28 February 2019
EMA/137008/2019

Assessment report

Procedure No. EMEA/H/C/WS1554

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Riarify	beclometasone dipropionate / formoterol fumarate dihydrate / glycopyrronium	EMEA/H/C/004836/WS1554/0002
Trydonis	beclometasone dipropionate / formoterol fumarate dihydrate / glycopyrronium	EMEA/H/C/004702/WS1554/0002

Worksharing applicant (WSA): Chiesi Farmaceutici S.p.A.

Note

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

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List of abbreviations

* This is a general list of abbreviations. Not all abbreviations are used in this Assessment report.

ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BDI	Baseline dyspnoea index
BDP	Beclometasone dipropionate
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
bid	Twice daily
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CAT	COPD assessment test
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CS	Clinically significant
CSR	Clinical study report
DBP	Diastolic blood pressure
DD	Delivered dose
DDI	Drug-drug interaction
DPI	Dry powder inhaler
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
E-RS	Exacerbations of chronic pulmonary disease tool-respiratory symptoms
EU	European Union
FDC	Fixed dose combination
FEV_1	Forced expiratory volume in 1 second
FF	Formoterol fumarate
FPM	Fine particle mass
FVC	Forced vital capacity
GB	Glycopyrronium bromide
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
γGT	Gamma-glutamyltransferase
HFA	Hydroxyfluoroalkane
HR	Heart rate
IC	Inspiratory capacity
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IND	Indacaterol
IRS	Interactive response system
ITT	Intent-to-treat
i.v.	Intravenous
LABA	Long-acting β_2-agonist

LAMA	Long-acting muscarinic antagonist
LOCF	Last observation carried forward
MAA	Marketing authorisation application
MACE	Major adverse cardiovascular event
MCID	Minimal clinically important difference
MD	Metered dose
MMRM	Mixed model for repeated measures
NA	Not applicable
NCS	Non-clinically significant
od	Once daily
OIP	Orally inhaled products
PD	Pharmacodynamic
PE	Point estimate
PK	Pharmacokinetic
pMDI	Pressurised metered dose inhaler
PP	Per protocol
PT	Preferred term
QoL	Quality of life
QTcF	Fridericia-corrected QT interval
QTcP	Population-corrected QT interval
RI	Renal impairment
SABA	Short-acting β_2-agonist
SBP	Systolic blood pressure
SD	Standard deviation
SGRQ	St George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SOC	System organ class
SS	Steady-state
TDI	Transition dyspnoea index
TEAE	Treatment-emergent adverse event
TQT	Thorough QT
vs.	Versus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Chiesi Farmaceutici S.p.A. submitted to the European Medicines Agency on 26 November 2018 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication for TRYDONIS / RIARIFY to "Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1)."

Consequently, the indication section (4.1), Undesirable effects section (4.8) and Pharmacodynamic Properties section (5.1) of the EU SmPC to add the results of two Phase III studies (TRIPLE 7 and TRIPLE 8). The Package Leaflet and the Risk Management Plan are updated in accordance.

In addition, changes as requested by PRAC in the frame of Trimbow/Trydonis/Riarify PSUR (PRAC recommendation dated 12 July 2018), following beclometasone PSUSA/00000306/201612 were introduced in section 4.4. and 4.8 of the SmPC.

The Package Leaflet and the Risk Management Plan (version 6.0) are updated in accordance.

In addition, the WSA took the opportunity to update the list of local representatives in the Package Leaflet.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	26 November 2018
Start of procedure:	31 December 2018
CHMP Rapporteur Assessment Report	25 January 2019
PRAC Rapporteur Assessment Report	29 January 2019
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	14 February 2019
CHMP members comments	18 February 2019
Updated CHMP Rapporteur Assessment Report	20 February 2019
Opinion	28 February 2019

2. Scientific discussion

2.1. Introduction

Trydonis / Riarify (hereafter also referred to as CHF 5993 pMDI) is a triple combination of an inhaled corticosteroid (ICS), a long-acting beta2 agonist (LABA) and a long-acting muscarinic receptor antagonist (LAMA). The product is a fixed dose combination of beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium bromide (GB). Trydonis / Riarify is formulated as a hydroxyfluoroalkane (HFA) solution to be delivered via a pressurised metered dose inhaler (pMDI) with a nominal dose per actuation of BDP 100 mcg (87 mcg delivered dose), FF 6 mcg (5 mcg delivered dose), and GB 12.5 mcg (9 mcg delivered dose). The doses of BDP and FF are the same as used in the dual combination of BDP/FF (Foster) which has already been licensed for the treatment of COPD in all European Countries.

The European Commission (EC) granted a marketing authorisation valid throughout the European Union for Trydonis on 26 April 2018 and for Riarify on 23 April 2018.

The application for Trydonis and Riarify were informed consent application to Trimbow application.Therefore the content of the application are similar for these medicinal product and support the same scientific information as the reference product Trimbow.

The approved indication is:

“Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist (for effects on symptoms control and prevention of exacerbations see section 5.1)”.

The posology is two inhalations of Trydonis / Riarify 87/5/9 micrograms twice daily.

The main clinical studies supporting the approval of Trydonis / Riarify were study TRIPLE 5 (TRILOGY) and study TRIPLE 6 (TRINITY), both 52-week active controlled studies in high risk COPD patients (FEV1 less than 50% predicted, symptomatic at screening despite treatment as evidenced by a COPD assessment test [CAT] score of 10 or above, and with at least one documented moderate to severe COPD exacerbation in the year prior to study participation. Study TRIPLE 5 compared Trydonis / Riarify with a fixed combination of BDP/FF (Foster 100/6 pMDI) whereas study TRIPLE 6 compared Trydonis / Riarify with tiotropium and the open triple combination of BDP/FF (Foster) + tiotropium.

The MAH is now applying for an extension of the indication as follows:

"Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1)."

The extension of indication is primarily based on data from Study TRIPLE 8 (TRIBUTE) that compared Trydonis / Riarify with a fixed combination of IND/GB (Ultibro Breezhaler) over 52 weeks in subjects with COPD using a primary endpoint of moderate-to-severe COPD exacerbation rate over 52 weeks. Additional revisions are based on data from Study TRIPLE 7 (TRISTAR) evaluating the non-inferiority of Trydonis / Riarify compared with the open triple combination of Fluticasone/Vilanterol (Relvar Ellipta) + Tiotropium over 26 weeks in subjects with COPD.

2.2. Non-clinical aspects

No new Non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The present variation to extend the indication to include 'a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist' will not lead to a change of the initial environmental risk assessment. It is considered that the only impact could be in terms of the market penetration factor (FPEN) used in the calculation of the predicted environmental concentration (PEC). However, since the FPEN in the calculation of the initial PEC encompassed the entire population of COPD patients, the change is considered not to have an impact on the Fpen and the initial PEC. Therefore, the initial environmental risk assessment (ERA) is also applicable to the present variation.

However, the initial ERA has not been finalised yet as still open issues need to be addressed. The applicant agreed at the time to submit studies on OECD 308 and OECD 305 by 31 December 2018. In order to finalise the ERA, the applicant is asked to provide the announced study reports and the respective ERA update by 30 September 2019 within the appropriate variation. This delay was justified and agreed by the CHMP.

2.2.2. Discussion on non-clinical aspects

Based on the data submitted within the initial MAA considering already the entire population of COPD patients, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of BDP. No new Non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.3. Conclusion on the non-clinical aspects

There are no updated data have been submitted in this application, which is considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

The proposed extension of indication is primarily based upon data from one pivotal phase IIIb study TRIPLE 8 and the supporting, phase IIIb study TRIPLE 7.

Data characterising the pharmacokinetics of the three active components of Trydonis / Riarify, their pharmacokinetic interactions, the pharmacokinetics in special populations and potential drug-drug interactions were included in the original submission supporting the first marketing authorisation application for Trydonis / Riarify. No new pharmacology/ pharmacokinetic data were part of the present submission, which is acceptable by the CHMP.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

An overview on the GCP compliance audits performed by the MAH is provided in Table 1.

Table 1: List of GCP compliance audits performed by the MAH

No.	Type	Site	Dates/Duration	Participation in TRIPLE 7/ 8	Patients SCR failure/ randomised
1	Quality System Maintenance Audit (covering both studies)	[not indicated]	19-20MAY15	NA	NA
2	Site Audit	#040805 Hallein (Austria)	11-12FEB16	N / Y	N=7 / N=25
3	Site Audit	#428817 Jekabpils (Latvia)	20APR16	N / Y	N=0 / N=17
4	Site Audit	#616805 Sochaczew (Poland)	28-29JUL16	N / Y	N=22 /N=23

- Tabular overview of clinical studies

Table 1: Phase IIIb studies performed by the MAH in support of the type II variation

	Study Triple 7 CCD-05993AA1-07	Study Triple 8 CCD-05993AA1-08
Study type	Phase IIIb	Phase IIIb
Design	Phase IIIb, randomised, open-label, active-controlled, 2-arm parallel-group, multicentre, multinational	Phase IIIb, randomised, double-blind, double-dummy, active-controlled, 2-arm parallel-group, multicentre, multinational
Primary objective	To demonstrate the non-inferiority of CHF 5993 pMDI vs. fixed combination of Fluticasone/Vilanterol + Tiotropium in terms of quality of life (change from baseline in SGRQ total score at Week 26)	To demonstrate the superiority of CHF 5993 pMDI vs. Indacaterol/GB in terms of moderate/severe COPD exacerbation rate
Study treatment and total (daily) dose	CHF 5993 pMDI, 2 puffs bid (total daily dose: 400/24/50 µg BDP/FF/GB)	CHF 5993 pMDI, 2 puffs bid (total daily dose: 400/24/50 µg BDP/FF/GB)
Patients	Severe and very severe COPD patients	Severe and very severe COPD patients
Number of randomised patients	1157	1532
Comparators and total daily dose	Fluticasone/Vilanterol 1 inhalation od + Tiotropium 1 inhaled capsule od (total daily dose: 100/25 µg Fluticasone/Vilanterol + 18 µg Tiotropium)	Indacaterol/GB 1 inhalation od (total daily dose: 85/43 µg Indacaterol/GB)
Treatment duration	26 weeks	52 weeks

2.3.2. Discussion and conclusion on clinical pharmacology

No updated data have been provided in this application. Overall, the clinical pharmacology properties of three active components of Trydonis / Riarify have been appropriately described in the previous applications. This is acceptable by the CHMP.

2.4. Clinical efficacy

2.4.1. Introduction

The clinical development programme of Trydonis / Riarify (hereafter also referred to as CHF 5993 pMDI) in COPD which was the basis for the original marketing authorisation issued by the European Commission in April 2018 included three phase II (studies GLYCO 2, TRIPLE 3 and CARSAF), one phase IIb (study TRIPLE 9) and two pivotal efficacy and safety phase III clinical studies (studies TRIPLE 5 and 6).

Results of two new phase IIIb studies (TRIPLE 7 and TRIPLE 8) are now submitted by the MAH.

Support for the extension of the initially authorised indication to all adult patients with moderate to severe COPD mainly comes from the 52-week, randomised, double-blind, double-dummy, active controlled study TRIPLE 8 comparing Trydonis / Riarify with a fixed combination of a LABA (indacaterol) and a LAMA (GB) without inhaled corticosteroid. The primary objective of this study was to provide evidence by testing whether triple therapy with ICS/LABA/LAMA is superior to dual bronchodilator therapy with a LABA/LAMA combination in terms of preventing moderate to severe COPD exacerbation episodes over one year.

Main objective of study TRIPLE 7 was to demonstrate that Trydonis / Riarify is non-inferior to extemporary triple therapy (fixed combination of fluticasone and vilanterol plus tiotropium) in terms of the St. George's Respiratory Questionnaire (SGRQ) total score at week 26 as a measure of quality of life.

Efficacy outcomes of this study are considered supportive evidence and not contributing relevant new knowledge to this type II variation as a consequence of the study design which substantially differs from that of other phase III-IIIb studies, namely by the open-label treatment and the shorter total treatment duration of 26 weeks only (thereby not preventing seasonal influences on the exacerbation rate).

Therefore and in order to avoid unnecessary complexity of this assessment report, in the remainder of this section, efficacy results of study TRIPLE 7 are brief, to the point and addressing the essential aspects only.

2.4.2. Main study TRIPLE 8

Title of Study

A 52-week, double blind, double dummy, randomized, multinational, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide administered via pMDI (CHF 5993) versus indacaterol / glycopyrronium (Ultibro) via DPI in patients with Chronic Obstructive Pulmonary Disease (Study Number: CCD-05993AA1-08, Eudra-CT Number: EudraCT no. 2014-001704-22).

- *Study design*

Individual study participation lasted for about 52 weeks and comprised the following eight (8) investigator site on-visits as presented below and in

Figure 1:

- Pre-screening visit (Visit 0, V0) within no more than seven days prior to screening, performed in order to obtain written informed consent, also for restrictions to be observed prior to the screening visit;
- Screening visit (Visit 1, V1) to assess a patient's preliminary eligibility for inclusion into the study, followed by a 2-week open-label run-in period (treatment with IND/GB (85/43µg/day) and salbutamol pMDI or terbutaline DPI as rescue medication);
- Randomisation visit (Visit 2, V2) at week 0 (W0) when a patient's final eligibility was confirmed and eligible subjects randomised in a 1:1 ratio to receive for the next 52 weeks either

  CHF 5993 pMDI, 2 puffs twice daily or matching placebo (total daily nominal dose of 400/24/50µg BDP/FF/GB)

  or

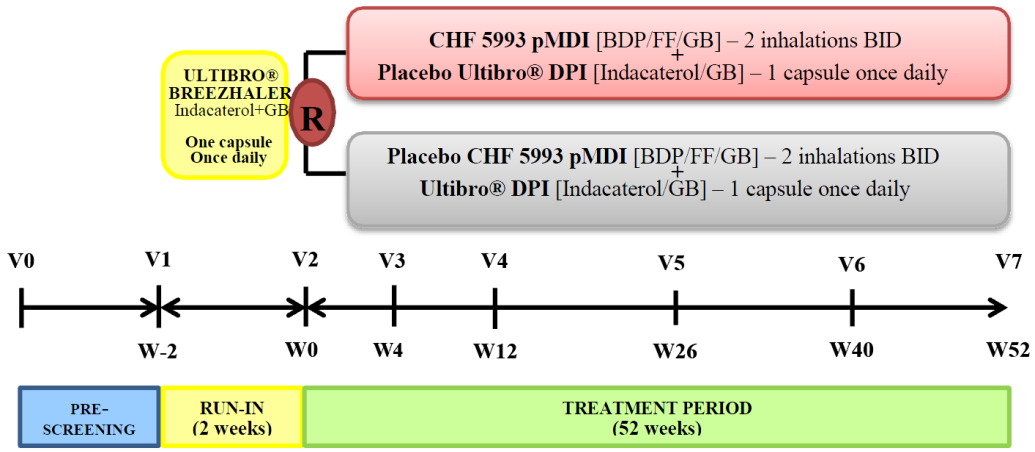
  IND/GB DPI, 1 capsule once daily or matching placebo (total daily nominal dose of 85/43µg IND/GB)

- Subsequent visits were performed after 4 weeks (V3), 12 weeks (V4), 26 weeks (V5), 40 weeks (V6) and 52 weeks (V7) of treatment.

Throughout study participation (i.e. during the run-in and the double-blind treatment periods), patients were requested to complete on a daily basis a validated digital diary (DIARYpro) in order to record

randomised medication intake, permitted rescue medication use (salbutamol pMDI or terbutaline DPI), and EXACT-PRO questionnaire data.

Figure 1: Study design and schedule of visits



Study participants

In order to be eligible, patients had to meet the following main inclusion criteria:

- Male or non-pregnant female, ≥40 years of age, current or former smokers, smoking history of >10 pack years;
- Diagnosis of severe or very severe airflow limitation as per GOLD update 2014 (post-bronchodilator FEV1 <50% of predicted normal; post-bronchodilator FEV1/FVC ratio <0.7);
- Symptomatic at screening (CAT score ≥10);
- Documented history of at least one moderate to severe exacerbation in the year prior to screening (i.e. prescription of systemic corticosteroids and/or antibiotics, COPD-triggered visit to emergency department or hospitalisation);
- Under dual treatment (ICS/LABA, ICS/LAMA or LABA/LAMA) or LAMA monotherapy (but not triple therapy) for at least two months prior to screening.

The presence of any of the following excluded a patient from trial participation (key exclusion criteria):

- Current clinical diagnosis of asthma or physician-judged need for an oral or inhaled corticosteroid therapy for the disorder;
- Known respiratory disorder other than COPD which in the opinion of the investigator may interfere with the IMPs efficacy (e.g. α1-antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension or interstitial lung disease);
- Patients requiring systemic corticosteroids (>3 days) or antibiotics (>7 days) due to COPD exacerbation, antibiotic treatment for lower respiratory tract infection or PDE4 inhibitor use within 4 weeks prior to screening;
- Occurrence of a moderate to severe COPD exacerbation during the run-in period;
- Patients requiring long term (≥12 hours daily) oxygen therapy for chronic hypoxaemia.

Treatments

For retaining the blind, a double dummy design was used. Patients randomised to receive CHF 5993 pMDI were administered IND/GB-matched placebo and vice versa as detailed in Table 3.

Table 3: Study treatments (Study TRIPLE 8)

Product description	Dosage	Form/ Route of administration	Packaging Batch Number Manufacturing Batch/Commercial Batch		Expiry Date
CHF 5993 pMDI (BDP/FF/GB)	BDP 100 µg/FF 6 µg/GB 12.5 µg per puff	pMDI	E122447-19	1016493	April 2016
			E122447-32 E122447-33 E122447-34	1027039	February 2017
			E122447-42	1043891	March 2018
			E122447-48	1043891	March 2018
CHF 5993 pMDI-matched placebo	Only excipients		E122447-19	B21206	April 2016
			E122447-20 E122447-30 E122447-31	1024720	February 2017
			E122447-42	1024720	March 2018
			E122447-48	1024720	March 2018
Indacaterol/GB (Ultibro®)	Indacaterol 85 µg/GB 43 µg per hard capsule	DPI	E122447-21	1022765 / S0031	November 2015
			E122447-22	1026829 / S0050	February 2016
			E122447-28	1031301 / S0090	July 2016
			E122447-29	1031305 / S0112 1031307 / S0099	July 2016
			E122447-35	1038098 / S0118	November 2016
			E122447-38	1038531 / S0119	November 2016
			E122447-40	1043984 / S0178	April 2017
			E122447-41	1047665 / S0207	June 2017
			E122447-47	1053606 / S0242	August 2017
Indacaterol/GB-matched placebo	Only excipients		E122447-21	1021415	November 2015
			E122447-22	1021316	February2016
			E122447-28	1021415	July 2016
			E122447-29	1021415	July 2016
			E122447-35	1021316	November 2016
			E122447-38	1021316	November 2016
			E122447-40	1034088	April 2017
			E122447-41	1034088	June 2017
			E122447-47	1034088	August 2017

Patients who were used taking previous COPD pMDI medications via a spacer were requested to use the AeroChamber Plus™ for administration of the study medication.

Salbutamol pMDI or terbutaline DPI were permitted for use as rescue medication and prescribed / purchased locally. The maximum doses allowed for salbutamol and terbutaline were 8 and 4 puffs per day, respectively. The Investigator had to be contacted in case the patient's need for rescue medication exceeded the maximum doses allowed for more than 2 consecutive days.

Objectives

Primary objective:

To demonstrate the superiority of CHF 5993 pMDI over IND/GB (Ultibro) in terms of moderate and severe chronic obstructive pulmonary disease (COPD) exacerbation rate over 52 weeks of treatment.

Secondary objectives:

- To evaluate the effect of CHF 5993 pMDI on other lung function parameters, patient's health status and clinical outcome measures;
- To assess the safety and the tolerability of the study treatments.

Outcomes/endpoints

The TRIPLE 8 study had a single primary outcome, i.e. the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment.

Definition: A COPD exacerbation was defined as "*A sustained worsening of the patient's condition (dyspnoea, cough and/or sputum production/purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics or need for hospitalisation*." Exacerbations were classified as moderate or severe as per EMA/Committee for Medicinal Products for Human Use (CHMP) guidelines definitions:

- Moderate: exacerbations that required treatment with systemic corticosteroids and/or antibiotics;
- Severe: exacerbations that required hospitalisation or resulted in death.

Any unscheduled visit at any healthcare institution (e.g. emergency department, pneumological division or physician) was also classified to be an exacerbation, provided systemic corticosteroids and or antibiotics were prescribed (moderate severity); if in addition the episode required a stay of >24h, it was considered as hospitalisation and therefore classified as severe.

The recognition of potential COPD exacerbations by the investigators was supported by the daily report of worsened symptoms through an electronic diary and completion of the EXACT questionnaire. According to the clinical study report, investigators and site personnel were notified by electronic means when the EXACT score "*changed beyond the normal day-to-day variability"*.

Sample size

The sample size was calculated to demonstrate the superiority of CHF 5993 pMDI over the active reference treatment (Ultibro) in terms of the moderate and severe COPD exacerbations rate over 52 weeks of treatment. Based on a log-normal distribution for the time to drop-out (estimated drop-out rates of 13%, 16.5%, and 20% at weeks 12, 26 and 52), an overdispersion of 0.56, and an exacerbation rate in the reference arm equal of 0.90, a total of 1534 evaluable patients (767 patients per arm) was expected to provide sufficient statistical power (85%) to detect a rate ratio of 0.80 between CHF 5993 pMDI and the reference treatment at a two-sided significance level of 0.05.

Since each subject with a follow-up of non-null duration provided a contribution to the analysis, all randomised subjects were considered to be evaluable, irrespective of whether they withdrew from the study prematurely.

Moreover, approximately 20% of patients randomised were expected to suffer from very severe airflow limitation (i.e. post-bronchodilator FEV1 at screening < 30% of predicted normal value).

Randomisation

Patients were randomly assigned to treatment groups by central balanced block randomisation scheme, stratified by country and severity of airflow limitation (post-bronchodilator FEV1 categories <30%

predicted or 30% to <50% predicted) in accordance with a randomisation list generated by an interactive response technology system.

Blinding (masking)

Patients, investigators, site staff, and sponsor personnel were masked to treatment assignment for the duration of the study by use of a double dummy approach. Chiesi Global Pharmacovigilance staff had their own unblinding codes to unblind patients in case of suspected unexpected serious adverse reactions (SUSARs) to be reported to the competent Regulatory Authorities and/or the EC/IRB.

Statistical methods

Primary Efficacy Variable

The study had a single primary endpoint, i.e. the number of moderate to severe COPD exacerbations over 52 weeks of treatment. The number of moderate and severe COPD exacerbations was analysed using a negative binomial model including treatment, country, number of COPD exacerbations during the previous year (1, > 1), severity of airflow limitation (i.e. post-bronchodilator FEV1 at screening < 30% or ≥ 30% of the predicted normal value) and smoking status as fixed effects and log-time on study in years as an offset. The adjusted exacerbation rate in each treatment group and the adjusted rate ratio with associated 95% Wald confidence intervals (CIs) were estimated by the model.

Superiority of CHF 5993 pMDI over IND/GB was demonstrated if the upper limit of the 95% CI for the adjusted exacerbation rate ratio was < 1.

Secondary Efficacy Variables

- Time to first moderate or severe COPD exacerbation and time to first severe COPD exacerbation were analysed using a Cox proportional hazard regression model including treatment, country, number of COPD exacerbations during the previous year (1, > 1), severity of airflow limitation and smoking status as factors. A Kaplan-Meier plot was also presented;
- Number of severe COPD exacerbations and number of moderate COPD exacerbations were analysed using the same model as for the primary efficacy variable;
- Changes from baseline in pre-dose morning FEV1 and FVC as well as changes from baseline in the SGRQ total score and domain scores, at each visit and over the entire treatment period were analysed using a linear MMRM including treatment, country, visit, treatment by visit interaction, number of COPD exacerbations during the previous year (1, > 1), severity of airflow limitation and smoking status as fixed effects, and baseline and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed;
- FEV1 and SGRQ responses at Week 26 and Week 52 were analysed using a logistic regression model including treatment, country, number of COPD exacerbations during the previous year (1, > 1), severity of airflow limitation and smoking status as factors and baseline FEV1 or SGRQ as a covariate;
- Changes from baseline to each inter-visit period and over the entire treatment period in the percentage of days, nights and complete days (i.e. day + night) without intake of rescue medication as well as in the average day-time, night-time and overall (i.e. day-time + night-time) use of rescue medication were analysed using a linear MMRM including treatment, country, inter-visit period, treatment by inter-visit period interaction, number of COPD exacerbations during the previous year, severity of airflow limitation and smoking status as fixed effects, as well as baseline and baseline by

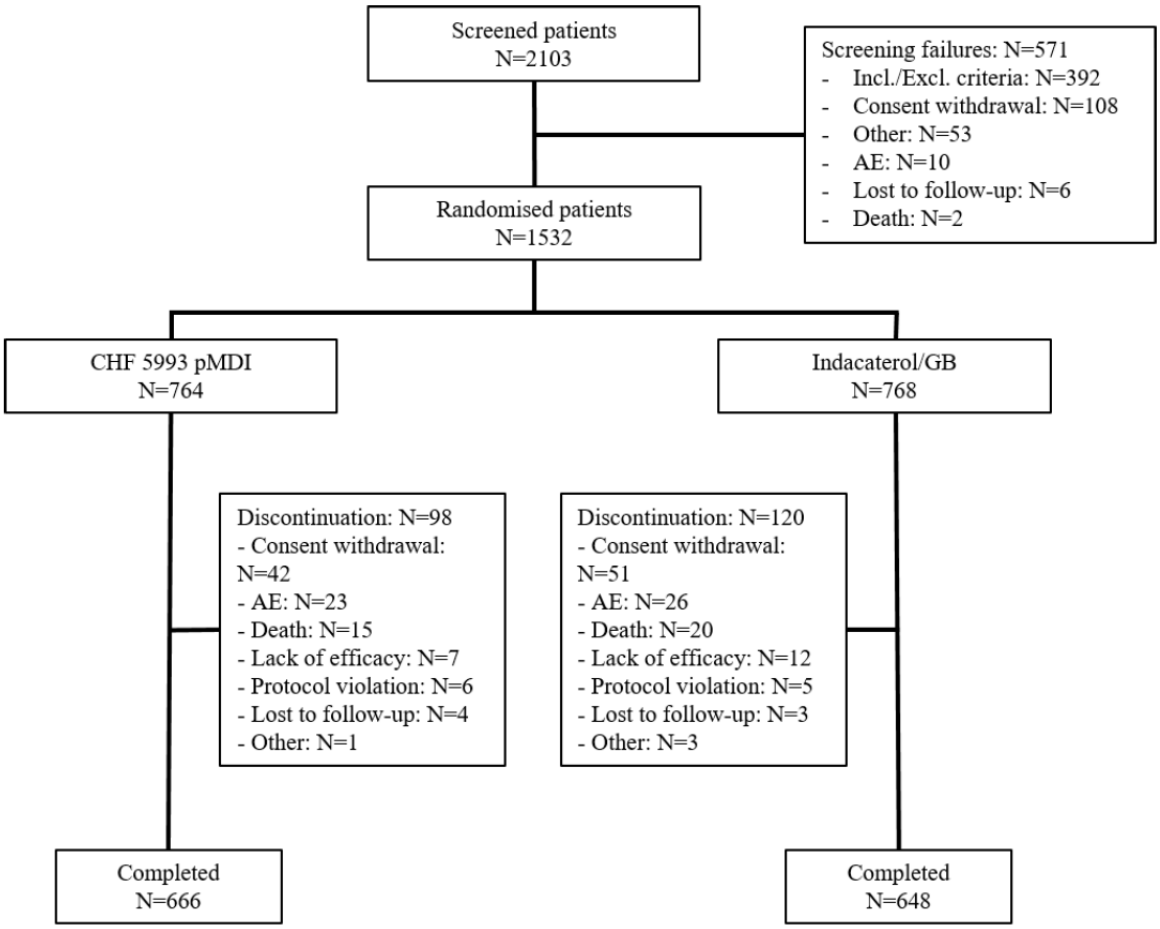
inter-visit period interaction as covariates. An unstructured covariance matrix was assumed and weights proportional to their duration were assigned to inter-visit periods;

- Changes from baseline to each inter-visit period and over the entire treatment period in the average EXACT-PRO total score and domain scores were analysed using the same model as for the rescue medication use ;
- Nocturnal symptoms were collected in the EXACT-PRO domain number 13 and were analysed using the same model as for the rescue medication use;
- Change from baseline in the CAT score at the end of treatment was summarised using descriptive statistics.

Results

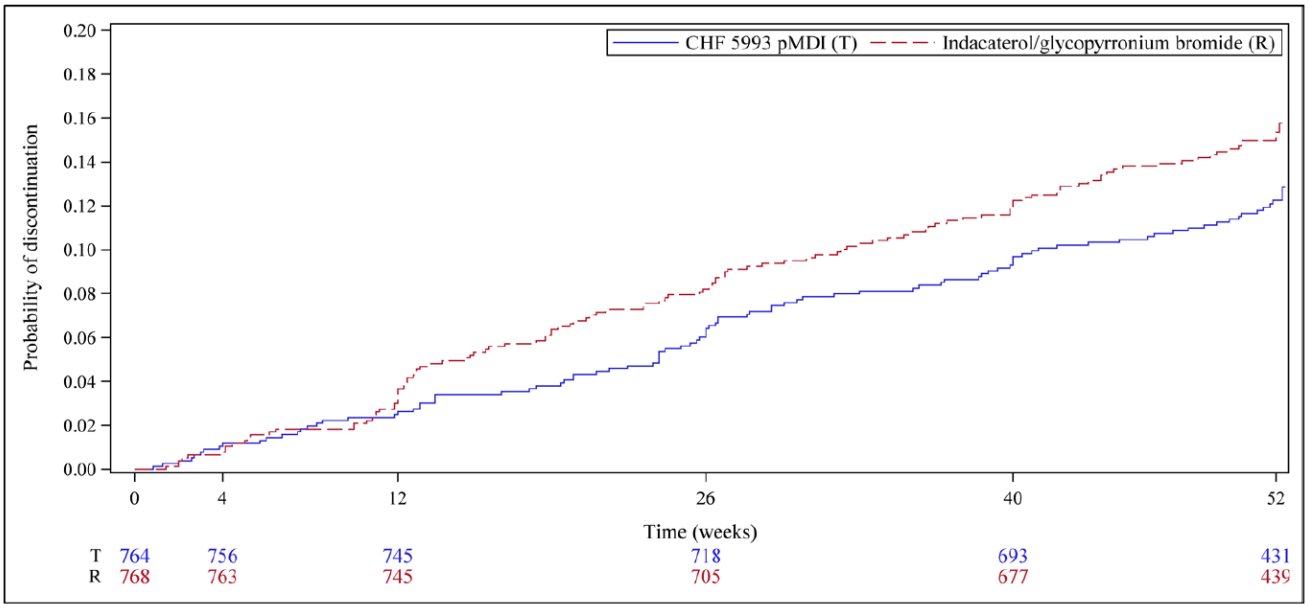
Participant flow

Figure 2: Subject disposition in study TRIPLE 8



Notes: Among the screening failures, 2 patients were reported with pre-treatment AEs leading to death (PTs: sudden cardiac death and acute myocardial infarction, respectively). Among the discontinuations, 2 other patients had AEs leading to death and were recorded as discontinued due to AEs.

Figure 3: Time to discontinuation from study TRIPLE 8 (Kaplan-Meier analysis, randomised population)



Source Data: Listing 16.2.1.2.2

Notes: [1] Time to discontinuation from study (weeks) = (date of completion/discontinuation – date of start of randomized treatment period)/7.

[2] Completed patients are censored at the date of completion.

[3] At each time point, the number of patients at risk is presented.

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Overall, the vast majority of patients randomised completed at least visit 6/40 weeks of treatment (90.1% in group CHF 5993 pMDI and 87.5% in group IND/GB, respectively), and 87.2 and 84.4 in the CHF 5993 pMDI and IND/GB groups respectively completed ≥52 weeks of treatment.

According to a Kaplan-Meier analysis, the probability of treatment discontinuation in the two groups was comparable during the first 12 weeks of treatment whereas for the remainder of the treatment period it was somewhat lower in group CHF 5993 pMDI as compared with IND/GB.

Recruitment

A total of 1532 patients were randomised by 17 countries (average screening failure rate 27.2% with important between-site variability). The majority of countries were European (N=14, 82%), two were South-American (Argentina, Chile) and one Central American (Mexico). The largest proportion of randomised patients came from Europe (N=1343, 88%); five Eastern European countries accounted for about 70% of study population (Bulgaria 20%, Romania 14%, Poland 13%, Latvia 12% and the Czech Republic 10%).

Conduct of the study

- *Time schedule*

Clinical trial protocol	03 December 2014 (Version 1) (There was only one global, non-substantial amendment and one local substantial amendment in France)
First patient first visit (FPFV)	29 May 2015
Last patient last visit (LPLV)	10 July 2017
Data review meetings	15-16 December 2016, 22-23 May 2017, and 02-04 August 2017

Date of data review report	24 August 2017
Statistical analysis plan	21 August 2017 (Version 1 Final)
Database lock	24.08.2017
Final study report	22 November 2017 (Final 1.0)

Baseline data

Independently of the population assessed (safety, ITT, PP), demographics were comparable between treatment groups (Table 4). The vast majority of patients in the safety population were white (92.2%) and predominantly male (71.8%). The median age upon screening was 65 years (range: 41 to 87 years) and the median BMI 25.6 kg/m^2 (range: 13-47). About half of the patients in both groups were between 40 and 64 years old and 10% had an age of ≥75 years.

Important characteristics of the underlying COPD were well balanced between treatment groups (Table 5). Prior to study entry, the vast majority of patients (80.8%) had experienced a single exacerbation only in the previous year. More than 85% of patients in both groups received dual therapy consisting of a LABA and an ICS (about 60%) or dual bronchodilator therapy (LABA / LAMA, about 25%).

Table 4: Demographic data (randomised = safety population)

	CHF 5993 pMDI N=764	Indacaterol/GB N=768	Overall N=1532
Age (years)			
n	764	768	1532
Mean (SD)	64.4 (7.7)	64.5 (7.7)	64.5 (7.7)
Range (min ; max)	42 ; 87	41 ; 84	41 ; 87
Age group, n (%)			
< 65 years	389 (50.9)	376 (49.0)	765 (49.9)
65-74 years	294 (38.5)	312 (40.6)	606 (39.6)
≥ 75 years	81 (10.6)	80 (10.4)	161 (10.5)
Gender, n (%)			
Male	548 (71.7)	552 (71.9)	1100 (71.8)
Female	216 (28.3)	216 (28.1)	432 (28.2)
Race, n (%)			
White	705 (92.3)	708 (92.2)	1413 (92.2)
Other	51 (6.7)	52 (6.8)	103 (6.7)
Missing[a]	8 (1.0)	8 (1.0)	16 (1.0)
Weight (kg)[b]			
n	764	768	1532
Mean (SD)	74.5 (16.8)	76.8 (17.5)	75.7 (17.2)
Range (min ; max)	40 ; 140	32 ; 138	32 ; 140
Height (cm)			
n	764	768	1532
Mean (SD)	170.1 (9.1)	169.7 (9.2)	169.9 (9.2)
Range (min ; max)	141 ; 198	138 ; 200	138 ; 200
BMI (kg/m²)[b]			
n	764	768	1532
Mean (SD)	25.7 (5.1)	26.6 (5.4)	26.1 (5.3)
Range (min ; max)	14 ; 43	14 ; 47	14 ; 47

BMI = Body mass index; GB = Glycopyrronium bromide; Max = Maximum; Min = Minimum; pMDI = Pressurised metered dose inhaler; SD = Standard deviation.
N = Number of patients in the Safety population; n = Number of patients with available data.
[a] Per local regulations in Portugal, patients' race could not be recorded.
[b] At baseline (i.e. V2).

Table 5: COPD history (randomised = safety population)

	CHF 5993 pMDI N=764	Indacaterol/GB N=768	Overall N=1532
Time since first COPD diagnosis (years)			
n	764	768	1532
Mean (SD)	8.16 (5.76)	7.99 (5.64)	8.08 (5.70)
Range (min ; max)	1.1 ; 41.4	1.1 ; 40.3	1.1 ; 41.4
COPD phenotype[a] (n, %)			
Chronic bronchitis	434 (56.8)	421 (54.8)	855 (55.8)
Emphysema	227 (29.7)	235 (30.6)	462 (30.2)
Chronic bronchitis and emphysema	103 (13.5)	112 (14.6)	215 (14.0)
COPD medication at study entry, n (%)			
ICS/LABA	467 (61.1)	465 (60.5)	932 (60.8)
ICS/LAMA	36 (4.7)	24 (3.1)	60 (3.9)
LABA/LAMA	183 (24.0)	199 (25.9)	382 (24.9)
LAMA	77 (10.1)	80 (10.4)	157 (10.2)
Missing	1 (0.1)	0	1 (0.1)
Use of spacer at screening, n (%)			
Yes	123 (16.1)	133 (17.3)	256 (16.7)
No	641 (83.9)	635 (82.7)	1276 (83.3)
Number of COPD exacerbations in the previous 12 months			
n	764	768	1532
Mean (SD)	1.2 (0.6)	1.2 (0.5)	1.2 (0.5)
Range (min ; max)	1 ; 6	1 ; 4	1 ; 6
1, n (%)	612 (80.1)	626 (81.5)	1238 (80.8)
2, n (%)	124 (16.2)	112 (14.6)	236 (15.4)
≥ 3, n (%)	28 (3.7)	30 (3.9)	58 (3.8)
Time since last documented COPD exacerbation (months)			
n	764	768	1532
Mean (SD)	5.31 (2.82)	5.45 (2.84)	5.38 (2.83)
Range (min ; max)	0.2 ; 12.0	0.3 ; 12.0	0.2 ; 12.0
Last documented COPD exacerbation (n, %)			
Treated with systemic corticosteroids and antibiotics	370 (48.4)	369 (48.0)	739 (48.2)
Treated with systemic corticosteroids only	105 (13.7)	140 (18.2)	245 (16.0)
Treated with antibiotics only	289 (37.8)	259 (33.7)	548 (35.8)
Hospitalisation/ER	174 (22.8)	164 (21.4)	338 (22.1)

COPD = Chronic obstructive pulmonary disease; ER = Emergency room; GB = Glycopyrronium bromide; ICS = Inhaled corticosteroid; Max = Maximum; Min = Minimum; LABA = Long-acting β_2-agonist; LAMA = Long-acting muscarinic antagonist; pMDI = Pressurised metered dose inhaler; SD = Standard deviation.
N = Number of patients in the Safety population; n = Number of patients with available data.
[a] Recorded COPD phenotype was based on physician judgement and knowledge of the patient

Numbers analysed

All patients randomised (N=1532) were treated (i.e. received at least one dose of IMP) and had at least one day of follow-up after the first IMP intake. Safety and ITT populations were identical and included 100% of patients; the PP population included 1479 / 1532 patients (96.5%).

Major protocol violations were thus reported in a total of 53 patients, 22 (2.9%) in group CHF5993 pMDI and 31 (4.0%) in group IND/GB. An overview is presented in Table 6.

Table 6: Major protocol deviations leading to exclusion from the PP population (violated eligibility criteria not shown)

Deviation Type Deviation	CHF 5993 pMDI (N=764)	Indacaterol/glycopyrronium bromide (N=768)
Number of Patients with at Least One Major Deviation	22 (2.9)	31 (4.0)
NON-ADEQUATE COMPLIANCE TO THE STUDY DRUG	9 (1.2)	11 (1.4)
NON-ADEQUATE COMPLIANCE TO THE STUDY DRUG	9 (1.2)	11 (1.4)
NON PERMITTED MEDICATION	4 (0.5)	12 (1.6)
USE OF SYSTEMIC CORTICOSTEROIDS FOR COPD EXACERBATION FOR >30 DAYS	2 (0.3)	7 (0.9)
USE OF ICS, LABA, LAMA, SABA (OTHER THAN RESCUE), SAMA AND COMBINATIONS FOR >30 DAYS	0	4 (0.5)
USE OF NASAL CORTICOSTEROIDS	1 (0.1)	1 (0.1)
USE OF OXYGEN (>12 HOURS/DAY) FOR COPD EXACERBATION FOR >120 DAYS	1 (0.1)	1 (0.1)
USE OF NON-CARDIOSELECTIVE BETA-BLOCKERS	0	1 (0.1)
USE OF SABA (OTHER THAN RESCUE), SAMA, SABA+SAMA OR ICS FOR COPD EXACERBATION FOR >30 DAYS	0	1 (0.1)

Source Data: Listing 16.2.2.1.1
Notes: [1] Patients can have more than one major protocol deviation.
[2] Table presents number and percentage of patients (n (%)).
[3] Percentages are based on the number of patients in the relevant treatment/population (N).
[4] Local deviations (i.e. deviations affecting only single visits) are presented in the listings only.

Outcomes and estimation

Rate of Moderate-to-Severe COPD Exacerbations over 52 weeks of treatment (Primary Endpoint)

Over 52 weeks of treatment, less patients in group CHF 5993 pMDI experienced less moderate-to-severe exacerbations (35.7%, 433 events) as compared with IND/GB (37.5%, 485 events) (ITT population). Thus, the adjusted exacerbation rate per patient per year was lower with CHF 5993 pMDI (0.504, 95% CI [0.447, 0.569]) as compared with IND/GB (0.595 [0.530, 0.668]) (Table 6).

The resulting adjusted rate ratio was 0.848 (95% CI [0.723, 0.995]), thereby confirming a statistically significant reduction of 15.2% in the rate of moderate-to-severe COPD exacerbations and thus the superiority of CHF 5993 pMDI over IND/GB (p=0.043).

Results of the PP analysis for the primary variable evolved in the same direction though no more meeting statistical significance (adjusted rate ratio of 0.849, 95% CI [0.721, 1.000], p=0.05) (Table 7). The pre-defined sensitivity analyses (conducted to evaluate the impact of different methods for handling missing data or the impact of discrepancies in the severity of airflow limitation as recorded in IRS and eCRF) showed similar trends and thereby confirmed the overall conclusions.

Table 7: Rate of moderate-to-severe COPD exacerbations (ITT population)

			CHF 5993 pMDI N=764	Indacaterol/GB N=768
Total follow up time (years)			717.97	707.36
All Moderate/ Severe COPD Exacerbations	Number (%) of Patients with Exacerbations		273 (35.7)	288 (37.5)
	Number of Exacerbations		433	485
	Exacerbation Rate per Patient per Year		0.603	0.686
	Adj. Exacerbation Rate per Patient per Year (95% CI)		0.504 (0.447, 0.569)	0.595 (0.530, 0.668)
	CHF 5993 pMDI vs. Indacaterol/GB	Adj. rate ratio (95% CI)	0.848 (0.723, 0.995)	
		p-value	0.043	

Adj. = Adjusted; CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; GB = Glycopyrronium bromide; ITT = Intention-to-treat; pMDI = Pressurised metered dose inhaler; vs. = Versus.
N = Number of patients in the ITT population.

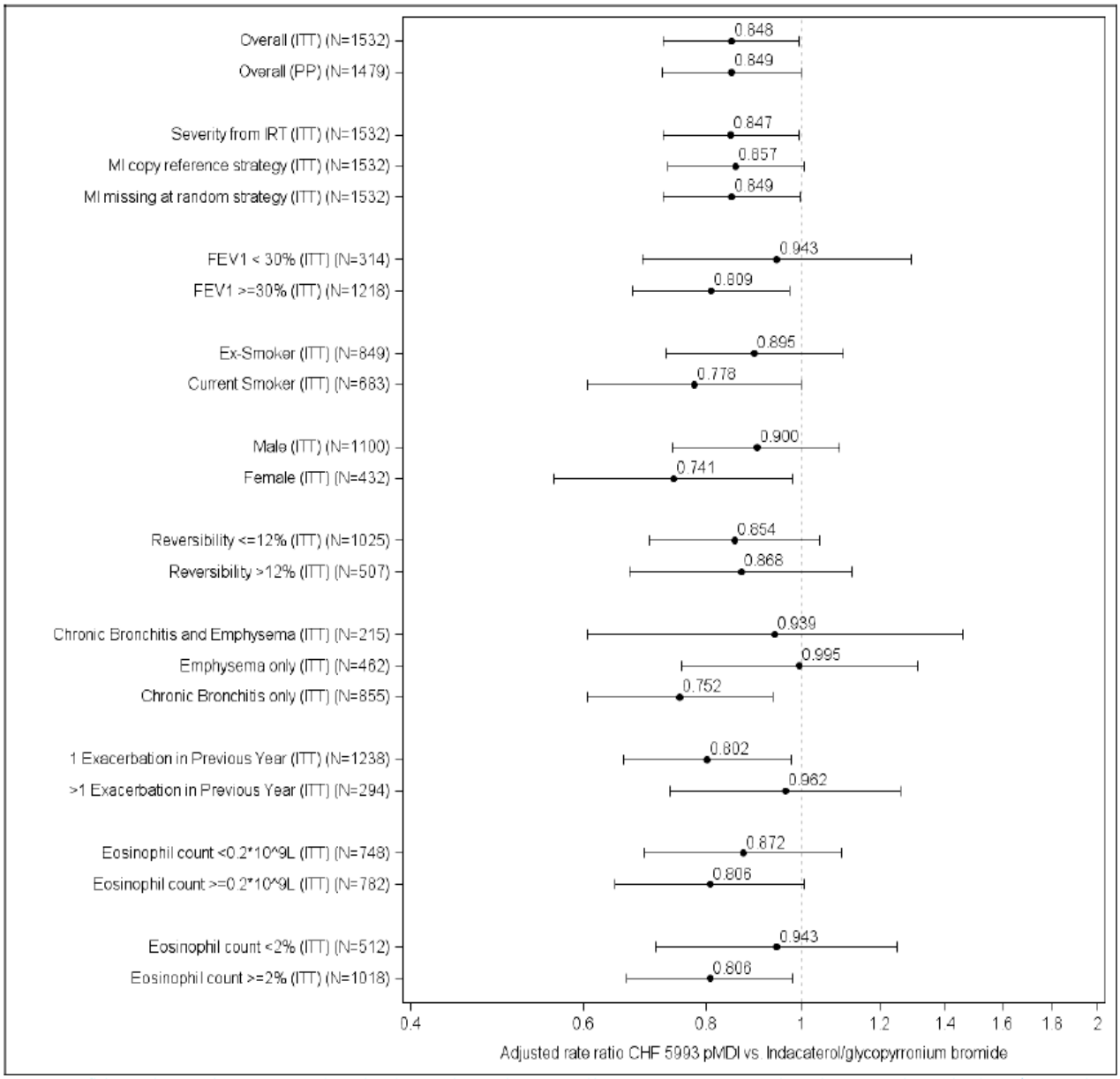
Table 8: Rate of moderate-to -severe COPD exacerbations (PP population)

			CHF 5993 pMDI N=744	Indacaterol/GB N=739
Total follow up time (years)			701.60	682.74
All Moderate/ Severe COPD Exacerbations	Number (%) of Patients with Exacerbations		265 (35.7)	271 (36.8)
	Number of Exacerbations		412	456
	Exacerbation Rate per Patient per Year		0.587	0.668
	Adj. Exacerbation Rate per Patient per Year (95% CI)		0.486 (0.430, 0.551)	0.573 (0.508, 0.645)
	CHF 5993 pMDI vs. Indacaterol/GB	Adj. rate ratio (95% CI)	0.849 (0.721, 1.000)	
		p-value	0.050	

Adj. = Adjusted; CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; GB = Glycopyrronium bromide; pMDI = Pressurised metered dose inhaler; PP = Per-protocol; vs. = Versus.

The treatment effect was greater in patients with severe airflow limitation (30%≤FEV1<50% predicted), current smokers, females, patients with chronic bronchitis phenotype COPD, patients who had only a single documented COPD exacerbation in the year prior to enrolment, and those with a relative eosinophil count at screening of ≥2% (Figure 4).

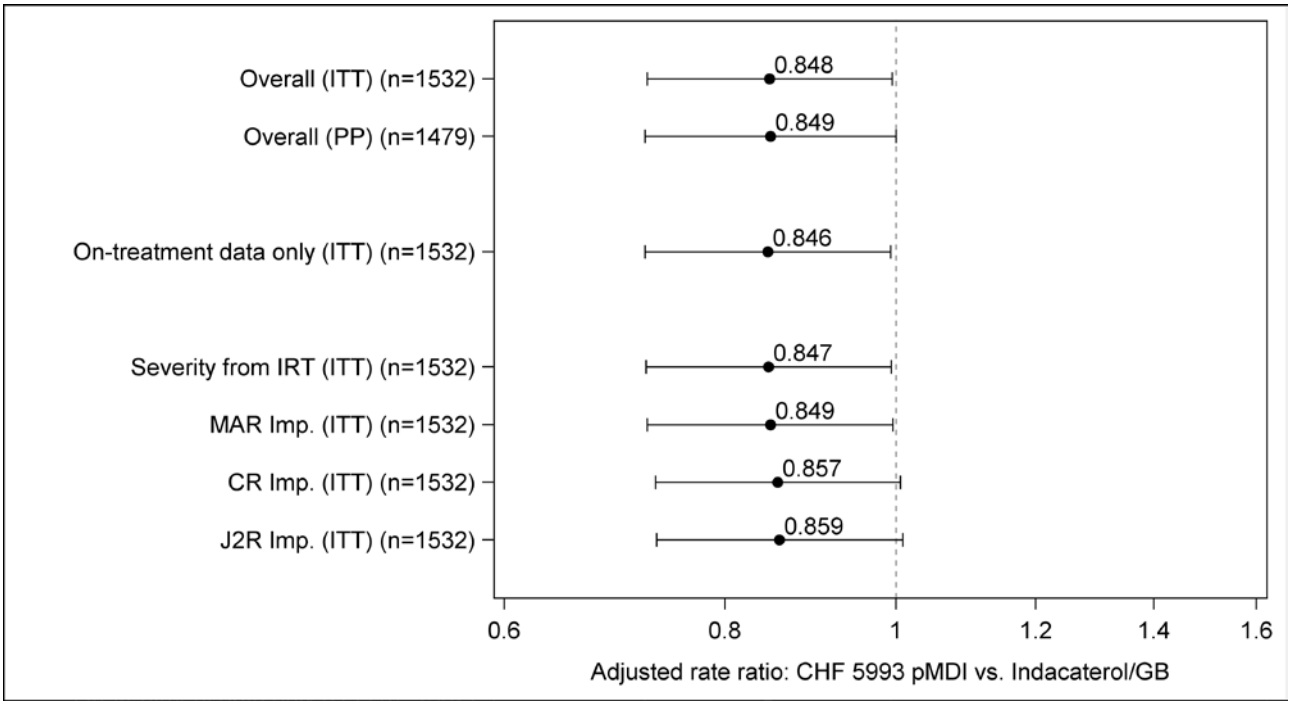
Figure 4: Forest plot for moderate-to-severe COPD exacerbation adjusted rate ratios over 52 weeks



CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; FEV_1 = Forced expiratory volume in the 1st second; IRT = Interactive response technology; ITT = Intention-to-treat; MI = Multiple imputation; pMDI = Pressurised metered dose inhaler; PP = Per-protocol.
N = Number of patients in the population.
Note: Bars represent 95% CI, vertical dotted line at 1 represents the limit for the demonstration of superiority.

The results of the primary efficacy analysis and of all the sensitivity analyses of the moderate/severe COPD exacerbation rate, including the additional one based on the J2R approach, are summarised in Figure 5. The sensitivity analyses confirmed the results of the primary efficacy analysis with very similar estimates of the exacerbation rate ratio (range: 0.847 – 0.859) despite the conservative assumptions considered in some scenarios (CR and J2R). Such consistent results support the superior efficacy of Trydonis / Riarify compared Indacaterol/GB in the reduction of moderate/severe COPD exacerbations.

Figure 5: Adjusted Moderate/Severe COPD Exacerbation Rate Ratio, TRYDONIS / RIARIFY vs. Indacaterol/GB – Study TRIPLE 8



Note: Bars represent 95% CI.

Rate of moderate exacerbation and severe exacerbation over 52 weeks (Secondary Endpoints)

Table 9: Severe COPD exacerbations – ITT population

		CHF 5993 pMDI N=764	Indacaterol/GB N=768
Total follow up time (years)		717.97	707.36
Severe COPD Exacerbations			
Number (%) of Patients with Exacerbations		62 (8.1)	69 (9.0)
Number (%) of Exacerbations[a]		72 (16.6)	91 (18.8)
Exacerbation Rate per Patient per Year		0.100	0.129
Adj. Exacerbation Rate per Patient per Year (95% CI)		0.074 (0.055, 0.099)	0.094 (0.072, 0.123)
CHF 5993 pMDI vs. Indacaterol/GB	Adj. rate ratio (95% CI)	0.787 (0.551, 1.125)	
	p-value	0.189	
COPD Exacerbations leading to deaths			
Number (%) of Patients with Exacerbations		2 (0.3)	2 (0.3)
Number (%) of Exacerbations[a]		2 (0.5)	2 (0.4)
Exacerbation Rate per Patient per Year		0.003	0.003
COPD Exacerbations leading to hospitalisation[b]			
Number (%) of Patients with Exacerbations		62 (8.1)	68 (8.9)
Number (%) of Exacerbations[a]		72 (16.6)	90 (18.6)
Exacerbation Rate per Patient per Year		0.100	0.127

Adj. = Adjusted; CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; GB = Glycopyrronium bromide; ITT = Intention-to-treat; pMDI = Pressurised metered dose inhaler; vs. = Versus.
N = Number of patients in the ITT population.
[a] Percentages are based on the number of moderate/severe COPD exacerbations in the relevant treatment/population.
[b] Emergency room admissions with at least 24 hours of stay have been also considered as hospitalisations.

Table 10: Moderate COPD exacerbations – ITT population

		CHF 5993 pMDI N=764	Indacaterol/GB N=768
Total follow up time (years)		717.97	707.36
Moderate COPD Exacerbations			
Number (%) of Patients with Exacerbations		231 (30.2)	237 (30.9)
Number (%) of Exacerbations[a]		361 (83.4)	394 (81.2)
Exacerbation Rate per Patient per Year		0.503	0.557
Adj. Exacerbation Rate per Patient per Year (95% CI)		0.408 (0.356, 0.468)	0.471 (0.413, 0.537)
CHF 5993 pMDI vs. Indacaterol/GB	Adj. rate ratio (95% CI)	0.866 (0.723, 1.037)	
	p-value	0.118	

Adj. = Adjusted; CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; GB = Glycopyrronium bromide; ITT = Intention-to-treat; pMDI = Pressurised metered dose inhaler; vs. = Versus.
N = Number of patients in the ITT population.
[a] Percentages are based on the number of moderate/severe COPD exacerbations in the relevant treatment/population.

Time to First Moderate-to-Severe Exacerbation (Secondary Endpoint)

Time to the first moderate-to-severe exacerbation was prolonged with CHF 5993 pMDI, resulting in a numerically lower probability of exacerbation in the Cox proportional hazards analysis (hazard ratio of 0.901, 95% CI [0.763; 1.064], p=0.219).

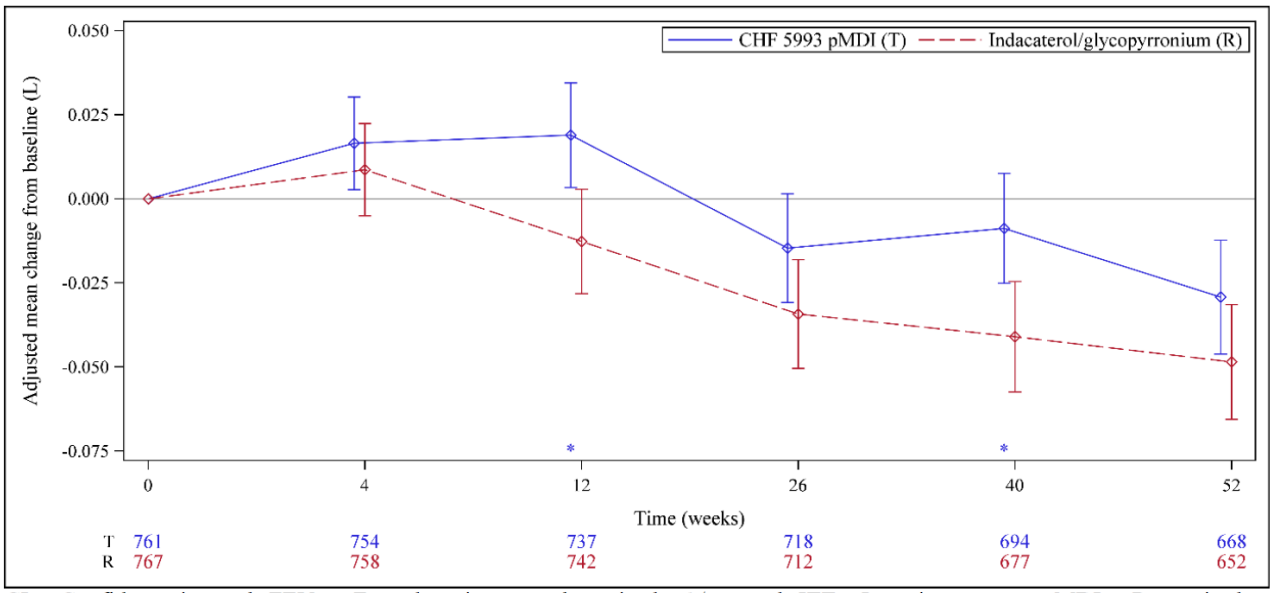
Change from Baseline in Trough FEV1 at Week 52 (Secondary Endpoint)

In both treatment groups, there was a small decline in pre-dose morning FEV1 over the 52-week treatment period. The adjusted mean difference in trough FEV1 between treatments was consistently in favour of CHF 5993 pMDI (Figure 6 and Table 11). At week 52, the pre-dose morning FEV1 had a slightly, but statistically significantly decrease in both groups with no significant between group difference (adjusted mean changes of -0.029, 95%CI [-0.046; -0.012] in group CHF 5993 pMDI and -0.049, 95%CI [-0.066; -0.031] in group IND/GB; adjusted mean difference 0.019, 95%CI [-0.005; 0.043].

The adjusted mean change in pre-dose morning FEV1 from baseline averaged over the entire treatment period did not differ from baseline with CHF 5993 pMDI (-0.003L, 95%CI [-0.016; 0.010], p=0.602), while it slightly decreased under treatment with IND/GB (-0.026 L, 95%CI [-0.039; -0.013], p<0.001). The adjusted mean difference between groups was small, but statistically significant (0.022, 95%CI [0.004; 0.040], p=0.018).

In the FEV1 responder analysis, the percentage of patients in whom the pre-dose morning FEV1 had increased by ≥100 mL at week 52 was numerically greater in group CHF 5993 pMDI (19%) as compared with IND/GB (16.3%), resulting in an odds ratio of 1.190 (95%CI [0.913; 1.550], p=0.198).

Figure 6: Adjusted mean change from baseline in pre-dose morning FEV1 in L (ITT population)



CI = Confidence interval; FEV_1 = Forced expiratory volume in the 1st second; ITT = Intention-to-treat; pMDI = Pressurised metered dose inhaler; R = Indacaterol/GB; T = CHF 5993 pMDI.
Note: Bars represent 95% CI and the symbol * statistically significant difference between treatments ($p < 0.05$).

Table 11: Change from baseline in pre-dose morning FEV1 in L at week 52 and over the entire treatment period (ITT population)

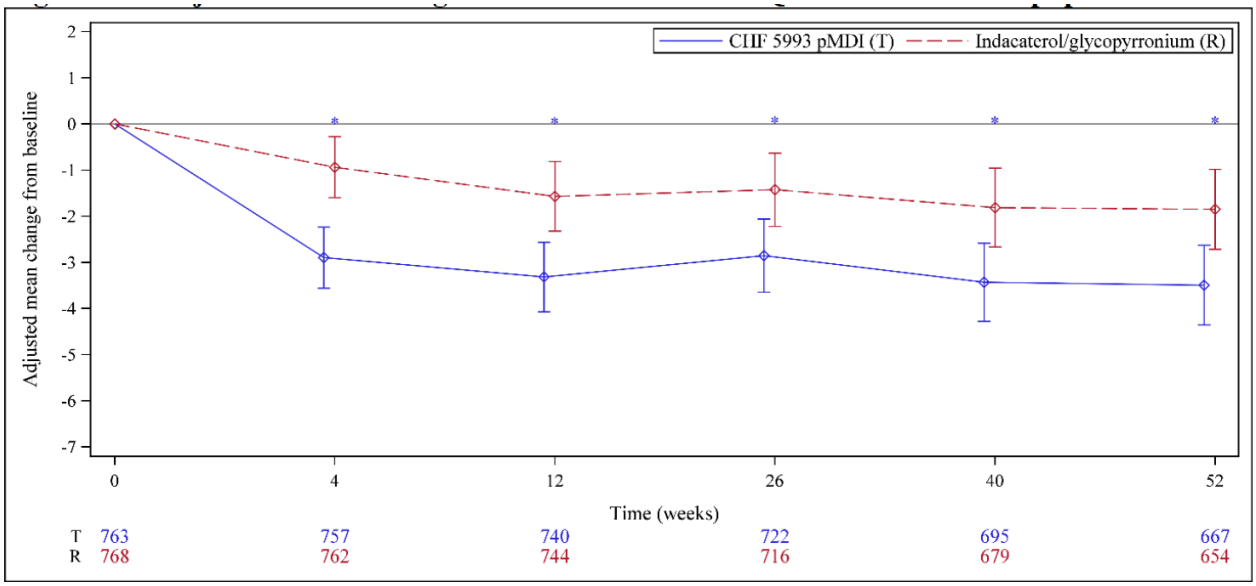
			CHF 5993 pMDI N=764	Indacaterol/GB N=768
Baseline		n	761	767
		Mean (SD)	1.122 (0.364)	1.130 (0.387)
Week 52	**Actual values**	n	669	652
		Mean (SD)	1.110 (0.403)	1.103 (0.406)
	Change from baseline	n	668	652
		Mean (SD)	-0.025 (0.244)	-0.052 (0.224)
		Adj. mean (95% CI)	-0.029 (-0.046, -0.012)	-0.049 (-0.066, -0.031)
		p-value	< 0.001	< 0.001
	CHF 5993 pMDI vs. Indacaterol/GB	Adj. mean difference (95% CI)	0.019 (-0.005, 0.043)	
		p-value	0.116	
Average over treatment period	**Change from baseline**	Adj. mean (95% CI)	-0.003 (-0.016, 0.010)	-0.026 (-0.039, -0.013)
		p-value	0.602	< 0.001
	CHF 5993 pMDI vs. Indacaterol/GB	Adj. mean difference (95% CI)	0.022 (0.004, 0.040)	
		p-value	0.018	

Adj. = Adjusted; CI = Confidence interval; FEV_1 = Forced expiratory volume in 1st second; GB = Glycopyrronium bromide; ITT = Intention-to-treat; pMDI = Pressurised metered dose inhaler; SD = Standard deviation; vs. = Versus.
N = Number of patients in the ITT population; n = Number of patients with available data.

Change from Baseline in SGRQ Total Score at Week 52 (Secondary Endpoint)

In both treatment groups, there was a decrease in the SGRQ total score from baseline averaged over the 52-week treatment period, indicating an improvement with triple and dual treatment (adjusted mean changes of -3.20 and -1.52 units, respectively; p<0.001 in both cases) (Figure 6). CHF 5993 pMDI resulted in a greater improvement in this health-related quality of life (HRQoL) tool as evidenced by the adjusted mean difference between treatments of -1.68 units (95%CI [-2.55; -0.81], p<0.001). The greatest improvements were observed in the SGRQ symptoms and impact scores.

Figure 7: Adjusted mean change from baseline in SGRQ total score (ITT population)



CI = Confidence interval; ITT = Intention-to-treat; pMDI = Pressurised metered dose inhaler; R = Indacaterol/GB; SGRQ = St. George's Respiratory Questionnaire; T = CHF 5993 pMDI.
Note: Bars represent 95% CI and the symbol *, statistically significant difference between treatments (p < 0.05).

Table 12: SGRQ responders at Week 26 and Week 52 – ITT population

			CHF 5993 pMDI N=764	Indacaterol/GB N=768
Week 26				
Responder	n (%)		310 (40.6)	292 (38.0)
	CHF 5993 pMDI vs. Indacaterol/GB	Odds ratio (95% CI)	1.130 (0.915, 1.395)	
		p-value	0.255	
Non-responder	n (%)		454 (59.4)	476 (62.0)
	Change > -4	n (%)	412 (53.9)	424 (55.2)
	Missing data	n (%)	42 (5.5)	52 (6.8)
Week 52				
Responder	n (%)		311 (40.7)	279 (36.3)
	CHF 5993 pMDI vs. Indacaterol/GB	Odds ratio (95% CI)	1.220 (0.985, 1.511)	
		p-value	0.068	
Non-responder	n (%)		453 (59.3)	489 (63.7)
	Change > -4	n (%)	356 (46.6)	375 (48.8)
	Missing data	n (%)	97 (12.7)	114 (14.8)

CI = Confidence interval; GB = Glycopyrronium bromide; ITT = Intention-to-treat; pMDI = Pressurised metered dose inhaler; SGRQ = St. George's Respiratory Questionnaire; vs. = Versus
N = Number of patients in the ITT population; n = Number of patients with available data.
[a] SGRQ response = Change from baseline in total score ≤ -4; non-response = Change from baseline in total score > -4 or missing data.

Use of Rescue Medication (Secondary endpoint)

Table 13: Change from baseline in the percentage of days, nights and complete days without rescue medication intake – ITT population

			CHF 5993 pMDI N=764	Indacaterol/GB N=768
Percentage of days without rescue medication use				
Baseline		n	756	763
		Mean (SD)	40.30 (39.57)	41.48 (39.86)
Entire treatment period (Week 1 – Week 52)	**Actual values**	n	763	766
		Mean (SD)	45.73 (41.12)	48.22 (40.79)
	Change from baseline	n	755	761
		Mean (SD)	5.64 (29.30)	6.86 (31.10)
		Adjusted mean (95% CI)	5.53 (3.48, 7.58)	7.01 (4.96, 9.06)
		p-value	< 0.001	< 0.001
	CHF 5993 pMDI vs. Indacaterol/GB	Adjusted mean difference (95% CI)	-1.47 (-4.37, 1.42)	
		p-value	0.318	
Percentage of nights without rescue medication use				
Baseline		n	758	764
		Mean (SD)	58.26 (39.47)	60.75 (39.31)
Entire treatment period (Week 1 – Week 52)	**Actual values**	n	763	765
		Mean (SD)	66.80 (39.02)	67.43 (38.53)
	Change from baseline	n	757	761
		Mean (SD)	8.66 (31.40)	6.79 (31.48)
		Adjusted mean (95% CI)	8.27 (6.22, 10.33)	7.08 (5.02, 9.13)
		p-value	< 0.001	< 0.001
	CHF 5993 pMDI vs. Indacaterol/GB	Adjusted mean difference (95% CI)	1.20 (-1.71, 4.11)	
		p-value	0.420	
Percentage of complete days without rescue medication use				
Baseline		n	753	759
		Mean (SD)	34.60 (39.06)	35.74 (38.92)
Entire treatment period (Week 1 – Week 52)	**Actual values**	n	763	765
		Mean (SD)	42.89 (40.73)	44.99 (40.39)
	Change from baseline	n	752	756
		Mean (SD)	8.39 (29.41)	9.42 (31.46)
		Adjusted mean (95% CI)	8.31 (6.24, 10.37)	9.66 (7.60, 11.73)
		p-value	< 0.001	< 0.001
	CHF 5993 pMDI vs. Indacaterol/GB	Adjusted mean difference (95% CI)	-1.36 (-4.28, 1.56)	
		p-value	0.361	

CI = Confidence interval; GB = Glycopyrronium bromide; ITT = Intention-to-treat; pMDI = Pressurised metered dose inhaler; SD = Standard deviation; vs. = Versus.
N = Number of patients in the ITT population; n = Number of patients with available data.

Ancillary analyses

N/A

Summary of main study

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

Table 14: Summary of Efficacy for study TRIPLE 8

Title: A 52-week, double blind, double dummy, randomized, multinational, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclomethasone dipropionate plus formoterol fumarate plus glycopyrronium bromide administered via pMDI (CHF 5993) versus indacaterol/glycopyrronium (Ultibro®) via DPI in patients with Chronic Obstructive Pulmonary Disease (TRIBUTE)			
Study identifier	CCD-05993AA1-08 EudraCT no. 2014-001704-22		
Design	double blind, double dummy, randomized, multinational, multicentre, 2-arm parallel group, active controlled clinical trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks 2 weeks <not applicable>	
Hypothesis	Superiority		
Treatments groups	CHF 5993 pMDI (test)	fixed dose combination (BDP+FF+GB) 2 puffs b.i.d. 100/6/12.5 µg per actuation (nominal daily dose: 400/24/50 µg) 52 weeks N=764 randomised	
	IND/GB DPI (reference)	fixed dose combination (IND+GB) 1 capsule once daily 85/43 µg per capsule (nominal daily dose: 85/43 µg) 52 weeks N=768 randomised	
Endpoints and definitions	Primary endpoint	COPD exacerbation rate	adjusted rate of moderate to severe COPD exacerbations per patient per year
	Secondary endpoint	Time to first exacerbation	time to first moderate-to-severe exacerbation and time to first severe exacerbation
		Number of COPD exacerbations	adjusted rate of moderate / severe COPD exacerbations
		trough FEV1	Change from baseline in trough FEV1 at each visit and over the entire treatment period; trough FEV1 response ≥100 mL at weeks 26 and 52;
		SGRQ	change from baseline at each visit and over the entire treatment period (total score and domain scores); SGRQ response ≤ -4 at weeks 26 and 52
		use of rescue medication	change from baseline in the days / nights / complete days without intake of rescue medication; data on quantitative use of rescue medication change from baseline at each visit and over the entire treatment period
Database lock	24 August 2017		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	ITT, week 52, test versus reference		
Descriptive statistics and estimate variability	Treatment groups	CHF 5993 pMDI (test)	IND/GB DPI (reference)

	adjusted rate of moderate-to-severe exacerbations per patient and year		
	Number of subjects	N=764	N=768
	point estimator	0.504	0.595
	95%CI	[0.447; 0.569]	[0.530; 0.668]
	adjusted rate ratio (95%CI)	0.848 [0.723; 0.995] p=0.043	
Analysis description	Secondary analysis		
	time to first moderate-to-severe exacerbation		
	Number of subjects	N=764	N=768
	Cox hazard ratio (95%CI)	0.901 [0.763; 1.064] p=0.219	
	adjusted rate of moderate exacerbations per patient and year		
	Number of subjects	N=764	N=768
	point estimator	0.408	0.471
	95%CI	[0.356; 0.468]	[0.413; 0.537]
	adjusted rate ratio (95%CI)	0.866 [0.723; 1.037] p=0.118	
	adjusted rate of severe exacerbations per patient and year		
	Number of subjects	N=764	N=768
	point estimator	0.074	0.094
	95%CI	[0.055; 0.099]	[0.072; 0.123]
	adjusted rate ratio (95%CI)	0.787 [0.551; 1.125] p=0.189	
	change from baseline in pre-dose morning FEV1 (in L) as averaged over the treatment period		
	Number of subjects	N=764	N=768
	point estimator	-0.003	-0.026
	95%CI	[-0.016; 0.010]	[-0.039; -0.013]
	adjusted mean difference (95%CI)	0.022 [0.004; 0.040] p=0.018	
	change from baseline in SGRQ total score (in units) over the entire treatment period		
	Number of subjects	N=764	N=768
	point estimator	-3.20	-1.52
	95%CI	[-3.81; -2.58]	[-2.13; -0.90]
	adjusted mean difference (95%CI)	-1.68 [-2.55; -0.81] p<0.001	
	SGRQ total score responders (change from baseline ≤-4) at week 52 (ITT population)		
	Number of subjects	N=764	N=768
	Responder (N / %)	311 (40.7)	279 (36.3)
	Odds ratio (95%CI)	1.220 [0.985; 1.511] p=0.068	

	change from baseline in % age of days without rescue medication intake over randomized treatment period		
	Number of subjects	N=764	N=768
	point estimator	5.53	7.01
	95%CI	[3.48; 7.58]	[4.96; 9.06]
	adjusted mean difference (95%CI)	-1.47 [-4.37; 1.42] p=0.318	
Notes			

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

N/A

Clinical studies in special populations

N/A

Supportive study TRIPLE 7

The design of the study substantially differs from that of other phase III-IIIb studies, namely by the open-label treatment and the shorter total treatment duration of 26 weeks only (thereby not preventing seasonal influences on the exacerbation rate).

The main objective of the open-label, active-controlled study TRIPLE 7 was to demonstrate that TRYDONIS / RIARIFY is non-inferior to commercially available, extemporary triple therapy (fixed combination of fluticasone and vilanterol plus tiotropium) in terms of a single primary endpoint, the St. George's Respiratory Questionnaire (SGRQ) total score as a measure of health-related quality of life (HRQoL).

For that purpose, the change from baseline in SGRQ at week 26 of treatment was compared. Based on scientific literature and available clinical evidence, the putative MCID of 4 units for the total SGRQ score was chosen as the non-inferiority margin (i.e. upper limit of the two-sided 95% CI <4 units, one-sided significance level of 0.025). Since non-inferiority was to be demonstrated, the MAH postulated that PP and ITT populations had equal importance for the statistical analysis of the primary efficacy variable.

Secondary objectives were to evaluate the effect of CHF5993 pMDI on lung function parameters, patient's health status and on clinical outcome measures, to assess the impact of study treatments on health economic outcomes, and to evaluate the overall safety and tolerability of the administered study treatments.

After a 2-week open-label run-in period of tiotropium (18 µg/day), patients were randomised in a 1:1 ratio to receive one of the following open-label treatments for 26 weeks:

- CHF5993 pMDI 100/6/12.5 µg (delivered dose: 87/5/9 µg BDP/FF/GB), 2 puffs twice daily (total daily nominal dose: 400/24/50 µg BDP/FF/GB);
- fluticasone/vilanterol 100/25 µg DPI (delivered dose: 92/22 µg fluticasone furoate/vilanterol trifenatate), 1 inhalation once daily plus tiotropium 18 µg inhalation powder (delivered dose by hard capsule: 10 µg tiotropium bromide), 1 capsule once daily.

Subsequent visits were performed after 4 weeks (V3), 12 weeks (V4) and 26 weeks (V5) of treatment and a follow-up call 1 week after V5.

Patient characteristics

Starting on 29MAY2015 (FPFV), a total of 1477 patients were screened, of whom 1157 were randomised to either CHF5993 pMDI (N=578) or fluticasone/vilanterol plus tiotropium (N=579). The majority of patients (94.6%) completed the study (LPLV on 05 January 2017). Overall, the probability of premature discontinuation from the study was comparable in the two treatment groups.

Demographic characteristics were comparable between treatment groups. Patients enrolled were predominantly white and male (N=874, 75.5%), the mean age was 63.9 years (53.5% aged <65 years, 37.2% aged between 65 and 74 years and 9.3% aged ≥75 years).

On average, patients were diagnosed with COPD about 8 years prior to enrolment with no relevant between-group differences (8.1 years in group CHF5993 pMDI and 7.7 years in group fluticasone/vilanterol + tiotropium). Patients were either current or ex-smokers, with an overall mean of 37.7 pack-years and a mean smoking duration of 38.6 years. Only a small percentage of patients changed their smoking status during the study.

At study entry, disease severity was comparable and the majority of patients were on double treatment, combining either a LABA with an ICS (73.5% vs. 72.5% of patients) or two bronchodilators (LABA / LAMA 18.7% vs. 19.3%). LAMA monotherapy was taken by 7.4% of patients in each group.

The mean number of COPD exacerbations in the previous year was comparable in the two treatment groups, with a vast majority of patients having one such episode recorded in their medical files. About 20% of patients had very severe airflow limitation as demonstrated by an FEV1 of <30% of the predicted normal value.

Results

A total of 1157 patients were randomized at 103 recruiting sites in 12 countries (Belgium, Germany, Hungary, Lithuania, Netherlands, Poland, Romania, Russia, South Africa, Sweden, Turkey, and UK):

- CHF 5993 pMDI: N=578 patients
- fluticasone/vilanterol + tiotropium N=579 patients

The majority of patients in both groups completed the study as planned by the clinical trial protocol (94.3% vs. 94.8%).

At baseline, the mean SGRQ total score was comparable in both groups (SGRQ total scores of 52.7 and 53.0 in groups CHF 5993 pMDI and fluticasone / vilanterol plus tiotropium, respectively). With both treatments and independent of the analysis population, there was a (clinically) significant adjusted mean decrease from baseline in SGRQ total score (-6.82 units vs. -7.82 units), indicating that the health-related patient status had improved over the 26-week treatment period in both groups (Table 15 and Table 16.

The adjusted mean difference between groups was in favour of group fluticasone/vilanterol plus tiotropium (i.e. slightly more important improvement under the extemporaneous triple therapy), but since the upper 95% confidence interval of the adjusted mean difference was <4 units (i.e. 2.64 units in the PP analysis and 2.65 units in the ITT analysis), from a formal point of view the non-inferiority of CHF 5993 pMDI over extemporary triple therapy (fluticasone / vilanterol plus tiotropium) was demonstrated.

Results of sensitivity and post hoc stratified analyses confirmed the overall conclusions of the trial (Figure 8).

At week 26, about 50% of patients in both treatment groups were responders, i.e. had a change from baseline in the total SGRQ score of ≤-4 units (51.3% vs. 53.1%; odds ratio 0.929, 95%CI [0.728; 1.186]; PP population). Statistically significant improvements were seen in each of the three SGRQ domain scores (symptoms, impact, and activity scores).

Table 15: Change from baseline in the SGRQ total score at week 26 (PP population)

			CHF 5993 pMDI N=559	Fluticasone/vilanterol + tiotropium N=557
Baseline		n	559	557
		Mean (SD)	52.61 (16.77)	52.76 (17.34)
Week 26	**Actual values**	n	537	532
		Mean (SD)	45.79 (18.06)	44.64 (18.19)
	Change from baseline	n	537	532
		Mean (SD)	-6.80 (14.97)	-7.84 (15.06)
		Adjusted mean (95% CI)	-6.82 (-7.97; -5.66)	-7.82 (-8.98; -6.66)
		p-value	< 0.001	< 0.001
	CHF 5993 pMDI vs. fluticasone/vilanterol + tiotropium	Adjusted mean difference (95% CI)	1.00 (-0.64; 2.64)	
		p-value	0.231	

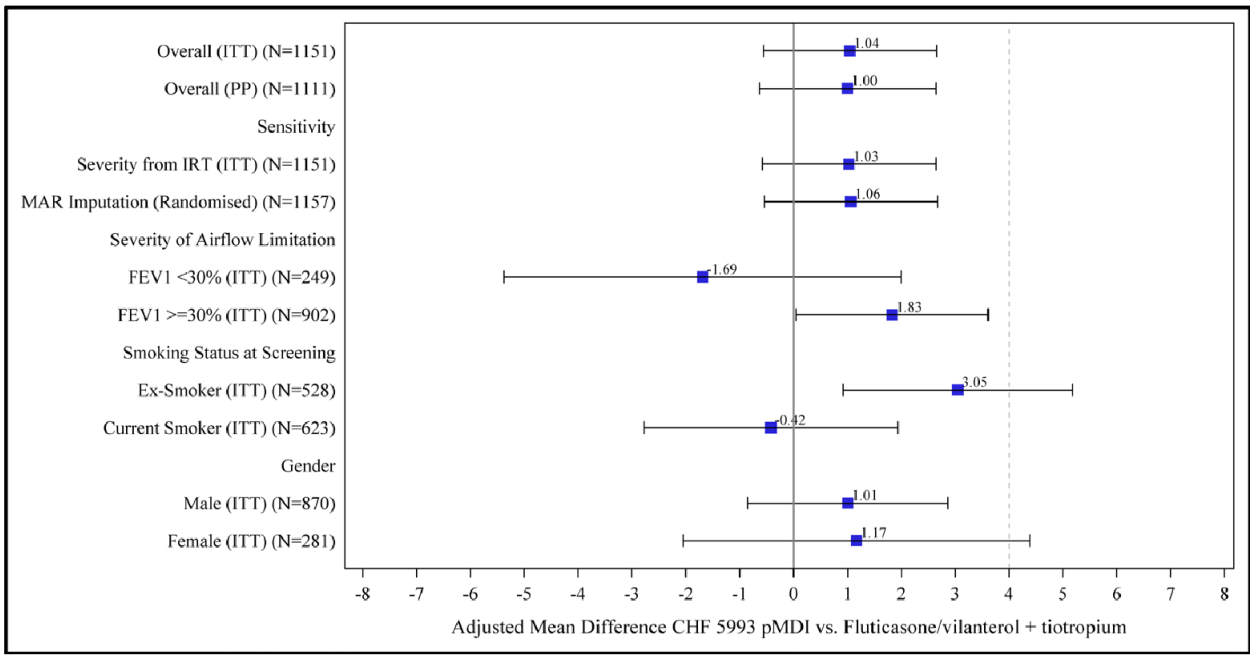
CI = Confidence interval; pMDI = Pressurised metered dose inhaler; PP = Per=protocol; SD = Standard deviation; SGRQ = St. George's Respiratory Questionnaire; vs. = Versus.
N = Number of patients in the PP population; n = Number of patients with available data.

Table 16: Change from baseline in the SGRQ total score at week 26 (ITT population)

			CHF 5993 pMDI N=577	Fluticasone/vilanterol + tiotropium N=579
Baseline		n	577	579
		Mean (SD)	52.72 (16.71)	52.96 (17.38)
Week 26	**Actual values**	n	553	553
		Mean (SD)	45.97 (18.10)	44.86 (18.23)
	Change from baseline	n	553	553
		Mean (SD)	-6.76 (14.98)	-7.80 (15.03)
		Adjusted mean (95% CI)	-6.77 (-7.91; -5.64)	-7.82 (-8.95; -6.68)
		p-value	< 0.001	< 0.001
	CHF 5993 pMDI vs. fluticasone/vilanterol + tiotropium	Adjusted mean difference (95% CI)	1.04 (-0.56; 2.65)	
		p-value	0.204	

CI = Confidence interval; ITT = Intention-to-treat; pMDI = Pressurised metered dose inhaler; SD = Standard deviation; SGRQ = St. George's Respiratory Questionnaire; vs. = Versus.
N = Number of patients in the ITT population; n = Number of patients with available data.

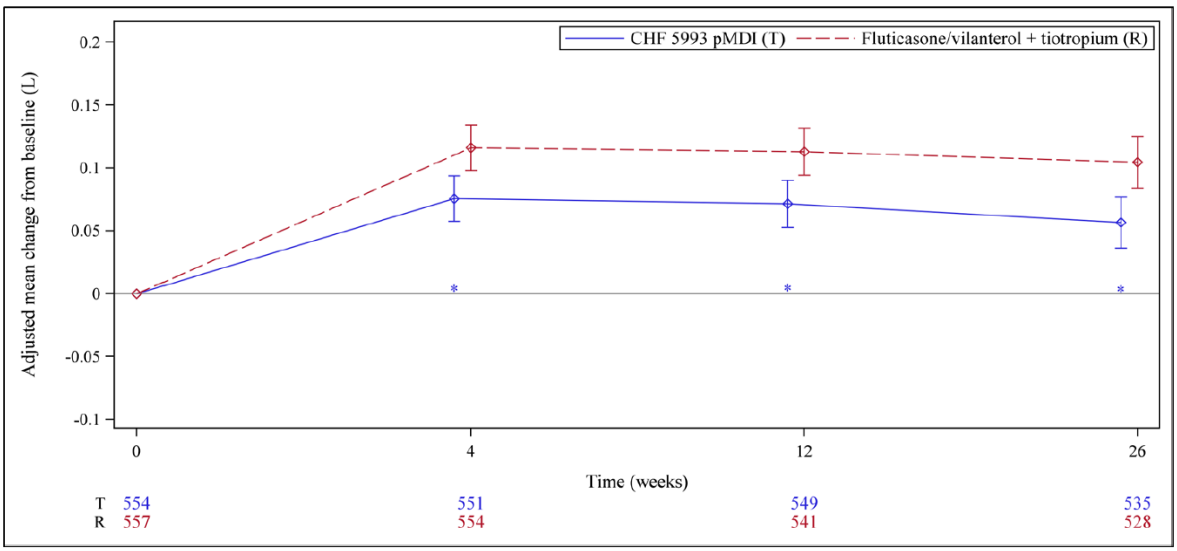
Figure 8: Forest plot for the adjusted mean differences between treatments in the SGRQ total score at week 26



At baseline, the mean pre-dose morning FEV1 was comparable between treatments (1.093 L in group CHF5993 pMDI and 1.111 L in group fluticasone/vilanterol + tiotropium). A statistically significant mean increase from baseline in pre-dose morning FEV1 was observed in both groups (0.060 L vs. 0.108 L, PP population), the between-group difference reaching statistical significance and favoring the reference group at week 26 (adjusted mean difference -0.048 L, 95%CI [-0.077; -0.019], p=0.002, PP population).

When calculating FEV1 responder rates, CHF5993 pMDI was statistically significantly inferior to the reference treatment when higher cut-off values were used, i.e. the percentage of patients with relevant improvements in FEV1 of ≥100 mL (Table 17) or ≥120 mL (not shown).

Figure 9: Adjusted mean change from baseline in pre-dose morning FEV1 in L (PP population)



Source Data: Table 14.2.4.4
Notes: [1] Bars represent 95% CI.
*[2] * Statistically significant difference between treatments (p-value < 0.05)*

Table 17: FEV1 responders and respective odds ratio at week 26 as based on cut-off (change from baseline in pre-dose morning FEV1 ⩾100 mL; PP population)

	CHF 5993 pMDI (N=559)	Fluticasone/vilanterol + tiotropium (N=557)
Responders	203 (36.3)	238 (42.7)
Non-Responders	356 (63.7)	319 (57.3)
Change < 100 mL	332 (59.4)	290 (52.1)
Missing data	24 (4.3)	29 (5.2)

Source Data: Listing 16.2.6.4.1
Notes: [1] FEV1 response = change from baseline in pre-dose morning FEV1 >= 100 mL; non-response = change from baseline in pre-dose morning FEV1 < 100 mL or missing data.
[2] Table presents number and percentage of patients (n (%)).
[3] Percentages are based on the number of patients in the relevant treatment/population (N).
[4] Data from patients who discontinued prematurely and performed the Visit 5 assessments are re-allocated to the most appropriate visit.

Odds Ratio (95% CI); p-value (CHF 5993 pMDI / Fluticasone/vilanterol + tiotropium)	0.737 (0.577, 0.943); 0.015*

2.4.3. Discussion on clinical efficacy

The currently approved indication wording "*…[COPD patients] who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist*" highlights the lack of evidence to claim a step-up indication from the combination of a long-acting muscarinic receptor antagonist (LAMA) and a long-acting beta2 agonist (LABA) due to the absence of the combination of LAMA and LABA as comparator in the pivotal Phase III study at time of the MAA of TRYDONIS / RIARIFY, a triple combination of an inhaled corticosteroid (ICS), and LABA and LAMA.

The MAH is now applying for a broader indication including newly a step-up indication from the combination of a LAMA and LABA (e.g. Indacaterol/GB). Two completed clinical safety and efficacy trials (one pivotal study TRIPLE 8 and one supportive study TRIPLE 7) in support of the extension of variation are presented.

In studies TRIPLE 7 and TRIPLE 8, a total of 1157/1532 patients were randomised at 103/187 sites in 12/17 countries, respectively.

A single two-day systems audit covering both studies (TRIPLE 7 and TRIPLE 8) and three site audits covering TRIPLE 8 (each lasting for one to two days only) were performed by or on behalf of the MAH. Moreover, (routine?) inspections were performed at unidentified sites by local authorities in Austria and Latvia. The MAH claims that the annual audit plan / programme follows a risk-based approach; SOP DRQA-SP-11-008 - Audits of Clinical Trials however permits to select clinical sites for an audit activity because a (routine) health authority inspection has been announced. This means that for the pivotal study TRIPLE 8, two out of three site visits / audits were performed in a reactive manner but not using a prospective, risk-based approach.

No critical observations or relevant GCP issues were identified during the sponsor audits or health authority inspections of the pivotal study TRIPLE 8.

For study TRIPLE 7, critical observations were reported from both internal audits and health authority inspections. In the quality systems audit of the CRO's data management unit (ICON Clinical Research, South County Business Park, Dublin, Ireland) performed from 04 to 05NOV2015, a critical finding was identified, i.e. unsatisfactory oversight by project management. The impact or consequences of this non-conformity are not revealed. Reportedly, satisfactory CAPA measures were implemented.

This contrasts with the observation that in study TRIPLE 8 erroneous treatment compliance figures were distributed prior to each of the three blinded data review meeting, making it necessary to modify the assignment of six subjects to the PP population after unblinding.

Overall, the MAH has undertaken limited efforts to assess and assure the reliability and integrity of the trial systems against own written standards and applicable laws and regulations. Annual audit plans / programmes were finalised with significant delay and for the pivotal study TRIPLE 8, only a single site audit was performed that followed a proactive and risk-based approach. This finding may challenge the internal validity of the study / data reliability.

TRIPLE 8

Design and conduct of clinical study

According to the most recent GOLD recommendation (update 2017), a dual bronchodilator therapy with a LABA plus LAMA is the first choice when treating patients with COPD who are symptomatic and at risk of exacerbations. The choice of the active comparator in TRIPLE 8 and more specifically the recently approved combination therapy (IND/GB, tradename Ultibro Breezehaler) is acceptable.

Eligibility criteria in study TRIPLE 8 were comparable to those defined for the pivotal studies included in the application to obtain the initial MAs of TRYDONIS / RIARIFY. Though the severity of airflow limitation is no longer used as a criterion for the COPD severity classification by the GOLD update 2017, patients enrolled in TRIPLE 8 belonged to GOLD groups B and D as based on their symptom severity and exacerbation risk. Study patients were thus at the more severe end of the COPD spectrum and symptomatic despite dual therapy.

Of note, there was no step down in treatment upon enrolment. Solely patients already receiving dual treatment or LAMA monotherapy were included.

As was the case for prior studies, the MAH excluded patients with clinically significant cardiovascular conditions from study participation, e.g. those with unstable ischaemic heart disease, NYHA Class III/IV left ventricular failure, acute ischaemic heart disease in the year prior to the screening examination or a history of sustained cardiac arrhythmias. In combination with the limited number of patients enrolled, this limits the assessment of the cardiovascular safety of the compound.

- *Outcomes/endpoints*

Primary endpoint

Study TRIPLE 8 had a single primary outcome, i.e. the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment. Measuring the rate of moderate and severe COPD exacerbations is an accepted primary endpoint as the prevention/reduction of such events is recognised to be a primary goal of COPD therapy, due to the important negative impact of such events on health status, health-related QoL, and disease progression. The definition of what represents a COPD exacerbation was in line with the one proposed by the respective EMA/CHMP guideline issued in 2012. A number of clarifications and refinements were included in the clinical trial protocol which appears acceptable.

Overall, it is acknowledged that the primary endpoint chosen was a clinically relevant one. However, the EMA guidance document's recommendation to have all exacerbation episodes evaluated by a blinded external adjudication committee was not followed. Instead, an arbitrary numerical criterion (i.e. a 10 day time gap) was defined in the SAP in order to decide whether an episode was a new event rather than being a relapse or continuation of a previously recorded one. The applicant confirmed that the arbitrary 10-day time gap for the primary exacerbation endpoint was chosen early in line with previous studies (e.g. TRIPLE 5 and TRIPLE 6) and already specified in the first draft version of the SAP (v0.1 dated 21DEC2015).

No attempts were made by the MAH to follow all patients for the full duration of the study and to record subsequent exacerbation events, should they have stopped IMP intake. Instead, the log-time in the study was included as offset in the negative binomial model used for the analysis of the primary response variable. This seems to be acceptable as 88.7% of patients in the TRYDONIS / RIARIFY and 85.4% in the IND/GB group completed more than 48 weeks of treatment, and 87.2% and 84.4% in the CHF 5993 pMDI and IND/GB groups respectively completed at ≥52 weeks of treatment (source: Table 14.3.1.1).

The MAH was requested to make available a copy of report resulting from the blinded data review meeting (Chiesi terminology: Data Review Report) which is repeatedly referenced in the Clinical study report and its appendices. From the requested documentation it becomes apparent that the secondary population for analysis (i.e. the per-protocol population) was modified after unblinding. The reason given by the applicant is an error in the reported treatment compliance values for a total of six patients. Five of them were classified post hoc to be major protocol violators (and thus excluded from the PP analysis), and another one confirmed to have adequate compliance (and thus included in the PP analysis). Reportedly, this was done by applying the same pre-defined criteria as for other patients.

The post hoc modifications applied to the PP population appear to have had no impact on the primary results of the study, but quality problem. The criticality of this observation also appears to result more from the fact that this important incident (i.e. unblinded modification of the per-protocol population) was omitted and not made transparent in the final CSR. Instead, the false impression was given that all decisions were taken and the populations to be used in the analysis entirely defined prior to database lock and prior to unblinding. In its response, the applicant however agreed that this incident should have been made transparent in the clinical study report of study TRIPLE 8 and the overall submission.

Patients in both groups were comparable in terms of demography and baseline characteristics, in particular COPD history. In accordance with inclusion criterion #6, patients received either mono- or double therapy, but no triple therapy prior to study entry. Thus, in this study there was no step-down in therapy upon randomisation which might have penalised the comparator group.

The study population is predominantly (Eastern) European and may be a representative sample though the course of COPD and rate of exacerbations may be influenced by country-level socioeconomic and environmental factors.

Primary analysis and sensitivity analyses

Over 52 weeks of treatment, less patients in group TRYDONIS / RIARIFY experienced less moderate-to-severe exacerbations (35.7%, 433 events) as compared with IND/GB (37.5%, 485 events) (ITT population). Thus, the adjusted exacerbation rate per patient per year was lower with TRYDONIS / RIARIFY (0.504, 95% CI [0.447, 0.569]) as compared with IND/GB (0.595 [0.530, 0.668]). The resulting adjusted rate ratio was 0.848 (95% CI [0.723, 0.995]), thereby formally confirming a statistically significant reduction of 15.2% in the rate of moderate-to-severe COPD exacerbations and thus the superiority of TRYDONIS / RIARIFY over IND/GB (p=0.043). Notable, the p-value of the primary analysis of the primary endpoint (ITT dataset) are slightly less than the conventional 0.05 significance level (p=0.043). The upper limit of the 95% CI for the adjusted exacerbation rate ratio was 0.995. Results of the PP population confirmed the estimated effect size, but barely missed statistical significance (p=0.050, upper limit of 95% CI=1.000). Also, results of the additional sensitivity analyses (see below “Definition of a single exacerbation”) support the consistently borderline results for the primary endpoint. Depending on the analysis, results are non-significant or borderline significant. Furthermore, since a treatment policy estimand is of higher relevance than a hypothetical one, an analysis based on reference data (CR or J2R) would have been the preferred option from a regulatory point of view. Both reference-based imputation approaches failed to reach statistical significance (see below “Missing data”). Overall, although treatment effect estimates favour TRYDONIS / RIARIFY, the study results are not

associated with the statistically compelling evidence. These issues are further discussed in the overall conclusions of the clinical efficacy section.

Clinical relevance

There is currently no consensus as to what constitutes the minimal clinical important difference (MCID) for COPD exacerbations as the impact of their reduction/prevention appears to be influenced by various factors, including but not limited to the choice of the comparator, baseline status/characteristics of the patient population assessed as well as by the definitions used for grading exacerbation severity and frequency. Recently, Chapman and coll. (2013) suggested that interventions reducing exacerbations by as little as 11% may be considered as clinically relevant. In TRIPLE 8 study, the rate of moderate-to-severe COPD exacerbations over 52 weeks was lower with BDP/FF/GB than with IND/GB, with a rate ratio of 0.848 (95% CI [0.723, 0.995], p-value=0.043) indicating a 15% reduction in the exacerbation rate. However, it should be stressed that this difference, in absolute terms (an estimated reduction in 0.09 exacerbations per patient per year, from 0.594 with LABA/LAMA to 0.504 with the triple therapy), is considered modest from a clinical perspective. It is conceded that the chosen study design and population – in contrast to other recently published studies - did not penalise the comparator group nor did it inflate artificially the rate of moderate and severe COPD exacerbations.

When reviewing the data, an instance was seen where a fatal SAE in a patient of group CHF 5993 pMDI may not have been correctly classified and reported as COPD exacerbation. The case involves a 58-year old white male patient randomised to receive CHF5993 pMDI. The last study visit preceding the event was Visit 5, at week ´26. Reportedly, the patient experienced an event of acute respiratory failure (coded PT: *acute respiratory failure*) and was successfully reanimated while transported to a hospital. More detailed clinical and laboratory diagnostic criteria (e.g. arterial blood gas test results) are not reported. The event was considered to be serious, severe in intensity, but not related to the study medication. The patient remained in a serious condition and died two days later from a second episode of cardiac arrest. Only a single COPD exacerbation of moderate intensity is reported for this patient. The acute respiratory failure did not result in recording an acute exacerbation of the underlying COPD.

The MAH was requested to comment on the case and to set out the reasons why it was excluded that the acute respiratory failure reported in patient was the result of an acute exacerbation of COPD. The MAH claims that the reason for the ICU admission and cardiopulmonary admission was a myocardial infarction and that the inappropriate SAE term reported by the investigator (preferred term, PT: «acute respiratory failure») was not further challenged by the MAH. However, according to applicable guidance of how MedDRA terms should be selected, the triggering event and preferably a diagnosis (and not signs / symptoms or sequelae) should be reported. No relevant pre-existing cardiovascular conditions besides mild hypertension were reported for this patient. The patient in question had already experienced a COPD exacerbation of moderate intensity. The reason for administering ceftriaxone sodium and metronidazole (dose and route for both unknown) during his 2-day ICU stay has not been addressed in the response.

Notable, in study TRIPLE 7, another patient had suddenly and unexpectedly died a few days only after having had an uneventful study visit 3. The case was reported by the investigator as «respiratory failure», but in this case autopsy results clearly pointed towards an acute and purulent infection of the lung as the direct cause of death. In spite of this evidence, the event was not counted by the MAH as an acute exacerbation of COPD. No compelling arguments and well-founded epicrisis were forwarded by the applicant why an (acute) infectious pulmonary event (leading to an acute coronary syndrome) was excluded in a patient. The applicant considers that ceftriaxone and metronidazole (dose unknown) were given during the two-day ICU stay to «*prevent or treat ventilator-acquired pneumonia*», but once notified of the event did not make an effort to confirm why these two antibiotics were administered. It is noted that the prophylactic short-term administration of antibiotics is not a recommendation in the cited guidance document (Torres et al., 2018) and that there is no uniform management of intubated patients across Europe. As was also the case for one patient, the applicant did not challenge the AE term reported

by the investigator in order to have a more accurate event term in the study documentation, i.e. the triggering event or preferably a diagnosis.

Thus and in conclusion, based on these two examples, doubts remain on whether due care and diligence were exercised by the applicant (or its service providers) throughout trial conduct in fully assessing fatal / serious events and potential COPD exacerbations.

Definition of a single exacerbation

In order to support the primary evaluation and the chosen time gap to define single exacerbations several additional analysis were requested and provided by the applicant.

Re-analysis of exacerbation data applying different time gaps to define single exacerbations overall support the borderline study results. Irrespective of the time gap applied, point estimates are very similar (slightly smaller for time gaps <10 days and slightly larger for time gaps >10) and borderline significant/non-significant depending on the time-gap applied (for 15 and 20 day time gaps results are not significant).

In absence of a blinded external adjudication committee to define single exacerbations and given the arbitrary rule to define two exacerbations periods as a single one if they are not more than 10 days apart, analyses not depending on the specific number of exacerbations per patients were requested; in particular, analysis of the binary endpoint “any exacerbation” and analysis of the number of exacerbation days per patient were provided. The proportion of patient with any exacerbations was rather similar between both groups and only slightly lower for TRYDONIS / RIARIFY (35.7% vs, 37.5%; odds-ratio 0.918). This analysis is not significant due to the low treatment difference and the low sample size (power) for binary evaluation. Counting the number of exacerbation days per patient revealed on average a lower number of days for TRYDONIS / RIARIFY (7.32 vs. 9.62). Based on an ANOVA model this difference of -2.3 was significant. Similar results were observed applying a negative binomial model to analyse exacerbation days. A rank ANOVA failed to show statistical significance by far; probably due to the large number of patients without exacerbations (i.e. zero exacerbation days). These tied values (~63%) reduce the power of a rank based analysis. Given the low number of exacerbations per patient (around 95% of patients had 0, 1 or 2 exacerbations) evaluation of the number of exacerbations as categorical variable seems a reasonable approach. While this analysis suggested a trend in favour of TRYDONIS / RIARIFY it by far failed to reach statistical significance.

In summary, none of these analyses were pre-specified and they overall show and support the consistently borderline results for the evaluation of exacerbations. Treatment effect estimates are mostly similar and are depending on the analysis (borderline) significant or not-significant. Additional analyses overall support the consistency of borderline significant study results.

The primary analysis that was used targets a hypothetical estimand of the treatment effect if all subjects adhered to treatment. Although it remains unclear, the primary analysis is apparently based on on-treatment data only and no observation was recorded after treatment discontinuation. Hence, a treatment policy estimand on the treatment effect irrespective of treatment discontinuation is difficult to estimate.

The MAH clarified that patients were not planned to be followed up after treatment discontinuation. Still, some patients were observed after they stopped treatment. For most patients the follow-up after treatment discontinuation (TD) was short. Total planned follow-up time over all patients was 763. 5 and 767.5 years for TRYDONIS / RIARIFY and comparator, respectively. Total on-treatment time (time prior to TD) was 716.3 and 707.4 years and total off-treatment time (time between TD and study discontinuation) was 1.7 and 2.6 years. Furthermore, only 3 exacerbations occurred during off-treatment follow-up.

Hence, follow-up is overall rather complete. The analysis was based on the total follow-up time (including off-treatment follow-up). This is in principle supported, but given that off-treatment follow-up is extremely limited the primary analysis rather addresses a hypothetical effect had all patients adhered to

study treatment. The effect regardless of treatment discontinuations (treatment policy estimand) is considered of higher relevance as compared to the hypothetical estimand. However, in lack of sufficient off-treatment follow-up the treatment policy estimand is difficult to estimate. The most appropriate option in this situation would be to use multiple imputation based on reference data to cover the missing follow-up time (copy reference (CR) and jump to reference (J2R)). In addition to an analysis based on on-treatment data only, these analyses were provided by the MAH and as expected (since only few patients were not completely followed-up) results are similar for all analyses. Point estimates only range from 0.846 to 0.859 and confidence intervals are also similar. J2R as expected yields slightly smaller point estimates as compared to CR, and results for the primary analysis and the MAR based imputation approach are almost identical (due to being based on the same assumption and addressing the same hypothetical estimand).

In summary, results of the additional analyses support the consistently borderline results for the primary exacerbation endpoint. Depending on the analysis, results are non-significant or borderline significant. Furthermore, since a treatment policy estimand is of higher relevance than a hypothetical one, an analysis based on reference data (CR or J2R) would have been the preferred option from a regulatory point of view. Both reference-based imputation approaches failed to reach statistical significance.

The MAH investigated the heterogeneity of treatment effects across different subgroups (including gender) by including a treatment by subgroup interaction term into the analysis as requested by the CHMP (see annex 1, Q8) interactions were significant (p-values ≥ 0.25). Furthermore, forest plots do not indicate relevant inconsistencies between subgroups.

In addition, country effects were further evaluated. The p-value for the treatment by country interaction was 0.871. For the primary and main secondary endpoint (time to first moderate/severe exacerbation, change from baseline in pre-dose morning FEV1 and SGRQ total score over the entire treatment period), none of the countries dominated the results; neither with regard to sample size nor treatment effect. Confidence intervals are largely overlapping and point estimates per country favour TRYDONIS / RIARIFY in most cases.

Although the optimum cut-off for blood eosinophils still is a matter of debate, not surprisingly, stratified analyses suggest that the magnitude of the treatment effect with the triple combination is greater in patients with higher blood eosinophil levels of ≥2%. The same trend in favour of TRYDONIS / RIARIFY was seen when analysing moderate and severe exacerbations separately. But as the study was not adequately powered to demonstrate a significant between-group difference, only a numerically lower adjusted exacerbation rate per patient per year was reported for the TRYDONIS / RIARIFY group.

Treatment with TRYDONIS / RIARIFY was favoured by patient-reported outcomes, i.e. the St George's Respiratory Questionnaire (SGRQ) total score. Improvement in mean SGRQ total score was significantly better with TRYDONIS / RIARIFY than with IND/GLY. In the responder analyses, a numerically higher proportion of patients responded to TRYDONIS / RIARIFY than to IND/GLY in terms of FEV1 and SGRQ total score change from baseline at both Week 52, although the odds ratios were not statistically significant. Though the MCID for the SGRQ total score is reported to be ≥4 units, an adjusted mean change from baseline over the 52 week treatment period of 3.2 and an adjusted mean between group difference of 1.7 may be considered to be indicative of patient benefit.

Supportive study TRIPLE 7

The open-label design and the short(er) treatment duration of 26 weeks limit efficacy evaluations.

The total SGRQ score used as a primary efficacy variable in this study is a generally accepted tool / questionnaire in order to measure the health status in COPD patients.

The non-inferiority margin of 4 units was not sufficiently justified and considered only clinical judgement, but not statistical reasoning as laid down as a requirement in the respective EMA guidance document

(EMEA/CPMP/EWP/2158/99 dated 27 July 2005). In addition to providing assurance that TRYDONIS / RIARIFY is not substantially inferior to the reference product, the chosen non-inferiority limit should be calculated or defined such that superiority over placebo is not left in doubt in such a two-arm trial (with no placebo reference). By pre-defining the MCID of 4 units (i.e. the smallest difference in the SGRQ score which patients perceive as beneficial) as the non-inferiority margin, it is no more guaranteed that this latter requirement is met. Thus, a more conservative approach for defining the non-inferiority margin should have been chosen by the MAH. This reflects the limitations of the data of the Triple 7 study in addition to the short direction of the study.

2.4.4. Conclusions on the clinical efficacy

The main efficacy assessment is based on data generated from a single pivotal phase 3b trial with study TRIPLE 8. Over 52 weeks of treatment, less patients in group TRYDONIS / RIARIFY experienced less moderate-to-severe exacerbations (35.7%, 433 events) as compared with IND/GB (37.5%, 485 events) (ITT population). The resulting adjusted rate ratio was 0.848 (p=0.043, 95% CI [0.723, 0.995]), thereby formally confirming a statistical significance. Results of the PP population confirmed the estimated effect size, but barely missed statistical significance (p=0.050, upper limit of 95% CI=1.000). Also, results of the additional analyses support the consistently borderline results for the primary endpoint. Depending on the analysis, results are either non-significant or borderline significant. Furthermore, since a treatment policy estimand is of higher relevance than a hypothetical one, an analysis based on reference data (CR or J2R) would have been the preferred option from a regulatory point of view. Both reference-based imputation approaches failed to reach statistical significance.

The rate of moderate-to-severe COPD exacerbations over 52 weeks was lower with TRYDONIS / RIARIFY than with IND/GB, with a rate ratio of 0.848 (95% CI [0.723, 0.995], p-value=0.043) indicating a 15% reduction in the exacerbation rate. However, it should be stressed that this difference, in absolute terms (an estimated reduction in 0.09 exacerbations per patient per year, from 0.594 with LABA/LAMA to 0.504 with the triple therapy), is considered modest from a clinical perspective.

In addition, several other issues emerged during the assessment of the submitted documentation which in this context may challenge the internal validity of the study and data reliability. These include but are not limited to the following:

- Erroneous subject-level data were included in the locked study database of the pivotal study TRIPLE 8, making it necessary to modify the composition of the per-protocol population after unblinding.

- Though apparently being of minor impact and not affecting the primary response variable, there was a lack of transparency by omitting information on this relevant incident in the CSR and claiming that both populations to be used in the analysis were defined prior to database lock and unblinding.

- Reportedly, annual audit plans / programmes were finalised with significant delay and for the pivotal study TRIPLE 8, only a single site audit was performed that followed a proactive and risk-based approach. Two others were performed in a reactive manner subsequent to the announcement of a (routine) health authority inspection.

Nevertheless, triple therapy is currently thought to be best used as an escalation therapy for those incompletely controlled with dual therapy, either ICS/LABA or LABA/LAMA (GOLD 2018) and superiority (although marginal statistically significant) of the triple combination over the dual components has been demonstrated.

2.5. Clinical safety

Introduction

This section focuses on safety data as generated in the pivotal study TRIPLE 8 in order to assess the potential (negative) effects if an inhaled corticosteroid is added to dual treatment with bronchodilators in patients with advanced COPD. These results are considered to be more important than those obtained in study TRIPLE 7 because of the longer treatment duration (52 weeks vs. 26 weeks) and the study design (double-blind, double-dummy vs. open label). In addition, results of the integrated safety analysis as now provided by the applicant by pooling data from trials TRIPLE 5, TRIPLE 6, TRIPLE 7 and TRIPLE 8 are discussed. This analysis was performed for TEAEs only which were at least possibly related to treatment with TRYDONIS / RIARIFY.

Patient exposure

In study TRIPLE 8, exposure to randomised study treatment shows the expected skewed and left-tailed distribution. Overall, the duration of study treatment was as planned per protocol and the proportion of patients prematurely discontinuing the trial was low and comparable between groups. Accordingly, median treatment duration was 365 days in both groups (Table 18).

About 88.7% and 85.4% of patients received at least 48 weeks of study treatment in groups TRYDONIS / RIARIFY and IND/GB, respectively.

Table 18: Exposure to randomised treatment (safety = ITT population)

	CHF 5993 pMDI (N=764)	Indacaterol/glycopyrronium bromide (N=768)
Exposure (days)		
n	764	768
Mean (SD)	342.4 (70.8)	335.2 (81.2)
Median	365.0	365.0
Min, Max	6, 406	3, 392
Exposure (weeks) (n (%))		
[0-4)	8 (1.0)	9 (1.2)
[4-8)	7 (0.9)	7 (0.9)
[8-12)	6 (0.8)	10 (1.3)
[12-16)	6 (0.8)	19 (2.5)
[16-20)	6 (0.8)	7 (0.9)
[20-24)	6 (0.8)	10 (1.3)
[24-28)	15 (2.0)	9 (1.2)
[28-32)	7 (0.9)	6 (0.8)
[32-36)	4 (0.5)	7 (0.9)
[36-40)	7 (0.9)	7 (0.9)
[40-44)	8 (1.0)	12 (1.6)
[44-48)	6 (0.8)	9 (1.2)
[48-52)	159 (20.8)	148 (19.3)
>=52	519 (67.9)	508 (66.1)

Source Data: Listing 16.2.5.3
Notes: [1] Where indicated, table presents number and percentage of patients (n (%)).
[2] Percentages are based on the number of patients in the relevant treatment/population (N).
[3] Extent of Exposure (Days) = Date of last randomised study medication intake - Date of first randomised study medication intake + 1
[4] Extent of Exposure (Weeks) = Extent of exposure (days)/7.

In study TRIPLE 7, the majority of patients completed at least 26 weeks of treatment as planned per protocol with only 33 (5.7%) patients in the BDP/FF/GB group and 30 (5.2%) patients in the Fluticasone/Vilanterol + Tiotropium group discontinuing the study. The mean extent of exposure was comparable in the TRYDONIS / RIARIFY and Fluticasone/Vilanterol + Tiotropium groups (178.3 and 179.3 days, respectively).

Adverse events

Overall summary of treatment-emergent Adverse Events (TEAE)

Study TRIPLE 8

With TRYDONIS / RIARIFY, 490 (64.1%) patients experienced 1292 TEAEs: 117 (15.3%) patients were reported with 170 serious TEAEs, 43 (5.6%) patients with 50 ADRs and 1 (0.1%) patient with 1 serious ADR (Table 18). A total of 86 (11.3%) patients were reported with 129 severe TEAEs and 45 TEAEs led to study medication discontinuation in 37 (4.8%) patients. With IND/GB, 516 (67.2%) patients experienced 1432 TEAEs: 130 (16.9%) patients were reported with 208 serious TEAEs, 37 (4.8%) patients with 53 ADRs and 1 (0.1%) patient with 1 serious ADR. A total of 87 (11.3%) patients were reported with 136 severe TEAEs and 56 TEAEs led to study medication discontinuation in 47 (6.1%) patients. There were 20 TEAEs that led to death in 16 (2.1%) patients with TRYDONIS / RIARIFY and 26 TEAEs that led to death in 21 (2.7%) patients with IND/GB. None of the deaths were considered related to study treatment. Most of the fatal TEAEs were from the SOCs "cardiac disorders" (11 TEAEs in 10 patients) and "general disorders and administration site conditions" (11 TEAEs in 11 patients). COPD exacerbation led to the death of 2 patients (0.3%) in each treatment group.

Table 19: Summary of TEAEs and ADRs (safety = ITT population)

	CHF 5993 pMDI N=764		Indacaterol/GB N=768	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
TEAEs	490 (64.1)	1292	516 (67.2)	1432
Serious TEAEs	117 (15.3)	170	130 (16.9)	208
Non-serious TEAEs	453 (59.3)	1122	471 (61.3)	1224
Treatment-emergent ADRs	43 (5.6)	50	37 (4.8)	53
Serious treatment-emergent ADRs	1 (0.1)	1	1 (0.1)	1
Severe TEAEs	86 (11.3)	129	87 (11.3)	136
TEAEs leading to study treatment discontinuation	37 (4.8)	45	47 (6.1)	56
TEAEs leading to death[a]	16 (2.1)	20	21 (2.7)	26

ADR = Adverse drug reaction; GB = Glycopyrronium bromide; pMDI = Pressurised metered dose inhaler; TEAE = Treatment-emergent adverse event.
N = Number of patients in the Safety population.
[a] Patient #032821002 and Patient #616803031 had AEs leading to death and were recorded as discontinued due to AEs.

Study TRIPLE 7

With TRYDONIS / RIARIFY, 255 (44.1%) patients experienced 530 TEAEs: 39 (6.7%) patients were reported with 63 serious TEAEs, 18 (3.1%) patients with 23 ADRs and no patients were reported with serious ADRs (Table 24). A total of 26 (4.5%) patients were reported with 42 severe TEAEs and 12 TEAEs led to study medication discontinuation in 11 (1.9%) patients. With Fluticasone/Vilanterol + Tiotropium, 246 (42.5%) patients experienced 491 TEAEs: 56 (9.7%) patients were reported with 87 serious TEAEs, 22 (3.8%) patients with 30 ADRs and no patients were reported with serious ADRs. A total of 32 (5.5%) patients were reported with 44 severe TEAEs and 14 TEAEs led to study medication discontinuation in 13 (2.2%) patients. There were 3 TEAEs that led to death in 3 (0.5%) patients with TRYDONIS / RIARIFY and 6 TEAEs that led to death in 5 (0.9%) patients with Fluticasone/Vilanterol + Tiotropium.

Common AE and ADR

Study TRIPLE 8

TEAEs reported in ≥1% of patients and listed by preferred term (PT) are presented in Table 20.

Table 20: Summary of TEAEs reported in ⩾1% of patients by PT (safety = ITT population)

PT	CHF 5993 pMDI N=764		Indacaterol/GB N=768	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
At least one TEAE	**490 (64.1)**	**1292**	**516 (67.2)**	**1432**
COPD[a]	273 (35.7)	444	288 (37.5)	501
Nasopharyngitis	43 (5.6)	56	37 (4.8)	41
Headache	44 (5.8)	50	35 (4.6)	39
Pneumonia[b]	28 (3.7)[c]	32	27 (3.5)[d]	29[d]
Back pain	21 (2.7)	21	23 (3.0)	27
Dyspnoea	21 (2.7)	25	21 (2.7)	23
Hypertension	15 (2.0)	16	22 (2.9)	24
Cough	13 (1.7)	14	21 (2.7)	25
Upper respiratory tract infection	11 (1.4)	11	11 (1.4)	11
Arthralgia	10 (1.3)	16	11 (1.4)	11
Rhinitis	7 (0.9)	8	13 (1.7)	13
Viral infection	12 (1.6)	13	7 (0.9)	7
Oral candidiasis	13 (1.7)	15	5 (0.7)	5
Respiratory tract infection viral	9 (1.2)	10	9 (1.2)	10
Toothache	5 (0.7)	5	13 (1.7)	13
Cardiac failure	9 (1.2)	9	7 (0.9)	7
Diabetes mellitus	6 (0.8)	6	10 (1.3)	10
Diarrhoea	8 (1.0)	8	8 (1.0)	8
Atrial fibrillation	5 (0.7)	7	10 (1.3)	11
Bronchitis	9 (1.2)	9	6 (0.8)	6
Influenza	8 (1.0)	9	6 (0.8)	6
Abdominal distension	8 (1.0)	8	5 (0.7)	6
Pain in extremity	1 (0.1)	1	10 (1.3)	13

COPD = Chronic obstructive pulmonary disease; GB = Glycopyrronium bromide; pMDI = Pressurised metered dose inhaler; PT = Preferred term; TEAE = Treatment-emergent adverse event.
N = Number of patients in the Safety population.
[a] COPD is the PT for the reported "COPD exacerbation".
[b] Pneumonia, as reported by the Investigators, includes the PTs of bronchopneumonia, interstitial lung disease, lobar pneumonia, pneumonia, pneumonia bacterial, pneumonia streptococcal, pneumonia viral and pulmonary tuberculosis.
[c] Patient #616806004 was reported with two events of pneumonia (PTs of pneumonia and bronchopneumonia) during treatment with CHF 5993 pMDI, so the patient was only counted once for the total number of patients with pneumonia (Listing 16.2.7.9).
[d] Patient #348801005 was reported with suspicion of lung tuberculosis (PT pulmonary tuberculosis) during treatment with indacaterol/GB, but pneumonia was not confirmed by the Investigator, and the patient was not counted for total pneumonias

Study TRIPLE 7

The most common TEAE was COPD exacerbation, reported in 122 (21.1%) and 108 (18.7%) patients with TRYDONIS / RIARIFY and Fluticasone/Vilanterol + Tiotropium, respectively. Other common TEAEs (reported in ≥ 2% patients) were nasopharyngitis, headache, pneumonia (PTs of bronchopneumonia, lobar pneumonia, pneumonia and pneumonia staphylococcal), respiratory tract infection viral, dyspnoea and oral candidiasis. The majority of these TEAEs were mild or moderate in intensity and resolved by the end of the study.

Integrated Analysis of Treatment-Emergent Adverse Drug Reactions for Studies TRIPLE 5, TRIPLE 6, TRIPLE 7 and TRIPLE 8

Table 21 presents all treatment-emergent ADRs with TRYDONIS / RIARIFY pooled from studies TRIPLE 5, TRIPLE 6, TRIPLE 7 and TRIPLE 8 in decreasing order of frequency by SOC and PT in the overall Safety population. The only SOC reported in ≥ 1% of patients with BDP/FF/GB was the Infections and Infestations SOC.

Table 21: All treatment-emergent ADRs by SOC and PT, Safety population – Studies Triple 5, Triple 6, Triple 7 and Triple 8 (integrated analysis)

SOC, PT	BDP/FF/GB 400/24/50 µg N=3106	
	Number of events	Number of patients (%)
At least 1 treatment-emergent ADR	**138**	**112 (3.6)**
Infections and infestations	**44**	**37 (1.2)**
Oral candidiasis	31	26 (0.8)
Oral fungal infection	5	4 (0.1)
Oropharyngeal candidiasis	2	2 (0.1)
Furuncle	1	1 (0.0)
Laryngitis	1	1 (0.0)
Lower respiratory tract infection fungal	1	1 (0.0)
Pharyngitis	1	1 (0.0)
Pneumonia	1	1 (0.0)
Respiratory tract infection	1	1 (0.0)
Gastrointestinal disorders	**21**	**19 (0.6)**
Dry mouth	15	14 (0.5)
Stomatitis	3	3 (0.1)
Nausea	2	2 (0.1)
Aphthous stomatitis	1	1 (0.0)
Respiratory, thoracic and mediastinal disorders	**17**	**17 (0.5)**
Dysphonia	8	8 (0.3)
Cough	3	3 (0.1)
Throat irritation	2	2 (0.1)
Dry throat	1	1 (0.0)
Oropharyngeal pain	1	1 (0.0)
Pharyngeal erythema	1	1 (0.0)
Pharyngeal inflammation	1	1 (0.0)
Musculoskeletal and connective tissue disorders	**17**	**14 (0.5)**
Muscle spasms	16	14 (0.5)
Myalgia	1	1 (0.0)
Cardiac disorders	**8**	**7 (0.2)**
Atrial fibrillation	2	2 (0.1)
Angina unstable	1	1 (0.0)
Atrioventricular block first degree	1	1 (0.0)
Nodal rhythm	1	1 (0.0)
Palpitations	1	1 (0.0)
Sinus bradycardia	1	1 (0.0)
Tachycardia	1	1 (0.0)
Skin and subcutaneous tissue disorders	**6**	**6 (0.2)**
Alopecia	2	2 (0.1)
Pruritus	2	2 (0.1)
Hyperkeratosis	1	1 (0.0)
Papule	1	1 (0.0)
Vascular disorders	**6**	**6 (0.2)**
Hypertension	5	5 (0.2)
Extravasation blood	1	1 (0.0)
Nervous system disorders	**5**	**5 (0.2)**
Headache	2	2 (0.1)
Dizziness	1	1 (0.0)

SOC, PT	BDP/FF/GB 400/24/50 µg N=3106	
	Number of events	Number of patients (%)
Hypersomnia	1	1 (0.0)
Tremor	1	1 (0.0)
Investigations	**4**	**4 (0.1)**
Electrocardiogram QT prolonged	2	2 (0.1)
Electrocardiogram PR prolongation	1	1 (0.0)
Hepatic enzyme increased	1	1 (0.0)
Metabolism and nutrition disorders	**3**	**3 (0.1)**
Decreased appetite	1	1 (0.0)
Diabetes mellitus	1	1 (0.0)
Hypokalaemia	1	1 (0.0)
Psychiatric disorders	**2**	**2 (0.1)**
Anxiety	1	1 (0.0)
Insomnia	1	1 (0.0)
Renal and urinary disorders	**2**	**2 (0.1)**
Dysuria	1	1 (0.0)
Urinary retention	1	1 (0.0)
General disorders and administration site conditions	**1**	**1 (0.0)**
Asthenia	1	1 (0.0)
Immune system disorders	**1**	**1 (0.0)**
Hypersensitivity	1	1 (0.0)
Reproductive system and breast disorders	**1**	**1 (0.0)**
Benign prostatic hyperplasia	1	1 (0.0)

Source: CSR study Triple 5, Listing 16.2.7.4; CSR study Triple 6, Listing 16.2.7.4; CSR study Triple 7, Listing 16.2.7.4; CSR study Triple 8 Listing 16.2.7.4.
Note: treatment doses = total daily doses.

Serious adverse event / deaths / other significant events

Deaths

In study TRIPLE 8, there were 20 TEAEs leading to death reported in 16 (2.1%) patients with TRYDONIS / RIARIFY and 26 TEAEs leading to death reported in 21 (2.7%) patients with IND/GB (Table 22). The most common TEAEs leading to death were from the General Disorders and Administration Site Conditions and Cardiac Disorders SOCs. In both SOCs the frequency of events was lower with BFP/FF/GB than with IND/GB. Of note, COPD exacerbation led to death in 2 (0.3%) patients in each treatment group. None of the deaths were considered related to study treatment.

Table 22: All TEAEs leading to death by SOC and PT, Safety population – Study Triple 8

SOC, PT	BDP/FF/GB 400/24/50 µg N=764		Indacaterol/GB 85/43 µg N=768	
	Number of events	Number of patients (%)	Number of events	Number of patients (%)
At least 1 TEAE leading to death	**20**	**16 (2.1)**	**26**	**21 (2.7)**
General disorders and administration site conditions	**3**	**3 (0.4)**	**8**	**8 (1.0)**
Death	2	2 (0.3)	3	3 (0.4)
Sudden cardiac death	0	0 (0.0)	3	3 (0.4)
Sudden death	1	1 (0.1)	2	2 (0.3)
Cardiac disorders	**2**	**2 (0.3)**	**9**	**8 (1.0)**
Acute myocardial infarction	0	0 (0.0)	4	4 (0.5)
Atrial fibrillation	0	0 (0.0)	2	2 (0.3)
Cardio-respiratory arrest	1	1 (0.1)	1	1 (0.1)
Arrhythmia	0	0 (0.0)	1	1 (0.1)
Cardiopulmonary failure	1	1 (0.1)	0	0 (0.0)
Left ventricular failure	0	0 (0.0)	1	1 (0.1)
Respiratory, thoracic and mediastinal disorders	**5**	**4 (0.5)**	**5**	**4 (0.5)**
COPD[a]	2	2 (0.3)	2	2 (0.3)
Pulmonary embolism	0	0	2	2 (0.3)
Acute respiratory distress syndrome	1	1 (0.1)	0	0 (0.0)
Acute respiratory failure	1	1 (0.1)	0	0 (0.0)
Respiratory distress	1	1 (0.1)	0	0 (0.0)
Respiratory failure	0	0 (0.0)	1	1 (0.1)
Infections and infestations	**2**	**2 (0.3)**	**2**	**2 (0.3)**
Pneumonia	2	2 (0.3)	1	1 (0.1)
Pneumonia	2	2 (0.3)	0	0 (0.0)
Pulmonary tuberculosis	0	0 (0.0)	1	1 (0.1)
Necrotising fasciitis	0	0 (0.0)	1	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4**	**4 (0.5)**	**0**	**0 (0.0)**
Lung neoplasm malignant	2	2 (0.3)	0	0 (0.0)
Bladder transitional cell carcinoma	1	1 (0.1)	0	0 (0.0)
Oesophageal carcinoma	1	1 (0.1)	0	0 (0.0)
Injury, poisoning and procedural complications	**2**	**2 (0.3)**	**1**	**1 (0.1)**
Multiple injuries	1	1 (0.1)	1	1 (0.1)
Post procedural complication	1	1 (0.1)	0	0 (0.0)
Nervous system disorders	**1**	**1 (0.1)**	**1**	**1 (0.1)**
Cerebrovascular accident	1	1 (0.1)	1	1 (0.1)
Vascular disorders	**1**	**1 (0.1)**	**0**	**0 (0.0)**
Circulatory collapse	1	1 (0.1)	0	0 (0.0)

In study TRIPLE 7, there were 3 TEAEs leading to death reported in 3 (0.5%) patients with TRYDONIS / RIARIFY and 6 TEAEs leading to death reported in 5 (0.9%) patients with Fluticasone/Vilanterol + Tiotropium. The only TEAE leading to death reported in ≥ 2 patients in either treatment group was COPD exacerbation, which led to death in 2 (0.3%) patients in the Fluticasone/Vilanterol + Tiotropium group. None of the deaths were considered related to study treatment.

Other Serious Adverse Events

In study TRIPLE 8, 170 serious TEAEs were reported in 117 (15.3%) patients with TRYDONIS / RIARIFY and 208 serious TEAEs were reported in 130 (16.9%) patients with IND/GB. The incidence of serious TEAEs reported in ≥ 2 patients by PT in either treatment group is presented in decreasing order of frequency in Table 23.

Table 23: Serious TEAEs reported in ≥ 2 patients by PT, Safety population –Study Triple 8

PT	BDP/FF/GB 400/24/50 µg N=764		Indacaterol/GB 85/43 µg N=768	
	Number of events	Number of patients (%)	Number of events	Number of patients (%)
At least 1 serious TEAE	**170**	**117 (15.3)**	**208**	**130 (16.9)**
COPD[a]	75	61 (8.0)	94	69 (9.0)
Pneumonia	18	18 (2.4)	18	17 (2.2)
Bronchopneumonia	0	0 (0.0)	2	2 (0.3)
Lobar pneumonia	1	1 (0.1)	3	2 (0.3)
Pneumonia	16	16 (2.1)	10	10 (1.3)
Pneumonia bacterial	1	1 (0.1)	0	0 (0.0)
Pneumonia streptococcal	0	0 (0.0)	1	1 (0.1)
Pneumonia viral	0	0 (0.0)	1	1 (0.1)
Pulmonary tuberculosis	0	0 (0.0)	1	1 (0.1)
Acute myocardial infarction	0	0 (0.0)	5	5 (0.7)
Atrial fibrillation	0	0 (0.0)	5	5 (0.7)
Death	2	2 (0.3)	3	3 (0.4)
Lung neoplasm malignant	4	4 (0.5)	1	1 (0.1)
Cardiopulmonary failure	2	2 (0.3)	2	2 (0.3)
Pulmonary embolism	2	2 (0.3)	2	2 (0.3)
Myocardial infarction	1	1 (0.1)	3	3 (0.4)
Respiratory failure	1	1 (0.1)	3	3 (0.4)
Atrial flutter	0	0 (0.0)	3	3 (0.4)
Sudden cardiac death	0	0 (0.0)	3	3 (0.4)
Bronchiectasis	1	1 (0.1)	2	2 (0.3)
Lung adenocarcinoma	1	1 (0.1)	2	2 (0.3)
Sudden death	1	1 (0.1)	2	2 (0.3)
Acute respiratory failure	2	2 (0.3)	0	0 (0.0)
Bladder transitional cell carcinoma	2	2 (0.3)	0	0 (0.0)
Cerebral ischaemia	2	2 (0.3)	0	0 (0.0)
Retinal detachment	2	2 (0.3)	0	0 (0.0)
Renal failure	0	0 (0.0)	2	2 (0.3)

The majority of serious TEAEs by PT were reported in ≤ 2 patients in either treatment group. Those reported in > 2 patients were COPD exacerbation, pneumonia, acute myocardial infarction, atrial fibrillation, death, lung neoplasm malignant, myocardial infarction, respiratory failure, atrial flutter and sudden cardiac death. Only 1 serious TEAE in each group was assessed as related to study treatment: 1 event of dysuria in the BDP/FF/GB group, which led to study treatment interruption and was resolved before study discontinuation due to withdrawal of consent, and 1 event of atrial fibrillation in the IND/GB group, which did not lead to study treatment modification and was not resolved before study participation ended.

In study TRIPLE 7, 63 serious TEAEs were reported in 39 (6.7%) patients with TRYDONIS / RIARIFY and 87 serious TEAEs were reported in 56 (9.7%) patients with Fluticasone/Vilanterol + Tiotropium.

The majority of serious TEAEs by PT were reported in ≤ 2 patients in either treatment group. Those reported in > 2 patients were COPD exacerbation, pneumonia (PTs of lobar pneumonia, pneumonia and pneumonia staphylococcal) and respiratory failure.

Other Significant Adverse Events - pneumonia

Study TRIPLE 8

There were 32 events of treatment-emergent pneumonia (including PTs of bronchopneumonia, interstitial lung disease, lobar pneumonia, pneumonia, pneumonia bacterial, pneumonia streptococcal, pneumonia viral and pulmonary tuberculosis) reported in 28 (3.7%) patients with TRYDONIS / RIARIFY and 29

events reported in 27 (3.5%) patients with IND/GB. Only one confirmed event of pulmonary tuberculosis was reported in 1 (0.1%) patient with IND/GB and none with TRYDONIS / RIARIFY (Table 24).

Table 24: Treatment-emergent pneumonias and pneumonia rates (safety = ITT population)

	CHF 5993 pMDI N=764		Indacaterol/GB N=768	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
All pneumonias	28 (3.7)	32	27 (3.5)	29
Community acquired pneumonia	27 (3.5)	29	25 (3.3)	26
Nosocomial pneumonia	1 (0.1)	2	1 (0.1)	1
Missing information	1 (0.1)	1	2 (0.3)	2
Lobar pneumonia	11 (1.4)	12	8 (1.0)	9
Bronchopneumonia	13 (1.7)	15	14 (1.8)	14
Interstitial pneumonia	3 (0.4)	3	4 (0.5)	4
Missing information	2 (0.3)	2	2 (0.3)	2
Total follow-up time (years)	718.20		707.37	
Pneumonia rate per 1,000 patients per year	44.556		40.997	

GB = Glycopyrronium bromide; pMDI = Pressurised metered dose inhaler.
N = Number of patients in the Safety population.

The majority of reported pneumonias were moderate in intensity and most of them resolved by the end of the study. A total of 18 serious pneumonias were reported in 18 (2.4%) patients with TRYDONIS / RIARIFY and 18 serious pneumonias were reported in 17 (2.2%) patients with IND/GB. None of the serious pneumonias were considered related to the study treatment and 1 non-serious pneumonia of moderate intensity with BDP/FF/GB was considered related to the study treatment. Of note, the treatment-related event of pneumonia reported above was also assessed as possibly caused by a severe acute respiratory syndrome.

Three events of pneumonia led to study medication discontinuation in 3 (0.4%) patients with TRYDONIS / RIARIFY and 1 event in 1 (0.1%) patient with IND/GB. Of these, 2 events of pneumonia in 2 (0.3%) patients in the BDP/FF/GB group and 1 event in 1 (0.1%) patient in the IND/GB group led to death and one event of pneumonia in the BDP/FF/GB group was assessed as ‘not verified’ by the site and the patient died from an unknown cause.

The pneumonia rate per 1,000 patients per year was comparable with TRYDONIS / RIARIFY and IND/GB (44.6 vs. 41.0).

With both treatments, most cases were classified by investigators to be community-acquired. Only one non-serious pneumonia of moderate intensity was considered by the investigators to be related to the study treatment (one patient in TRYDONIS / RIARIFY group).

Study TRIPLE 7

There were 13 events of treatment-emergent pneumonia (including PTs of bronchopneumonia, lobar pneumonia, pneumonia and pneumonia staphylococcal) reported in 11 (1.9%) patients with TRYDONIS / RIARIFY and 15 events reported in 15 (2.6%) patients with Fluticasone/Vilanterol + Tiotropium. The majority of reported pneumonias were moderate in intensity and most of them resolved by the end of the study. A total of 9 serious pneumonias were reported in 8 (1.4%) patients with TRYDONIS / RIARIFY and 11 serious pneumonias were reported in 11 (1.9%) patients with Fluticasone/Vilanterol + Tiotropium. None were considered related to the study treatment. One event of pneumonia led to study medication

discontinuation in 1 (0.2%) patient and 1 event of pneumonia led to death in 1 (0.2%) patient with Fluticasone/Vilanterol + Tiotropium.

The pneumonia rate per 1,000 patients per year was slightly lower with TRYDONIS / RIARIFY (44.2) than with Fluticasone/Vilanterol + Tiotropium (50.6).

Other Significant Adverse Events - cardiovascular safety

Study TRIPLE 8

About 60% of patients of the safety population were reported to suffer from vascular disorders (452 patients [59.2%] in TRYDONIS / RIARIFY group and 480 patients [62.5%] in IND/GB group), with hypertension being the most frequent PT (54.6% and 57.8% of patients, respectively). Pre-existing cardiac disorders were reported in 198 patients (25.9%) of group CHF 5993 pMDI and 214 patients (27.9%) in group IND/GB.

A similar proportion of patients in TRYDONIS / RIARIFY and IND/GB groups experienced any cardiovascular event (11.0% vs. 12.5%, respectively).

The most frequently reported cardiovascular events were cardiac failures, with 19 events in TRYDONIS / RIARIFY group and 18 events in IND/GB group and arrhythmias, with 20 events in TRYDONIS / RIARIFY group and 24 events in IND/GB group. Most arrhythmias were of the tachycardia-type (6 and 4 events, respectively). None of these cardiovascular events was considered related to treatment with TRYDONIS / RIARIFY.

Laboratory findings

Study TRIPLE 8

Overall, changes in all haematology and biochemistry parameters from screening to both Week 26 and Week 52 were minimal with TRYDONIS / RIARIFY and IND/GB, with no major differences between treatments. CS abnormalities in haematology parameters, which were associated with serious TEAEs, were reported in 2 patients with TRYDONIS / RIARIFY (PTs: bladder transitional cell carcinoma and Hodgkin's disease). Neither of these serious TEAEs were considered related to study treatment. CS abnormalities in biochemistry parameters, which were associated with serious TEAEs, were reported in 2 patients with TRYDONIS / RIARIFY (PTs: adenocarcinoma gastric and type 2 diabetes mellitus). Neither of these serious TEAEs were considered related to study treatment.

Study TRIPLE 7

Overall, changes in all haematology and biochemistry parameters from screening to Week 26 were minimal with TRYDONIS / RIARIFY and Fluticasone/Vilanterol + Tiotropium, with no major differences between treatments. For all haematology parameters, the majority of patients presented normal or NCS values at screening and Week 26. None of the CS abnormalities in haematology parameters assessed during the study were reported as serious TEAEs. Clinically significant abnormalities in biochemistry parameters were reported as a serious TEAE (PT: hepatic enzyme increased) in 1 (0.2%) patient with TRYDONIS / RIARIFY; this TEAE was not considered related to study treatment.

Safety in special populations

Table 25: TEAEs stratified by age group in patients treated with TRYDONIS / RIARIFY, Safety population – Studies TRIPLE 5, TRIPLE 6, TRIPLE 7 and TRIPLE 8 (integrated analysis)

TEAEs	Age <65 years	Age 65-74 years	Age 75-84 years	Age 85+ years
Total AEs	893 (52.7%)	628 (56.8%)	183 (60.4%)	3 (60.0%)
Serious AEs - Total	191 (11.3%)	166 (15.0%)	45 (14.9%)	0 (0.0%)
- Fatal	24 (1.4%)	25 (2.3%)	5 (1.7%)	0 (0.0%)
- Hospitalization/prolong existing hospitalization	176 (10.4%)	152 (13.8%)	38 (12.5%)	0 (0.0%)
- Life-threatening	12 (0.7%)	12 (1.1%)	4 (1.3%)	0 (0.0%)
- Disability/incapacity	3 (0.2%)	7 (0.6%)	3 (1.0%)	0 (0.0%)
- Other (medically significant)	21 (1.2%)	24 (2.2%)	10 (3.3%)	0 (0.0%)
AEs leading to drop-out	42 (2.5%)	57 (5.2%)	17 (5.6%)	0 (0.0%)
Psychiatric disorders	18 (1.1%)	10 (0.9%)	6 (2.0%)	0 (0.0%)
Nervous system disorders	86 (5.1%)	78 (7.1%)	30 (9.9%)	1 (20.0%)
Accidents and injuries	32 (1.9%)	28 (2.5%)	5 (1.7%)	0 (0.0%)
Cardiac disorders	78 (4.6%)	73 (6.6%)	20 (6.6%)	0 (0.0%)
Vascular disorders	59 (3.5%)	60 (5.4%)	11 (3.6%)	1 (20.0%)
Cerebrovascular disorders	8 (0.5%)	18 (1.6%)	2 (0.7%)	0 (0.0%)
Infections and infestations	307 (18.1%)	212 (19.2%)	59 (19.5%)	2 (40.0%)
Anticholinergic syndrome	28 (1.7%)	24 (2.2%)	10 (3.3%)	0 (0.0%)
Quality of life decreased (PT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Quality of life decreased (selection of PTs)	44 (2.6%)	35 (3.2%)	18 (5.9%)	0 (0.0%)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	44 (2.6%)	48 (4.3%)	9 (3.0%)	0 (0.0%)
Pneumonias	42 (2.5%)	38 (3.4%)	10 (3.3%)	0 (0.0%)

Number and percentage of patients with at least one TEAE are presented.
Source: CSR study TRIPLE 5, Listing 16.2.7.2; CSR study TRIPLE 6, Listing 16.2.7.2; CSR study TRIPLE 7, Listing 16.2.7.2; CSR study TRIPLE 8, Listing 16.2.7.2

Safety related to drug-drug interactions and other interactions

No new drug interaction studies or information have been conducted or collected since the approval of Trydonis / Riarify.

Discontinuation due to adverse events

In study TRIPLE 8, TEAEs leading to study medication discontinuation were reported in 37 (4.8%) and 47 (6.1%) patients with TRYDONIS / RIARIFY and IND/GB, respectively. The incidence of TEAEs leading to study medication discontinuation is presented in Table 26 when reported in ≥ 2 patients by PT in either treatment group.

Table 26: TEAEs leading to study medication discontinuation reported in ≥ 2 patients by PT, Safety population – Study Triple 8

PT	BDP/FF/GB 400/24/50 µg N=764		Indacaterol/GB 85/43 µg N=768	
	Number of events	Number of patients (%)	Number of events	Number of patients (%)
At least 1 TEAE leading to study medication discontinuation	**45**	**37 (4.8)**	**56**	**47 (6.1)**
COPD[a]	5	5 (0.7)	10	10 (1.3)
Death	2	2 (0.3)	3	3 (0.4)
Acute myocardial infarction	0	0 (0.0)	4	4 (0.5)
Lung neoplasm malignant	3	3 (0.4)	1	1 (0.1)
Pneumonia	3	3 (0.4)	1	1 (0.1)
Pneumonia	3	3 (0.4)	0	0 (0.0)
Pulmonary tuberculosis	0	0 (0.0)	1[b]	1 (0.1)[b]
Cardiopulmonary failure	1	1 (0.1)	2	2 (0.3)
Sudden cardiac death	0	0 (0.0)	3	3 (0.4)
Sudden death	1	1 (0.1)	2	2 (0.3)
Acute respiratory failure	2	2 (0.3)	0	0 (0.0)
Bladder transitional cell carcinoma	2	2 (0.3)	0	0 (0.0)
Dyspnoea	0	0 (0.0)	2	2 (0.3)
Pulmonary embolism	0	0 (0.0)	2	2 (0.3)

The majority of TEAEs that led to study medication discontinuation by PT were reported in ≤ 2 patients in either treatment group; those reported in > 2 patients were:

- COPD exacerbation which led to study medication discontinuation of 5 (0.7%) and 10 (1.3%) patients with TRYDONIS / RIARIFY and IND/GB, respectively;
- Death which led to study medication discontinuation of 2 (0.3%) and 3 (0.4%) patients with TRYDONIS / RIARIFY and IND/GB, respectively;
- Acute myocardial infarction which led to study medication discontinuation of 4 (0.5%) patients in the IND/GB group;
- Lung neoplasm malignant which led to study medication discontinuation of 3 (0.4%) and 1 (0.1%) patients with TRYDONIS / RIARIFY and IND/GB, respectively;
- Pneumonia (PTs of pneumonia and pulmonary tuberculosis) which led to study medication discontinuation of 3 (0.4%) and 1 (0.1%) patients with TRYDONIS / RIARIFY and IND/GB, respectively;
- Sudden cardiac death which led to study medication discontinuation of 3 (0.4%) patients in the IND/GB group.

Of the 101 TEAEs leading to study medication discontinuation, 5 were assessed to be related to treatment; 2 TEAEs in 2 patients with TRYDONIS / RIARIFY (1 event of dry cough and 1 event of headache) and 3 TEAEs in 2 patients with IND/GB (1 event of eye allergy, 1 event of itching with exanthema and 1 event of itch on all body). All these events were mild or moderate in intensity and 1 event resolved by the end of the study (PT: cough).

In study TRIPLE 7, TEAEs leading to study medication discontinuation were reported in 11 (1.9%) and 13 (2.2%) patients with TRYDONIS / RIARIFY and Fluticasone/Vilanterol + Tiotropium, respectively.

The majority of TEAEs that led to study medication discontinuation by PT were reported in ≤ 2 patients in either treatment group; the only TEAE reported in > 2 patients was COPD exacerbation which led to study medication discontinuation of 3 (0.5%) patients in each treatment group.

Of the 26 TEAEs leading to study medication discontinuation, 4 were assessed to be related to treatment; 2 TEAEs in 2 patients with TRYDONIS / RIARIFY (1 event of papule and 1 event of urinary retention) and 2 TEAEs in 2 patients with Fluticasone/Vilanterol + Tiotropium (1 event of muscle spasms and 1 event of dysgeusia). All these events were mild or moderate in intensity and resolved by the end of the study.

Post marketing experience

The following analysis refers to spontaneous reports of ADRs collected for TRIMBOW / TRYDONIS / RIARIFY received by the MAH and its partners in the period from 31 July 2017 (i.e. date of first launch of the product) to 31 January 2018 (the reference period).

The patient exposure in the reference period was calculated from the available sales volumes in the countries where the product is marketed. Especially during the initial phase of a product to be launched in more than one market, such sales data may overestimate the actual exposure by assuming that all wholesaler stocks are dispensed to patients, and also due to the fact that it does not account for patients' non-compliance with the prescribed amount of dispensed drug (e.g. 2 puffs bid). Finally, the product is currently sold in multipacks containing either 2 or 3 canisters each, thereby introducing another bias for the proper calculation.

In the reference period, a total number of 32 Individual Case Safety Reports (ICSRs, 5 serious and 27 non-serious, including spontaneous cases, literature cases, cases from regulatory authorities and cases from non-interventional studies) corresponding to 53 ADRs, were collected.

No significant safety information concerning serious and non-serious ADRs, fatal cases, drug interactions, drug abuse or misuse, experience in special patient groups or during pregnancy or lactation, or effects of long-term treatment has been reported in the post-marketing experience.

Overall, the safety profile of the product in COPD patients remains unchanged.

2.5.1. Discussion on clinical safety

Focus was made on safety data as generated in the pivotal study TRIPLE 8 in order to assess the potential (negative) effects if an inhaled corticosteroid is added to dual treatment with bronchodilators in patients with advanced COPD. These results are considered to be more important than those obtained in study TRIPLE 7 because of the longer treatment duration (52 weeks vs. 26 weeks) and the study design (double-blind, double-dummy vs. open label). In addition, results of the integrated safety analysis were provided by the applicant by pooling data from trials TRIPLE 5, TRIPLE 6, TRIPLE 7 and TRIPLE 8. The integrated safety analysis was used to update SmPC Section 4.8.

The safety population supporting the extension of indication comprised a total of 764 subjects treated with the closed triple combination TRYDONIS / RIARIFY in Study TRIPLE 8. About 88.7% of those patients received at least 48 weeks of study treatment. Similar to prior studies patients with significant cardiovascular (CV) disease were excluded. Overall, the safety database is considered to be adequate for the proposed extension of indication.

The percentage of patients who have had a fatal outcome was in the range expected for this population of COPD patients. No consistent between-groups differences or imbalances were noted for TEAEs having higher incidence rates. Random effects are most likely responsible for minor imbalances seen for TEAEs occurring in fewer patients.

Notable, in study TRIPLE 7, one patient had suddenly and unexpectedly died a few days only after having had an uneventful study visit 3. The case was reported by the investigator as «respiratory failure», but in this case autopsy results clearly pointed towards an acute and purulent infection of the lung as the direct cause of death. In study TRIPLE 8, another patient (#616803031) was admitted to the ICU of a remote

hospital, underwent cardiopulmonary resuscitation and died two days later. The applicant stated that the event term reported by the investigator («*acute respiratory failure*», coded PT: *acute respiratory failure*) was not challenged, thus accepting the «primary cause of death». No compelling arguments and well-founded epicrisis were forwarded by the applicant why an (acute) infectious pulmonary event (leading to an acute coronary syndrome) was excluded this second patient. Thus and in conclusion, based on these two examples, doubts remain on whether due care and diligence were exercised by the applicant (or its service providers) throughout trial conduct in fully assessing fatal / serious events and potential COPD exacerbations.

There were 32 events of treatment-emergent pneumonia (including PTs of bronchopneumonia, interstitial lung disease, lobar pneumonia, pneumonia, pneumonia bacterial, pneumonia streptococcal, pneumonia viral and pulmonary tuberculosis) reported in 28 (3.7%) patients with TRYDONIS / RIARIFY and 29 events reported in 27 (3.5%) patients with IND/GB. Only one confirmed event of pulmonary tuberculosis was reported in 1 (0.1%) patient with IND/GB and none with TRYDONIS / RIARIFY. The majority of reported pneumonias were moderate in intensity and most of them resolved by the end of the study. A total of 18 serious pneumonias were reported in 18 (2.4%) patients with TRYDONIS / RIARIFY and 18 serious pneumonias were reported in 17 (2.2%) patients with IND/GB. None of the serious pneumonias were considered related to the study treatment and 1 non-serious pneumonia of moderate intensity with TRYDONIS / RIARIFY was considered related to the study treatment.

ICS-containing treatments are known to increase the risk of pneumonia in COPD patients. This signal was first reported in a large clinical trial of 3 years treatment duration, comparing a fluticasone propionate/salmeterol combination with its component parts and placebo (TORCH study, *Calverley et al 2007*). Based on its results, the CHMP Pharmacovigilance Working Party concluded in 2010 that treatment with an ICS, either alone or in combination with a LABA, increases the risk of pneumonia in patients with COPD.

On 27 April 2015, the European Commission triggered a referral under Article 31 of Directive 2001/83/EC. The PRAC review confirms that COPD patients treated with inhaled corticosteroids are at increased risk of pneumonia; however the Committee's view is that the benefits of inhaled corticosteroids continue to outweigh their risks. The PRAC also looked whether there were any differences in the risk of pneumonia between these products, and did not find conclusive evidence of such difference. In addition, update of the product information including a specific warning in SmPC Section 4.4 was requested for all ICS containing products with a COPD indication to adequately reflect the current knowledge.

The provided data on pneumonia are not suggestive of a relevantly increased risk of pneumonia when an ICS is added to double bronchodilator therapy. In study TRIPLE 8, the pneumonia event rate per 1'000 subject-years under triple therapy (44.6) was slightly higher than those observed in the pivotal trials endorsing the initial marketing authorisation (TRIPLE 5: 38.9; TRIPLE 6: 29.2). However, in contrast to other studies comparing ICS/LABA/LAMA (e.g. Lipson DA at al. 2018), no higher risk was observed when adding an ICS to double bronchodilator therapy (IND/GB: 41.0). The interpretation of these observations is somehow difficult, but most likely the sample size/statistical power of TRIPLE 8 was not large enough to detect a difference among groups, even if one may have been present. Thus, at the time being no firm conclusions can be drawn given the limited nature of the data.

About 60% of patients of the safety population were reported to suffer from vascular disorders (452 patients [59.2%] in TRYDONIS / RIARIFY group and 480 patients [62.5%] in IND/GB group), with hypertension being the most frequent PT (54.6% and 57.8% of patients, respectively). Pre-existing cardiac disorders were reported in 198 patients (25.9%) of group CHF 5993 pMDI and 214 patients (27.9%) of group IND/GB.

Note: As mentioned earlier, inclusion/ exclusion criteria excluded patients with clinically significant cardio-vascular conditions from study participation. Also, in contrast to studies TRIPLE 5 and TRIPLE 6, the composite endpoint “major adverse cardiovascular events (MACE)” was not (centrally) adjudicated.

A slightly higher incidence in older patients was observed in the analyses considering all TEAEs (category “Total AEs”) and nervous system disorders while no clear signal of an increased risk with increasing age was found for any of the other categories of TEAEs.

The incidences of the treatment discontinuations in both studies are balanced across the different treatment groups.

- *ADRs proposed for inclusion in the PI*

Based on the safety data submitted, the following additional ADRs are proposed for inclusion in the TRYDONIS / RIARIFY SmPC: pharyngeal erythema, pharyngeal inflammation and dry throat (SOC: Respiratory, Thoracic and Mediastinal Disorders), (aphthous) stomatitis (SOC: Gastrointestinal Disorders). In addition, changes in frequency are proposed for the following existing ADRs in the TRYDONIS / RIARIFY SmPCX, based on the frequency reported in studies TRIPLE 5, TRIPLE 6, TRIPLE 7 and TRIPLE 8: hypertension from “rare” to “uncommon”; dysuria and urinary retention from “uncommon” to “rare” and asthenia from “uncommon” to “rare”, respectively. This is acceptable and supported by the safety data provided in the application.

Additionally in section 4.4 of the SmPC, a paragraph on the risk of visual disturbance is added following beclometasone PSUSA/00000306/201612 procedure and the PRAC recommendation dated July 2018. The ADR table in section 4.8 is updated accordingly.

2.5.2. Conclusions on clinical safety

The safety profile of TRYDONIS / RIARIFY in study TRIPLE 8 was in line with the pharmacologic class of each component and with the dual combination IND/GB. The known risk of pneumonia with ICS-containing products in COPD patients has to be taken into account when balancing the benefit against the risk.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 6.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 6.0 with the following content:

Safety concerns

Important identified risks	/
Important potential risks	- Cardio- and cerebrovascular events
Missing information	/

The list of safety concerns was updated to be in line with GVP Module V, revision 2 and focuses now on the risks that are likely to have an impact on the risk-benefit balance of the product.

Pharmacovigilance plan

Study (Study short name, and title) Status (planned/on-going)	Summary of objectives	Safety concerns addressed	Milestones (Required by regulators)	Due dates
Category 1 – Imposed mandatory additional Pharmacovigilance activities which are conditions of the marketing authorisation				
None	None	None	None	None
Category 2 – Imposed mandatory additional Pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None	None	None	None	None
Category 3 – Required additional Pharmacovigilance activities				
None	None	None	None	None

Having considered the data submitted, the CHMP agrees that Routine pharmacovigilance is sufficient to identify and characterise the risks of the product. The CHMP also considered that Routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Pharmacovigilance activities
Cardio- and cerebrovascular events	-Statement in section 4.4 and labelled in section 4.8 of the SmPC -Statement in section 2 and in section 4 of the PL.	Routine PhV activities also includes the monitoring of the results of the PASS on cardio- and cerebrovascular outcomes (EUPAS5035).

The CHMP, having considered the data submitted, was of the opinion that the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8 and 5.1 of the SmPC have been updated. In addition, a new warning with regard to the risk of visual disturbance associated with beclametasone has been added to the product information. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Ireland.

2.7.1. User consultation

A justification for not performing a user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the changes are minimal and would not affect the results of the original user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

TRYDONIS / RIARIFY is a triple combination of an ICS, LABA and LAMA. The product is a fixed dose combination of BDP, FF and GB and formulated as a HFA solution to be delivered via a pMDI with a nominal dose per actuation of BDP, FF and GB of 100 µg, 6 µg and 12.5 µg, respectively.

The approved indication is:

"Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist (for effects on symptoms control and prevention of exacerbations see section 5.1)."

COPD is a progressive disease characterised by increasing obstruction to airflow and the progressive development of respiratory symptoms including chronic cough, increased sputum production, dyspnoea and wheezing. The objective of pharmacological treatment of is to prevent and control symptoms, reduce the frequency and severity of exacerbations, and improve general health status and exercise tolerance.

Smoking cessation (including passive smoking) is extremely important. Ideally treatment of COPD would slow its progression but this has never been convincingly demonstrated. Long term domiciliary oxygen has been shown to prolong life but confines the patient to home for protracted periods. In recent years there has been increasing emphasis on physical training and rehabilitation. Moderate and severe COPD exacerbations are generally treated with antibiotics and oral corticosteroids. Maintenance treatment is by combinations of oral and inhaled bronchodilators and anti-inflammatory agents.

3.1.2. Available therapies and unmet medical need

Despite the availability of a multiplicity of pharmacological treatments none of them modifies the progress of the disease and none can be considered to have a really major benefit on its most common symptoms of cough, breathlessness, excess sputum production, and thoracic discomfort due to hyperinflation.

ICS/LABA combination products are considered key to the symptomatic management of COPD. The combination has been shown to improve lung function, health status, and to reduce COPD exacerbations compared with either agent alone. LAMAs have been shown to improve lung function, relieve symptoms, increase exercise capacity, improve quality of life, and reduce COPD exacerbations to a greater extent

than short-acting bronchodilators. As disease severity increases, COPD treatment guidelines recommend an incremental approach to pharmacological treatment, involving the use of combinations of drug classes with different or complementary mechanisms of action (GOLD 2018).

3.1.3. Main clinical studies

The main phase 3 clinical study supporting this extension of indication is one pivotal study (study TRIPLE 8). In this randomised, double-blind, double-dummy, 2-arm parallel group study involving 1532 patients with COPD, the fixed combination of BDP/FF/GB were compared with the dual combination IND/GB over 52 weeks. The primary outcome was the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment.

The inclusion and exclusion criteria for Study TRIPLE 8 were consistent with those from Study TRIPLE 5 and study TRIPLE 6 which were pivotal for the initial MAA.

3.2. Favourable effects

The currently approved indication wording "…[COPD patients] who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist" highlights the lack of evidence to claim a step-up indication from the combination of a long-acting muscarinic receptor antagonist (LAMA) and a long-acting beta2 agonist (LABA) due to the absence of the combination of LAMA and LABA as comparator (e.g. IND/GB) in the pivotal Phase III study at time of the MAA of TRYDONIS / RIARIFY, a triple combination of an inhaled corticosteroid (ICS), and LABA and LAMA.

In study TRIPLE 8 the MAH demonstrates advantages for the fixed combination of BDP/FF/GB over the dual therapy IND/GB in symptomatic COPD patients with a risk of exacerbation. In the ITT population, the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment was significantly lower with BDP/FF/GB than with IND/GB, with a rate ratio of 0.848 (95% CI [0.723, 0.995], p-value=0.043) indicating a 15% reduction in the exacerbation rate. Overall, the applicant has demonstrated the superiority of the triple combination over the dual components.

3.3. Uncertainties and limitations about favourable effects

Notable, the p-value of the primary analysis of the primary endpoint (ITT dataset) are slightly less than the conventional 0.05 significance level (p=0.043). The upper limit of the 95% CI for the adjusted exacerbation rate ratio was 0.995. Results of the PP population confirmed the estimated effect size, but barely missed statistical significance (p=0.050, upper limit of 95% CI=1.000).

The consistency of statistical significance is not guaranteed over a broad range of primary analyses and sensitivity analyses. The following analyses do not or did not yield a significant result at a p-level of <0.05:

- time to first moderate or severe COPD exacerbation (p=0.219);

- FEV1 responder analysis (change from baseline to week 52 ≥100 mL; p=0.198);

- missing data imputation for COPD exacerbation rate (CR, J2R);

- use of other time gaps in order to decide whether two (or more) episodes represent a single (or new) exacerbation episode (15 or 20 days);

- SGRQ responder analysis (change from baseline to week 52 ≤-4 units; p=0.068).

The difference in moderate-to-severe COPD exacerbations over 52 weeks, in absolute terms (an estimated reduction in 0.09 exacerbations per patient per year, from 0.594 with LABA/LAMA to 0.504

with the triple therapy), is considered modest from a clinical perspective. Nevertheless, it is conceded that the chosen study design and population – in contrast to other recently published studies - did not penalise the comparator group nor did it inflate artificially the rate of moderate and severe COPD exacerbations.

Doubts have emerged regarding the internal validity and data quality of the study. As is only now apparent from the requested documentation which was not submitted with the initial application (i.e. the so-called Data Review Report), the secondary population for analysis (i.e. the per-protocol population) modified after unblinding. Though these post hoc modifications applied to the PP population appear to have had no impact on the analysis of the primary response variable, they raise doubts as to the quality of reported data and the understanding of the applicant for GCP requirements and disclosure obligations of an applicant in the context of a marketing authorisation procedure.

In addition, the MAH has undertaken limited efforts to assess and assure the reliability and integrity of the trial systems against own written standards and applicable laws and regulations. Annual audit plans / programmes were finalised with significant delay and for the pivotal study TRIPLE 8, only a single site audit was performed that followed a proactive and risk-based approach. This finding may also challenge the internal validity of the study / data reliability.

3.4. Unfavourable effects

The safety profile of TRYDONIS / RIARIFY in study TRIPLE 8 was in line with the pharmacologic class of each component and also with the comparator IND/GB. The following additional ADRs are proposed for inclusion in the TRYDONIS / RIARIFY label: pharyngeal erythema, pharyngeal inflammation and dry throat (SOC: Respiratory, Thoracic and Mediastinal Disorders), (aphthous) stomatitis (SOC: Gastrointestinal Disorders). In addition, changes in frequency are proposed for the following existing ADRs in the TRYDONIS / RIARIFY label, based on the frequency reported in studies TRIPLE 5, TRIPLE 6, TRIPLE 7 and TRIPLE 8: hypertension from “rare” to “uncommon”; dysuria and urinary retention from “uncommon” to “rare” and asthenia from “uncommon” to “rare”, respectively.

Overall, the AE profile of TRYDONIS / RIARIFY is well understood; none of the active substances is a new active substance and all have been used over periods of at least years individually and in combination in treating COPD patients of various grades of severity. To date, 3106 patients have been treated with the triple combination (counting the free and fixed combinations) many of them for 52 weeks. There are no evident new safety signals and the treatment associated unwanted effects are of a frequency and nature to be expected given the nature of the clinical development.

3.5. Uncertainties and limitations about unfavourable effects

Pneumonia data collected for TRYDONIS / RIARIFY in study TRIPLE 8 and previous trials are not suggestive of a relevantly increased risk of pneumonia when BDP is added to a LABA LAMA combination. In study TRIPLE 8, the pneumonia event rate per 1’000 subject-years under triple therapy (44.6) was slightly higher than those observed in the pivotal trials endorsing the initial marketing authorisation (TRIPLE 5: 38.9; TRIPLE 6: 29.2). However, no firm conclusions can be drawn in that respect given the limited nature of the data. Due to the low observed event rate, study TRIPLE 8 (32 pneumonia events) and the pooled analysis integrating data from studies TRIPLE 5 to TRIPLE 8 (100 pneumonia events) only had low statistical power to generate a robust estimate of the true risk of pneumonia. Moreover, data and analyses presented are not sufficient to establish whether the risk of pneumonia of an ICS-containing regimen varies with the corticosteroid moiety and/or the formulation itself. Latest scientific data generated in 2015 in the framework of the referral triggered by the European Commission confirmed the risk of pneumonia with these combination products, but did not find any conclusive evidence of differences in this risk for different products. Differences in study design, methodology for confirming the

diagnosis of pneumonia, sample size and populations assessed also do not allow drawing meaningful conclusions of whether TRYDONIS / RIARIFY has a more favourable benefit-risk profile in that respect than the triple combination assessed in the IMPACT study.

3.6. Effects Table

Table 23: Effects Table for [TRYDONIS / RIARIFY, COPD]

Effect	Short description	Unit	BDP/FF/GB	IND/GB	Uncertainties / Strength of evidence	References
Favourable Effects						
COPD exacerbation rate	rate of moderate-to-severe COPD exacerbations over 52 weeks		0.504	0.594	Rate ratio (95% CI, p-value) 0.848 (0.723, 0.995, 0.043)	TRIPLE 8
Unfavourable Effects						
Pneumonia		Event rate per 1000 subjects	44.6	41.0	ICS-containing treatments are known to increase the risk of pneumonia in COPD patients.	TRIPLE 8
MACE			25.1	59.4	Results may be biased due to the non-adjudication of MACEs for TRIPLE 8 study, see also Annex 1 Q23	TRIPLE 8
Class effects of ICS/LAMA/LABA	Muscle spasms, dry mouth, oral candidiasis, dysphonia, headache, oropharyngeal pain, sinus tachycardia				Treatment adverse events were of similar natures. No particular pattern or concern emerges with respect to BDP/FF/GB	TRIPLE 8

Abbreviations: See list of Abbreviations

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

For patients at risk of COPD exacerbations, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document for the management of patients with COPD recommends an incremental approach to therapy, beginning with either a LAMA, LAMA/LABA, or ICS/LABA therapy [GOLD, 2018]. If patients develop further exacerbations, escalation of pharmacologic therapy is recommended. For example, patients on LAMA therapy can be switched to a LAMA/LABA or ICS/LABA with further escalation to triple ICS/LAMA/LABA therapy or those on a dual therapy can be switched to triple therapy if required.

In other words, triple therapy is currently thought to be best used as an escalation therapy for those incompletely controlled with dual therapy, either ICS/LABA or LABA/LAMA (GOLD 2018). The applicant has demonstrated the superiority (although marginal statistically significant) of the triple combination over LAMA/LABA combination.

From a safety point of view, the provided data on pneumonia are not suggestive of a relevantly increased risk of pneumonia when an ICS is added to double bronchodilator therapy. In contrast to other studies comparing ICS/LABA/LAMA (e.g. Lipson DA at al. 2018), no higher risk was observed when adding an ICS to double bronchodilator therapy. However, the interpretation of these observations is somehow difficult,

but most likely the sample size/statistical power of TRIPLE 8 was not large enough to detect a difference among groups, even if one may have been present.

3.7.2. Balance of benefits and risks

Although the effect on exacerbation rate is marginal statistically significant and modest from a clinical perspective, the applicant has sufficiently shown that the decrease in exacerbations demonstrated is sufficient to offset the well-known rate of pneumonia in patients taking an ICS containing triple therapy compared to patients on dual LABA/LAMA therapy in patients with moderate to severe COPD.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of TRYDONIS / RIARIFY in the extended indication is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication, based on results from two Phase III studies: Triple 7 (CCD-05993AA1-07) and Triple 8 (CCD-05993AA1-08), to include maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist. Sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated accordingly to reflect the studies' results and add a new warning with regards to the risk of visual disturbance associated with beclometasone following the PSUSA recommendation PSUSA/00000306/201612. The package leaflet and the risk management plan (version 6.0) are updated accordingly.

In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives in the Package Leaflet.

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in

accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication, based on results from two Phase III studies: Triple 7 (CCD-05993AA1-07) and Triple 8 (CCD-05993AA1-08), to include maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist. Sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated accordingly to reflect the studies' results and add a new warning with regards to the risk of visual disturbance associated with beclometasone following the PSUSA recommendation PSUSA/00000306/201612. The package leaflet and the risk management plan (version 6.0) are updated accordingly.

Summary

Please refer to the scientific discussion Riarify EMEA/H/C/004836/WS1554/0002 and Trydonis EMEA/H/C/004702/WS1554/0002.

Attachments

1. SmPC, Annex II, Package Leaflet as adopted by the CHMP on 28 February 2019.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information (CCI) in "track changes" and with detailed justification by 15 March 2019. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/documents/regulatory-procedural-guideline/principles-be-applied-deletion-commercially-confidential-information-disclosure-emea-documents_en.pdf.

2. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.

4. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, or prior to the next regulatory activity, whichever is first. For additional guidance see chapter 4.1 of the *Harmonised Technical Guidance for eCTD Submissions in the EU*.