comment 3:

There are multiple secondary endpoints and issues of multiplicity have not been factored into the statistical considerations.

Sponsor's response:

Sponsor has stated that whilst this is the case, 'the consistency of the results across key secondary outcomes demonstrates the robustness of the findings'.

Evaluator's comment:

The sponsor's response is noted. There still remains a statistical deficiency in that the findings did not factor in the issues of multiplicity.

Comment 4:

The incidence of pneumonia (as confirmed by radiographic imaging that is chest x-ray or CT scan) was numerically higher in the salmeterol/fluticasone arm (4.8%) compared to QVA149 arm (3.2%). This also suggests that the difference in exacerbations may be due to increased infections that are biologically plausible in the comparator group.

Sponsor's response:

The sponsor maintains that, 'given the consistency of the data of study A2318 favouring QVA149, it is unlikely that higher risk of infection due to the ICS component may have driven the overall exacerbation differences between the two groups'. Several subgroup analyses are provided to support this.

[3] Calverley PM, Anderson JA, Celli B (2007)] Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*; 356: 775-89.

Evaluator's comment:

The sponsor's response is noted.

Comments 5-11

These relate to amendments recommended to the proposed PI.

The sponsor's responses are acceptable except for the following:

The inclusion of 'clinical significant' results in relation to some endpoints. The evaluator maintains that this should be removed as the PI document expresses factual findings; the term 'clinically significant' for results, without confirmation from accepted relevant EU Guidelines, is inappropriate, in the opinion of the evaluator.

Reference to secondary endpoints in the PI should be removed.

Relating to the extension of indication: the evaluator maintains that the data are inadequate to approve 'prevention of exacerbations'.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

The benefits remain the same as the first round benefits, see Section 9.1.

13.2. Second round assessment of risks

The sponsor's response to the Round 1 clinical evaluation report attempts to address the concerns of the evaluator identified in Section 9.2.

The response discusses the concern that the margin of difference in relation to the primary efficacy endpoint (that is rate of all COPD exacerbations observed between the two groups) lacks clinical significance to approve the indication of 'prevention of exacerbations.'

The evaluator maintains that the difference of the rate of exacerbations, especially in relation to moderate and severe exacerbations is not of significant magnitude to warrant the extension. The sponsor cites several management guidelines to support the extension. However, the evaluator's conclusion is that the PI document reflects the evaluated data; the prescriber has adequate information in the clinical trials section to inform regarding treatment options.

The risks identified in section 9.2 are still the same.

13.3. Second round assessment of benefit-risk balance

The second round assessment is unfavourable to include the extension of indication, prevention of exacerbation. However the inclusion of FLAME study is acceptable in the clinical trials section.

It is noted in the EU where the FLAME study is included in the clinical trials section, the registered indication is, '*Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)'*.

14. Second round recommendation regarding authorisation

The second round assessment is unfavourable to include the extension of indication, prevention of exacerbation. However the inclusion of FLAME study is acceptable in the Clinical Trials section.

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