

Novartis Pharma GmbH, Germany

Seebri Breezhaler (glycopyrronium bromide, NVA237)
Ultibro Breezhaler (indacaterol maleate/glycopyrronium
bromide, QVA149)

CNVA237ADE01 Non-Interventional Study Final Report
(Recruitment Phase 3)

**Die ambulante Versorgung mit langwirksamen
Bronchodilatoren: COPD-Register in Deutschland**
(English translation: **Outpatient care with long-acting
bronchodilators: COPD register in Germany**)

REDACTED STUDY REPORT

Author



Document Status Final

Date of final version 27 October 2021
of the study report

EU PAS register EUPAS4207
number

<http://www.encepp.eu/encepp/viewResource.htm?id=6316>

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NIS Report Template Version 3.0 dated 14-August-2017

PASS information

Title	Die ambulante Versorgung mit langwirksamen Bronchodilatoren: COPD-Register in Deutschland (English translation: Outpatient care with long-acting bronchodilators: COPD register in Germany)
Version identifier of the final study report	1.0 (Recruitment Phase 3)
Date of last version of the final study report	27 October 2021
EU PAS register number	EUPAS4207 http://www.encepp.eu/encepp/viewResource.htm?id=6316
Active substance	Glycopyrronium bromide (NVA237) and indacaterol maleate/glycopyrronium bromide (QVA149)
Medicinal product	Seebri Breezhaler and Ultibro Breezhaler
Product reference	Seebri Breezhaler: EU/1/12/788/001-008 Ultibro Breezhaler: EU/1/13/862/001-008
Procedure number	Seebri Breezhaler (EMA/H/C/002430) Ultibro Breezhaler (EMA/H/C/002679)
Marketing authorization holder	Novartis Europharm Limited
Joint PASS	No
Research question and objectives	DACCORD Recruitment Phase 3 was conducted in patients with chronic obstructive pulmonary disease (COPD) who had been receiving a long-acting beta ₂ -agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) plus an inhaled corticosteroid (ICS) for at least 6 months prior to entry. The aim was to evaluate the effectiveness and safety over 1 year of a LABA/LAMA fixed-dose combination (FDC) in patients with COPD after switching from LABA+LAMA+ICS maintenance therapy, in comparison to the control arm, which was patients continuing LABA+LAMA+ICS maintenance therapy.
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1 Abstract

Title

Die ambulante Versorgung mit langwirksamen Bronchodilatoren: COPD-Register in Deutschland (English translation: Outpatient care with long-acting bronchodilators: COPD register in Germany)

Version and date

1.0 (Recruitment Phase 3), 27 October 2021

Name and affiliation of main author

██████████, Novartis Pharma GmbH, Germany

Keywords

Chronic obstructive pulmonary disease; exacerbations; symptoms

Rationale and background

A number of interventional randomized controlled trials (RCTs) have investigated step-down from inhaled triple therapy to a long-acting β_2 -agonist/long-acting muscarinic antagonist (LABA/LAMA combination) in patients with chronic obstructive pulmonary disease (COPD). RCTs generally recruit highly selected populations, often excluding patients with significant or unstable comorbidities. Although results from such RCTs can be helpful in informing treatment decisions, data that are more representative of 'real-life' populations are important. The main aim of Study CNVA237ADE01 (DACCORD) was to generate data on the course of COPD under real-life treatment conditions. In an analysis of data from DACCORD Recruitment Phase 1, more than a third of patients were receiving inhaled corticosteroid (ICS)-containing therapy, most commonly inhaled triple therapy. This suggests that many patients in Germany may be receiving ICS unnecessarily, and so may be candidates for step-down to a LABA/LAMA.

Research question and objectives

DACCORD Recruitment Phase 3 was conducted in patients with COPD who had been receiving inhaled triple therapy for at least 6 months prior to entry. The aim was to evaluate the effectiveness and safety over 1 year of a LABA/LAMA fixed-dose combination (FDC) in patients with COPD after switching from inhaled triple (LABA+LAMA+ICS) maintenance therapy, in comparison to the control arm, which was patients continuing inhaled triple therapy.

The primary objective of this phase of DACCORD was to assess the duration until worsening of COPD, defined as the occurrence of a moderate or severe exacerbation or of a clinically relevant worsening in health-related quality of life (i.e., an increase from baseline in COPD Assessment Test [CAT] score of ≥ 2 points) in patients with COPD treated with LABA/LAMA FDC after switching from inhaled triple therapy, versus patients continuing on inhaled triple therapy, assessed over the 1 year follow-up period.

Study design

DACCORD was a longitudinal, prospective non-interventional study, which sought to generate data on the course of COPD under real-life treatment conditions. The decision to treat patients was taken prior to inclusion in the study, and there were no limitations on concomitant treatment, or on changing, adding, or discontinuing treatment. Patients in Recruitment Phase 3 were followed for 1 year; given the non-interventional nature of the study, the only data collected were from assessments that would typically be conducted as part of the standard care of patients with COPD.

Setting

Primary and secondary care throughout Germany.

Subjects and study size, including dropouts

The inclusion criteria were:

- adults aged ≥ 40 years
- written informed consent for participation obtained from the subject
- diagnosed COPD
- inclusion in the Disease Management Program (DMP) for COPD OR fulfilling the criteria for inclusion in DMP for COPD
- LABA+LAMA+ICS therapy for at least 6 months prior to baseline
- decision to continue LABA+LAMA+ICS or switch to LABA/LAMA FDC treatment at study entry
- available blood eosinophil count (determined not longer than 1 year prior to inclusion).

Given the non-interventional nature of the study, the decision to continue or switch medication was to have been made prior to inclusion in DACCORD. Current, ex- and never-smokers were eligible.

Exclusion criteria were:

- unconfirmed diagnosis of COPD
- inclusion in DMP program for asthma
- patients not under regular supervision of the treating physician for the duration of the study
- foreseeable problems in follow-up of the patients across study duration
- current participation in an RCT
- concomitant asthma or history of asthma diagnosis.

The study aimed to demonstrate for Recruitment Phase 3 that the time to treatment failure, defined as a moderate or severe exacerbation or an increase in CAT score of ≥ 2 points, would be similar in both treatment arms, i.e., that the one-sided, 97.5% confidence interval for the hazard ratio did not exceed 1.2. Data from Recruitment Phase 2 suggested that 35% of patients would experience treatment failure within 1 year; this translates into an exponential parameter λ of 0.43, assuming an exponential survival curve and taking '1 year' as the unit of measurement. Assuming 20% of patients withdraw from the study within the one-year observation period (corresponding to an exponential withdrawal ratio of 0.22), 2000 patients per arm would be necessary to be able to respond to this hypothesis with high significance (4000 patients in total).

However, recruitment into this phase was slower than anticipated, although fewer patients were withdrawing; recruitment into Phase 3 was terminated after 1185 patients were enrolled, 361 of whom switched to a LABA/LAMA FDC upon study entry. Under the assumption that 14% of patients would withdraw from the study within the 1-year follow-up (translating into an exponential drop-out-rate of 0.15), based on the above statistical calculations, a power of 28.8% would be achieved in the registry arm with these 361 patients. The total number of 824 patients in the larger registry arm (LABA+LAMA+ICS therapy) was considered sufficient to investigate relevant subpopulations.

Variables and data sources

Since this was a non-interventional study, visit schedules could not be mandated in the protocol. It was anticipated that most patients would visit their physician once every three months (prescription of medication is usually quarterly); the COPD DMP mandates a minimum of one visit per year.

At the baseline visit, data collected were: demographic and disease characteristics (including comorbidities and smoking status); differential blood count; prescribed COPD and non-COPD medication; CAT; modified Medical Research Council [mMRC] dyspnea scale; exacerbations in the 12 months prior to entry (defined based on prescription of oral steroids and/or antibiotics or hospitalization); and lung function. Data on differential blood count, prescribed COPD medication, exacerbations and CAT were collected every three months, with demographic and disease characteristics and lung function recorded at the end of study visit. The occurrence of adverse events (AEs) and serious adverse events (SAEs) was collected throughout the study.

Statistical methods

Categorical data were analyzed by presenting adjusted frequency tables (absolute and relative). For numerical data the sample statistics mean, standard deviation, median, minimum and maximum, and quartiles were calculated. Data measured several times during the study were analyzed by visit, presenting absolute differences to baseline for numerical data and shift tables for categorical data.

The primary objective was to assess the duration until a worsening of COPD defined as either occurrence of a moderate or severe exacerbations or a clinically relevant worsening of the health related quality of life (= a deterioration of 2 or more in CAT score). The comparison to analyze the effect of a change of the treatment scheme on this endpoint was done using a Cox regression analysis, with cohort as fixed factor. This was performed in the per protocol V4 set.

Results

These analyses are based on data from 1124 patients in the safety set (340 in the LABA/LAMA FDC group and 784 in the triple therapy group) and 967 patients in the per protocol V4 set (292 and 675 patients, respectively). A significantly lower percentage of patients in the LABA/LAMA FDC group had a worsening of COPD than in the triple therapy group (32.5% vs. 55.7%; $p < 0.001$). The time to COPD worsening was extended in the LABA/LAMA FDC group, although as fewer than 50% of patients had a worsening in this group it was only possible to calculate the median value in the triple therapy group. Both of the components contributed to this overall result, with a significantly lower percentage of patients in the LABA/LAMA FDC group having a worsening based on CAT alone or exacerbations alone. Consistent with the primary endpoint data, the percentage of patients exacerbating during the study was lower at each visit in the LABA/LAMA FDC group than the triple therapy group, and a significantly higher proportion of patients in the LABA/LAMA FDC group had a clinically relevant improvement from baseline in CAT total score.

A lower proportion of patients in the LABA/LAMA FDC group reported non-serious AEs overall (12.9% vs. 15.1%) and for the majority of MedDRA system organ classes, with the most commonly reported system organ class in both groups being respiratory, thoracic and mediastinal, followed by infections and infestations. The most frequent non-serious AEs by preferred term in both groups were related to COPD – most commonly COPD (i.e., exacerbations or worsening).

Similarly, the proportion of patients with an SAE was lower in the LABA/LAMA FDC group than the triple therapy group (7.9% vs. 13.8%), with the most commonly-reported MedDRA system organ class in both groups again being respiratory, thoracic and mediastinal, and the most frequently reported SAEs by preferred term being those related to the underlying condition. The majority of SAEs were not considered study related. Of these that were considered related, the percentage of patients with at least one SAE was lower in the LABA/LAMA FDC group (1.5% vs. 4.0%). A total of 21 patients died during the study, with a lower proportion of patients in the LABA/LAMA FDC dying than in the triple therapy group (0.9% vs. 2.3%). Five patients had SAEs with fatal outcome that were considered study related, all in the triple therapy group (and none in the LABA/LAMA FDC group).

Discussion

The overall aim of Recruitment Phase 3 of DACCORD was to evaluate the effectiveness and safety over 1 year in patients with COPD who were switching from inhaled triple therapy to a LABA/LAMA FDC, in comparison to those who continued inhaled triple therapy. Importantly, the study was non-interventional (with treatment decisions not influenced by study participation), and patients received standard clinical care at primary and secondary practices throughout Germany.

During the 1-year follow-up period, patients switched to a LABA/LAMA FDC had overall better outcomes than those who continued inhaled triple therapy, with a lower percentage having a worsening of COPD (in terms of the overall analysis and the two components), an extension to the time to worsening of COPD, a reduction in exacerbation occurrence, and an improvement in health-related quality of life (CAT total score).

Overall, the safety and tolerability profile of the LABA/LAMA FDC group was better than that of the triple therapy group, with a lower proportion of patients experiencing non-serious AEs, SAEs or fatal adverse

events in the LABA/LAMA FDC group. Few patients in either treatment group were considered to have events considered related to the study – and most of the events that are recorded as being study related are due to the investigator not assigning causality.

Recruitment into this phase of DACCORD was not limited to specific molecules. A total of 58 patients in the safety set were receiving glycopyrronium bromide (one and 57 in the LABA/LAMA FDC and triple therapy groups, respectively) and 439 were receiving Ultibro Breezhaler (246 and 193, respectively). When analyzed in these patients, the occurrence of SAEs of special interest for glycopyrronium bromide or Ultibro Breezhaler were low. The results therefore do not change the overall risk-benefit profile of either Ultibro Breezhaler or Seebri Breezhaler.

Conclusion

Overall, DACCORD Recruitment Phase 3 builds on the results of Phases 1 and 2, providing useful data on the course of COPD in Germany, and supporting the potential benefit to selected patients in switching from triple therapy to a LABA/LAMA FDC. The safety data do not change the overall benefit-risk profile of glycopyrronium or the glycopyrronium/indacaterol FDC.

Marketing Authorization Holder(s)

Novartis Europharm Limited

Name(s) and Affiliation(s) of Principal Investigator(s)

[REDACTED], Germany

2 List of abbreviations

AE	adverse event
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CAT	COPD Assessment Test
CRF	case report/record form
CRO	contract research organization
DMP	Disease Management Program
ECG	electrocardiogram
eCRF	electronic case report form
FDC	fixed-dose combination
FEV ₁	forced expiratory volume in 1 sec
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	inhaled corticosteroid
LABA	long-acting beta ₂ -agonist
LAMA	long-acting muscarinic antagonist
MCID	minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
mMRC	modified Medical Research Council
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
SOP	standard operating procedure
WHO	World Health Organization

3 Investigators

Principal investigator: [REDACTED], Germany.

All other investigators are listed in Annex 1.

4 Other responsible parties

Not applicable.

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date	Comments
Start of data collection (Recruitment Phase 1)	5 November 2012	5 November 2012	Recruitment Phase 1
Registration in the EU PAS register	7 April 2014	7 April 2014	
Interim safety report 1	Not applicable	18 June 2015	Contains data from Recruitment Phases 1 and 2
Interim safety report 2	Not applicable	30 August 2016	Contains data from Recruitment Phases 1 and 2
Start of data collection (Recruitment Phase 3)	September 2017	18 January 2018	Recruitment Phase 3
Study report (Recruitment Phases 1 and 2)	Not applicable	25 January 2019	Study report for Recruitment Phases 1 and 2 is final; data for these Recruitment Phases are not contained in the current report.
End of data collection (Recruitment Phase 3)	1 July 2020	8 March 2021	This is the end of data collection for Recruitment Phase 3, which form the basis of the current report.
Final report of study results	1 July 2021	27 October 2021	Contains data from Recruitment Phase 3 only

6 Rationale and background

Randomized controlled trials (RCTs) generally recruit highly selected populations, often excluding patients with significant or unstable comorbidities. Although results from RCTs can be helpful in informing treatment decisions, data that are more representative of ‘real-life’ populations are important. The main aim of Study CNVA237ADE01 (DACCORD) was to

generate data on the course of chronic obstructive pulmonary disease (COPD) under real-life treatment conditions.

In 2017, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) treatment recommendations were amended. Dual bronchodilation comprising a long-acting beta₂-agonist (LABA) plus a long-acting muscarinic antagonist (LAMA), without an inhaled corticosteroid (ICS), became the preferred treatment option for patients who were symptomatic and at risk of exacerbations (GOLD D), symptomatic and then experienced further exacerbations (GOLD C), or at risk of exacerbations and then experienced persistent symptoms (GOLD B) (GOLD 2017). Inhaled triple therapy (LABA+LAMA+ICS) was recommended predominantly as step-up option for patients in GOLD D who develop further exacerbations when receiving LABA/LAMA.

In an analysis of data from DACCORD Recruitment Phase 1, more than a third of patients (independent of GOLD category) were receiving ICS-containing therapy, most commonly inhaled triple therapy (Buhl 2016). This suggests that many patients in Germany may be receiving ICS unnecessarily, and so may be candidates for step-down to a LABA/LAMA. Indeed, the recommendations for using ICS on top of LABA/LAMA for the management of COPD are based on limited evidence.

A number of interventional RCTs have investigated step-down from inhaled triple therapy to a LABA/LAMA combination. The WISDOM trial suggested that withdrawal of ICS is non-inferior compared to continuing inhaled triple therapy in terms of prevention of exacerbations in patients with severe COPD and a history of at least one exacerbation (Magnussen 2014). Furthermore, a *post-hoc* subgroup analysis of WISDOM indicated that only distinct patient populations may benefit from ICS, potentially patients with elevated blood eosinophil levels, especially in the presence of frequent (≥ 2) exacerbations (Ferguson 2020). These findings were supported by the SUNSET trial, in which de-escalation from inhaled triple therapy to indacaterol/glycopyrronium was non-inferior to continuation of inhaled triple therapy in terms of lung function, with no difference between arms in exacerbations (Chapman 2018). As with WISDOM, the population that could potentially benefit from ICS use was those with higher blood eosinophil levels (≥ 300 cells/ μ L).

7 Research question and objectives

DACCORD Recruitment Phase 3 was conducted in patients with COPD who had been receiving inhaled triple therapy for at least 6 months prior to entry. The aim was to evaluate the effectiveness and safety over 1 year of a LABA/LAMA fixed-dose combination (FDC) in patients with COPD after switching from inhaled triple (LABA+LAMA+ICS) maintenance therapy, in comparison to the control arm, which was patients continuing inhaled triple therapy.

The primary objective of this phase of DACCORD was to assess the duration until worsening of COPD, defined as the occurrence of a moderate or severe exacerbation or of a clinically relevant worsening in health-related quality of life (i.e., an increase from baseline in COPD Assessment Test [CAT] score of ≥ 2 points) in patients with COPD treated with LABA/LAMA FDC after switching from inhaled triple therapy, versus patients continuing on inhaled triple therapy, assessed over the 1 year follow-up period.

Secondary objectives for Recruitment Phase 3* were:

- Documentation of diagnostic measures performed during an outpatient visit.
- Documentation of co-morbidities.
- Course of progression of COPD.
- Time until first occurrence of moderate or severe exacerbations.
- Time until a clinically relevant worsening of health-related quality of life (worsening from baseline in CAT score of ≥ 2 points).
- Number, severity, and therapy of exacerbations, and time to next exacerbation.
- Annualized rate of moderate or severe exacerbations.
- Percentage of patients with a clinically relevant worsening from baseline of their health-related quality of life.
- Course of lung function.
- Evaluation of the predictive value of blood eosinophil count for therapy success.
- Safety and tolerability of therapies (in terms of non-serious and serious adverse events).

*Note: The overall DACCORD observational plan includes a number of additional secondary objectives that, due to the design of Recruitment Phase 3 (and in particular the requirement to have received LABA+LAMA+ICS therapy for at least 6 months prior to entry), only apply to Recruitment Phases 1 and 2. These objectives were reported in a previous study report [\[Bernschneider. CNVA237ADE01 Non-Interventional Study Final Report \(Recruitment Phases 1 and 2\). 25 January 2019\]](#).

8 Amendments and updates to the protocol

Amendments 1 to 3 involved Recruitment Phases 1 and 2 only, and are described in the Recruitment Phases 1 and 2 study report. None of the below amendments applied to Recruitment Phases 1 or 2.

Number	Date	Section of study protocol	Amendment or update	Reason
4	21 September 2017	All sections	This amendment added Recruitment Phase 3 to the study, resulting in additional inclusion/exclusion criteria, and altering the assessments performed.	To extend the overall study. None of these amendments applied to Recruitment Phases 1 or 2.
5	10 April 2018	Not applicable	Change in honorarium fee.	Practical consideration.
6	06 November 2018	Section 9.4 (visit schedule)	To enable optional documentation of eosinophil values at Visits 1–4 (in addition to baseline).	To be able to analyze changes in eosinophil values over time.

Number	Date	Section of study protocol	Amendment or update	Reason
7	08 May 2019	Not applicable	Change in honorarium fee.	Amendment 6 made documentation during visits more time consuming.
8	4 August 2020	Patient numbers	To terminate patient recruitment	It was not feasible to enroll the originally planned number of patients within a reasonable timeframe. A total of 1185 patients were included in Recruitment Phase 3 at that point (361 switched to LABA/LAMA and 824 patients continuing inhaled triple therapy). It was considered that these numbers would still be sufficient for the study aim.

9 Research methods

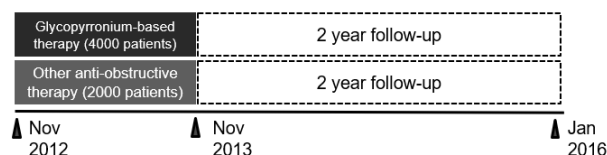
9.1 Study design

DACCORD was a longitudinal, prospective non-interventional study, which sought to generate data on the course of COPD under real-life treatment conditions. The decision to treat patients was taken prior to inclusion in the study, and there were no limitations on concomitant treatment, or on changing, adding, or discontinuing treatment.

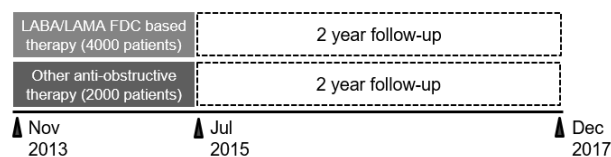
Recruitment into the study was in three phases, as illustrated in [Figure 9-1](#). Recruitment Phases 1 and 2 were described in the previous study report. Recruitment Phase 3 was of patients with COPD who had been receiving inhaled triple therapy for at least 6 months, and who were either continuing inhaled triple therapy or were being switched by their physician to a LABA/LAMA FDC, the aim being to recruit patients in an approximate equal ratio. It should be noted that there was no randomization of patients, and so there was no balancing of baseline characteristics, as would typically be the case in a RCT.

Figure 9-1 Recruitment phases of CNVA237ADE01

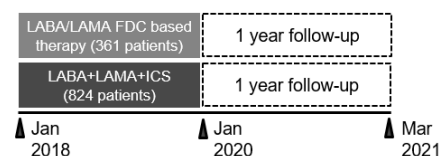
Recruitment Phase 1



Recruitment Phase 2



Recruitment Phase 3



Given the non-interventional nature of the study, the only data collected were from assessments that would typically be conducted as part of the standard care of patients with COPD. Visits were suggested at a three-monthly interval (in accordance with typical COPD management), and patients in Recruitment Phase 3 were followed for one year.

Data were reported by investigators via electronic case report forms (eCRFs) that were completed at study visits; since the schedule was only suggested and not mandated, many of these visits could be further than three months apart. The relationship of an adverse event to the study was the decision of the reporting investigator.

The start of Recruitment Phase 3 was submitted to the approving ethics committee as an amendment, receiving approval on 20 November 2017.

9.2 Setting

Primary and secondary care throughout Germany.

9.3 Subjects

The inclusion criteria were:

- adults aged ≥ 40 years
- written informed consent for participation obtained from the subject
- diagnosed COPD
- inclusion in the Disease Management Program (DMP) for COPD OR fulfilling the criteria for inclusion in DMP for COPD
- LABA+LAMA+ICS therapy for at least 6 months prior to baseline

- decision to continue LABA+LAMA+ICS or switch to LABA/LAMA FDC treatment at study entry
- available blood eosinophil count (determined not longer than 1 year prior to inclusion).

Given the non-interventional nature of the study, the decision to continue or switch medication was to have been made prior to inclusion in DACCORD. Current, ex- and never-smokers were eligible.

Exclusion criteria were:

- unconfirmed diagnosis of COPD
- inclusion in DMP for asthma
- foreseeable problems in follow-up of the patients across study duration
- current participation in an RCT
- concomitant asthma or history of asthma diagnosis.

9.4 Variables

9.4.1 Visit schedule

Since this was a non-interventional study, visit schedules could not be mandated in the protocol. It was anticipated that most patients would visit their physician once every three months (prescription of medication is usually quarterly); the COPD DMP mandates a minimum of one visit per year.

9.4.2 Effectiveness assessments

9.4.2.1 Assessment of effectiveness

At the baseline visit, data collected in eCRFs were: demographic and disease characteristics (including comorbidities and smoking status); differential blood count; prescribed COPD and non-COPD medication; CAT; modified Medical Research Council [mMRC] dyspnea scale; exacerbations in the 12 months prior to entry (defined based on prescription of oral steroids and/or antibiotics or hospitalization); and lung function. The treating physician was also asked to document the reasons for changing (or not changing) the patient's COPD maintenance medication prior to study entry. Data on differential blood count, prescribed COPD medication, exacerbations and CAT were collected every three months, with demographic and disease characteristics and lung function recorded at the end of study visit.

9.4.3 Safety assessments

9.4.3.1 Assessment of safety

Safety assessments consisted of collecting all adverse events (AEs) and serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies.

9.4.3.1.1 Adverse events

AEs were defined as any untoward medical occurrence (unfavorable and unintended sign or symptom, complication, significant change of laboratory parameters or electrocardiogram [ECG] etc.) in a patient after the administration of the medication irrespective of the relation to the therapy or intended use. Non-serious exacerbations in which the physician did not suspect a causal link with glycopyrronium bromide or indacaterol/glycopyrronium were not to be reported as AEs. This is because an exacerbation is often accompanied by progression of COPD, and a significant reduction in the exacerbation risk was demonstrated for this substance in Phase III studies. Note that all serious exacerbations, regardless of causality, were included in the analyses.

Each AE has to be documented in the eCRF independent of its causal relationship to the study. The physician has to report start and duration of the event and to assess the intensity and the causal relationship as well as to document the outcome and potential counteractive measures. Note that since patients could be receiving multiple COPD maintenance therapies, the assessment of causality is whether the event was related to the study, rather than related to study drug.

In general, SAEs and non-serious AEs are differentiated. Both of these terms are used to describe AEs regardless of their relationship to study. For the purpose of the statistical analysis, events are further distinguished according to their relationship to study.

SAEs are all events that:

- are fatal
- are life-threatening
- require inpatient hospitalization or result in prolongation of existing hospitalization
- result in persistent or significant disability/incapacity
- result in a congenital anomaly/birth defect
- are medically important events, i.e. require medical or surgical intervention to prevent one of the other outcomes listed in the definition above.

Inpatient hospitalization was not to be considered an SAE, if any of the following was the case:

- Hospitalizations that had already been planned before inclusion into the study.
- Elective hospitalizations for treatment of preexisting conditions, which had no relationship to the study indication or to the study medication.
- Outpatient hospital treatments, which did not lead to hospitalization (in this context it had to be checked whether one of the other criteria was present, e.g. life-threatening event)
- Hospitalizations that were part of the normal treatment or control of the study indication and that were not caused by a progression of the disease.

The assessment of seriousness was only dependent on the presence of any of the above mentioned formal criteria and was independent of the question whether a causal relationship between the intake of the medication and the occurrence of the SAE was assumed.

All SAEs that occurred after baseline examination and up to 30 days after discontinuation of the study participation were to be documented in the eCRF. All SAEs that occurred after the 30 days deadline only had to be reported if causality was suspected.

Reoccurring events, complications or worsening of documented SAE were documented as follow-up reports.

9.4.3.1.2 Pregnancies and breastfeeding

To ensure patient safety, each pregnancy in a patient administered any Novartis preparation was to be reported to Novartis.

9.5 Data sources and measurement

All data were recorded by the investigating physician following standard clinical assessments. Given the observational nature of the study, there were no standardized procedures or centralized assessments, and the only training provided was on the study protocol and how to complete the eCRFs.

9.6 Bias

As the study was not randomized, confounding cannot be ruled out. The observational plan suggests the inclusion of a propensity score to adjust for possible confounding. Instead, multivariate regression analysis, including relevant factors, was performed.

For the primary analysis of time until worsening, a Cox regression analysis was used to control confounding, including age, sex, forced expiratory volume in 1 sec (FEV₁) percent predicted, CAT score, mMRC score, number of exacerbations during the previous 12 months, and smoking status at baseline.

To minimize selection bias, investigators were asked to recruit consecutive eligible patients. Observer bias was minimized by recording data following standard clinical assessments, and by including a comparator group.

9.7 Study size

Recruitment Phase 3 aimed to demonstrate that the time to treatment failure, defined as a moderate or severe exacerbation or an increase in CAT score of ≥ 2 points, would be similar in both treatment arms, i.e., that the one-sided, 97.5% confidence interval for the hazard ratio did not exceed 1.2. Data from Recruitment Phase 2 suggested that 35% of patients would experience treatment failure within 1 year; this translates into an exponential parameter λ of 0.43, assuming an exponential survival curve and taking '1 year' as the unit of measurement. Assuming 20% of patients withdraw from the study within the one-year observation period (corresponding to an exponential withdrawal ratio of 0.22), 2000 patients per arm would be necessary to be able to respond to this hypothesis with high significance (4000 patients in total).

However, recruitment into this phase was slower than anticipated, although fewer patients were withdrawing; recruitment into Phase 3 was terminated after 1185 patients were enrolled, 361 of whom switched to LABA/LAMA-FDC upon study entry. Under the assumption that 14% of patients would withdraw from the study within the 1-year follow-up (translating into an

exponential drop-out-rate of 0.15), based on the above statistical calculations, a power of 28.8% would be achieved in the registry arm with these 361 patients. The total number of 824 patients in the larger registry arm (LABA+LAMA+ICS therapy) was considered sufficient to investigate relevant subpopulations.

Patients were recruited by general practitioners and resident pneumologists, with selection of sites aimed at a nationwide distribution. It was expected that about 10–15 patients per center could be included.

9.8 Data transformation

Data are presented for two main populations:

- The ‘safety set’, which comprises all patients with valid baseline data and post-baseline data from at least one visit. This population was used for all safety analyses, and for the analyses at baseline of demographics, disease characteristics and comorbid conditions.
- The ‘per protocol V4 set’, which comprises all patients with valid baseline data, who completed the visit at the end of 1 year and with at most one missing interim visit, and who had no relevant protocol deviations. This population was used for all effectiveness analyses.

9.9 Statistical methods

All endpoints are presented by the defined treatment groups.

9.9.1 Main summary measures

Categorical data were analyzed by presenting adjusted frequency tables (absolute and relative). For numerical data the sample statistics mean and standard deviation, or median and quartiles are presented.

9.9.2 Main statistical methods

Total count and percentages of patients who experienced a progression in COPD (worsening of COPD, worsening in CAT score, and worsening based on occurrence of exacerbations) are presented by visit and by showing number of new worsenings (in terms of cumulative frequencies up to the current visit).

The primary objective was to assess the duration until a worsening of COPD defined as either occurrence of a moderate or severe exacerbation or a clinically relevant worsening in health-related quality of life (= a deterioration of 2 or more in CAT score). The comparison to analyze the effect of a change of the treatment scheme on this endpoint was done using a Cox regression analysis, with cohort as fixed factor. This was performed in the per protocol V4 set.

A negative binomial regression model was used to compare exacerbation rates between treatment groups within subgroups. The model included the factors age, sex, FEV₁ percent predicted, CAT score, mMRC score and number of exacerbations during the 12 months prior to entry, and smoking status at baseline.

Changes in CAT score, minimum clinically important difference (MCID, based on CAT) and number of exacerbations were compared between treatment groups using either the Wilcoxon-test p-values or p-values based on Chi-squared-test.

9.9.3 Missing values

Missing values were not replaced with the following exceptions:

- number of exacerbations were counted as “0” if a visit was missing or if a visit was done, but information on exacerbations was unknown/missing.

While computing a negative binomial model to compare exacerbation rates per year, the documented value “>3” was set to “4”.

The following technical corrections were implemented while creating analysis data sets:

- Forced vital capacity (FVC): In case the documented value was recorded as percent predicted without ambiguity (e.g., a value between 20 and 100), then the value was transferred into a value in liters using the following formula:
 - for males: $FVC * 100 / (5.76 * \text{height (cm)} - 0.026 * \text{age (yrs.)} - 4.34)$
 - for females: $FVC * 100 / (4.43 * \text{height (cm)} - 0.026 * \text{age (yrs.)} - 2.89)$
- In case specific information on a variable was given and it was also stated that no data were available then the specific information was set to missing and the variable “no data” was kept. This particularly held for the variables “cough”, “symptoms of COPD”, “therapy of exacerbations” and “hospitalization”. If a visit contained no data at all, they were assessed as “not done” and “no data” was set to “yes”.
- In case any antibiotic or steroid therapy was documented as “other therapy”, then this information was shifted (e.g. antibiotic/steroid = YES, other = NO).
- In case FEV₁ was missing, then FEV₁ predicted was set to missing.
- Furthermore, variables were set to YES if detailed information was given (e.g. cough=YES if type of cough was given).
- If leukocyte count was documented as “0” the corresponding measurement for leukocytes and eosinophils were set to missing. If only the value for eosinophils was documented as “0”, but a positive value for leukocyte count was given, the value was accepted. If eosinophils were documented as % and leukocyte count was not available, then the corresponding value was set to missing.

9.9.4 Sensitivity analyses

The analysis of the primary objective was repeated for the two single components (moderate or severe exacerbations, and worsening in CAT) separately using the Cox regression model including only change of treatment scheme.

Kaplan-Meier analyses were performed to present median time until worsening (based on CAT and exacerbation, based on CAT only, based on exacerbations only) with Kaplan-Meier curves generated.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 Quality control

All data management processes are based on the respective valid standard operating procedure (SOP) for non-regulatory studies of the contracted contract research organization (CRO).

Programmed routines checked the information during data entry for plausibility and completeness and automatically generated respective queries to the study center personnel. The treating physician had to confirm that the data were correct and complete.

Data entry was checked daily by the CRO. Free text fields of newly entered or updated data via eCRF were checked for possible hidden AEs by the data management team. Open queries were tracked and communicated to the practices/centers. The processing of queries by the practices/centers were sent via post or fax; then the respective query form had to be filled and signed by the physician and sent back to the contracted CRO for data entry. A signed copy had to be filed by the physician.

Obvious incorrect data could be corrected and documented by the data management team in a final validation.

The reported concomitant medication was coded according to the anatomical therapeutic chemical classification system of the World Health Organization (WHO) drug dictionary. Coding of medical history and current concomitant diseases as well as AEs is performed according to Medical Dictionary for Regulatory Activities (MedDRA) system, using the most recent version available at the time of coding.

All procedures and guidelines for SAE reporting and cumulative AE reporting were according to SOPs of Novartis Pharma GmbH.

Paper CRFs (for this study only applicable in exceptional cases to AE/SAE-Forms) that arrived at the CRO were registered in the study database and checked for (S)AE or hidden (S)AE. After data entry predefined basic data were checked according to a query logic. Queries were generated and sent to the investigator for resolution and completion. In case of failure of response a reminder was sent. The processing of incomplete or missing documentation of (hidden) AEs was performed according to Novartis SOPs.

Regulations for data protection of the personal patient data were followed.

10 Results

10.1 Participants

Of the 1192 patients recruited into the study, 1185 had valid baseline data and 1124 had post-baseline data from at least one visit ([Table 10-1](#)). A total of 1022 patients completed the visit at the end of one year, 967 of whom had also completed at least two of the three quarterly visits with no major protocol deviations.

Table 10-1 Disposition of patients

	LABA/LAMA fixed (N=363)	LABA+LAMA+ICS (N=829)	Total (N=1192)
All patients recruited into the study	363	829	1192
Patients with no valid baseline data	2	5	7
Patients with valid baseline data	361	824	1185
Patients with no post-baseline data	21	40	61
Patients with post-baseline data	340	784	1124
Patients with 1-year visit not completed	31	71	102
- because lost to follow-up	2	3	5
- because withdrawn from study	29	68	97
Patients who completed the 1-year visit	309	713	1022
Patients excluded from per protocol V4 set	17	38	55
- because of major protocol deviation(s)	12	25	37
- because missing more than 1 quarterly visit	5	13	18
Patients included in per protocol V4 set	292	675	967

Source: Table 1.1-1

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid

10.2 Descriptive data

The majority of the baseline demographics were similar between the two groups, although patients in the LABA/LAMA FDC group were more likely to be female, and a higher proportion were aged >75 years (although the mean ages were similar) (Table 10-2). Disease characteristics were also similar in the two groups.

Table 10-2 Baseline demographics, disease characteristics and symptoms (safety set)

	LABA/LAMA fixed (N=340)	LABA+LAMA+ICS (N=784)	Total (N=1124)
Sex, n (%)			
Male	172 (50.6)	477 (60.8)	649 (57.7)
Female	168 (49.4)	307 (39.2)	475 (42.3)
Age (years), mean (SD)	69.9 (9.9)	68.8 (9.2)	69.1 (9.4)

	LABA/LAMA fixed (N=340)	LABA+LAMA+ICS (N=784)	Total (N=1124)
Age groups, n (%)			
< 65 years	100 (29.4)	258 (32.9)	358 (31.9)
65 - 75 years	129 (37.9)	312 (39.8)	441 (39.2)
> 75 years	111 (32.6)	214 (27.3)	325 (28.9)
Height (cm), mean (SD)	168.6 (9.2)	170.3 (8.8)	169.8 (9.0)
Weight (kg), mean (SD)	79.3 (19.1)	79.1 (18.2)	79.1 (18.5)
Body-mass index (kg/m ²), mean (SD)	27.8 (5.8)	27.2 (5.5)	27.4 (5.6)
Duration since primary diagnosis (years), mean (SD)	6.7 (4.7)	8.0 (5.6)	7.6 (5.4)
Duration since primary diagnosis, n (%)			
Less than or equal to one year	26 (7.6)	43 (5.5)	69 (6.1)
More than one year	305 (89.7)	707 (90.2)	1012 (90.0)
missing values	9 (2.6)	34 (4.3)	43 (3.8)
Symptoms of COPD*, n (%)			
None	0 (0.0)	0 (0.0)	0 (0.0)
Exertional dyspnea	314 (92.4)	747 (95.3)	1061 (94.4)
Dyspnea at rest	90 (26.5)	194 (24.7)	284 (25.3)
Chest tightness / chest pain	150 (44.1)	327 (41.7)	477 (42.4)
Cough	291 (85.6)	653 (83.3)	944 (84.0)
Wheezing or grunting	104 (30.6)	266 (33.9)	370 (32.9)
Prolonged expiration	123 (36.2)	251 (32.0)	374 (33.3)
Restricted exercise tolerance	265 (77.9)	653 (83.3)	918 (81.7)
missing values	4 (1.2)	7 (0.9)	11 (1.0)
mMRC [†] , mean (SD)	1.6 (0.9) N=292	1.9 (1.0) N=675	1.8 (1.0) N=967
FEV ₁ (liters), mean (SD)	1.7 (0.7)	1.5 (0.6)	1.6 (0.6)
FEV ₁ predicted, mean (SD)	66.9 (24.7)	57.7 (22.8)	60.5 (23.8)
Smoking status, n (%)			
Smoker	115 (33.8)	235 (30.0)	350 (31.1)
Ex-smoker	168 (49.4)	435 (55.5)	603 (53.6)
Non-smoker	57 (16.8)	114 (14.5)	171 (15.2)
Years smoking [‡] , mean (SD)	34.4 (10.1)	35.2 (11.8)	34.9 (11.3)
Pack-years [‡] , mean (SD)	35.2 (18.8)	36.1 (22.0)	35.8 (21.0)

Source: Tables 1.2, 1.3-1, 1.3-4 and 1.3-5

*More than one symptom possible per patient. [†]Assessed in the per protocol V4 set. [‡]Only smokers and ex-smokers. LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; SD = standard deviation; COPD = chronic obstructive pulmonary disease; mMRC, modified Medical Research Council dyspnea scale; FEV₁, forced expiratory volume in 1 sec.

The most common reason declared for a change in therapy in the LABA/LAMA FDC arm was 'patient's wish', followed by 'physician prefers FDC', although in most cases 'other' was selected ([Table 10-3](#)). In the triple therapy group, the most common reasons for remaining on therapy were to control COPD symptoms or prevent exacerbations.

Table 10-3 Treatment groups - Reasons for change and adherence (safety set)

	LABA/LAMA fixed (N=340)	LABA+LAMA+ICS (N=784)
Reason to change therapy*, n (%)		
Physician prefers other inhaler	14 (4.1)	
Physician prefers fixed dose combination	56 (16.5)	
Exacerbation(s) under current COPD medication	1 (0.3)	
Side effect(s) under current COPD medication	5 (1.5)	
Patient still symptomatic under current COPD medication	25 (7.4)	
Patient prefers fixed dose combination	31 (9.1)	
Patient prefers other inhaler	10 (2.9)	
Patient's wish	87 (25.6)	
Other main reason	96 (28.2)	
missing values	15 (4.4)	
Reason to remain on therapy†, n (%)		
Physician prefers current inhaler(s)		61 (7.8)
Established control of COPD symptoms		275 (35.1)
Good tolerability		101 (12.9)
Patient prefers current inhaler(s)		34 (4.3)
Patient's wish		37 (4.7)
Considered necessary for exacerbation prevention		255 (32.5)
Other main reason		12 (1.5)
missing values		9 (1.1)

Source: Table 1.1-4.2

*Only for patients from treatment group 'LABA/LAMA fixed'.

†Only for patients from treatment group 'LABA+LAMA+ICS'. LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; COPD = chronic obstructive pulmonary disease.

In terms of comorbid conditions at baseline, the only difference between groups was that patients in the LABA/LAMA FDC group were slightly more likely to have osteoporosis ([Table 10-4](#)).

Table 10-4 Comorbid conditions at baseline (safety set)

	LABA/LAMA fixed (N=340)	LABA+LAMA+ICS (N=784)	Total (N=1124)
Alpha-1 antitrypsin deficiency	2 (0.6)	7 (0.9)	9 (0.8)
Bronchiectasis (not otherwise specified)	4 (1.2)	16 (2.0)	20 (1.8)
Bronchial carcinoma	3 (0.9)	16 (2.0)	19 (1.7)
Sleep apnea	37 (10.9)	71 (9.1)	108 (9.6)
Cardiovascular disease	205 (60.3)	460 (58.7)	665 (59.2)
Diabetes mellitus type 2	67 (19.7)	160 (20.4)	227 (20.2)

	LABA/LAMA fixed (N=340)	LABA+LAMA+ICS (N=784)	Total (N=1124)
Osteoporosis	37 (10.9)	50 (6.4)	87 (7.7)
Psychiatric disorders	29 (8.5)	63 (8.0)	92 (8.2)
Dermatitis	1 (0.3)	9 (1.1)	10 (0.9)
Allergic rhinitis	8 (2.4)	41 (5.2)	49 (4.4)
Chronic bronchitis	185 (54.4)	460 (58.7)	645 (57.4)
Asthma	8 (2.4)	34 (4.3)	42 (3.7)

Source: Table 1.3-6

Data are number (percentage). LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

10.3 Outcome data

The safety set comprised 1124 patients, with the per protocol V4 set (used for the effectiveness analyses) comprising 967 patients (Table 10-5).

Table 10-5 Analysis populations

	LABA/LAMA fixed	LABA+LAMA+ICS	Total
Safety set	340	784	1124
Per protocol V4 set	292	675	967
Patients excluded from per protocol V4 set	48	109	157

Source: Table 1.1-3

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

10.4 Main results

10.4.1 Time until worsening of COPD

A significantly lower percentage of patients in the LABA/LAMA FDC group had a worsening of COPD than in the triple therapy group (Table 10-6). The time to worsening was extended in the LABA/LAMA FDC group, although as fewer than 50% of patients had a worsening in this group it was only possible to calculate the median value in the triple therapy group (Table 10-6 and Figure 10-1; note that due to the COVID-19 pandemic, Visit 4 was delayed for some patients, resulting in the follow-up period exceeding 12 months). Both of the components (i.e., CAT and exacerbations) contributed to this overall result, with a significantly lower percentage of patients in the LABA/LAMA FDC group having a worsening based on CAT alone (Table 10-7 and Figure 10-2) or exacerbations alone (Table 10-8 and Figure 10-3).

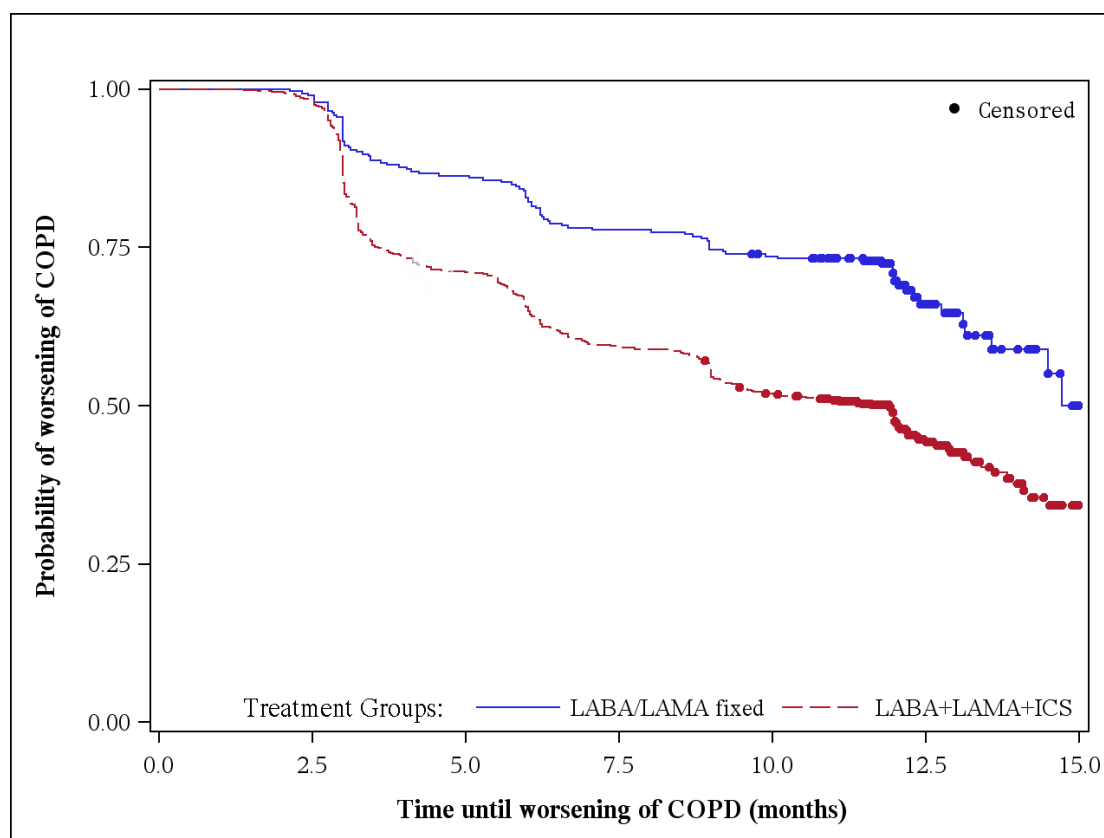
Table 10-6 Cumulative number (percentage) of patients experiencing a worsening of COPD by visit, and median time to worsening (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Cumulative number (percentages) of patients experiencing a worsening of COPD by visit			
Visit 1 after 3 months	40 (13.7)	192 (28.4)	232 (24.0)
Visit 2 after 6 months	64 (21.9)	277 (41.0)	341 (35.3)
Visit 3 after 9 months	79 (27.1)	330 (48.9)	409 (42.3)
Visit 4 after 12 months	95 (32.5)	376 (55.7)	471 (48.7)
Cox regression model, LABA/LAMA fixed vs. LABA+LAMA+ICS			
Estimate (SE)		0.695 (0.115)	
p value		<0.001	
Hazard ratio		2.004	
[95% CI]		[1.600; 2.512]	
Median time until worsening of COPD	-	11.93	12.75
[95% CI] in months	[13.57; -]	[9.17; 12.19]	[12.06; 13.63]

Source: Tables 2.1-1.3 (cumulative number), 2.1-1.1 (Cox regression) and 2.1-1.4 (time until worsening)

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; COPD = chronic obstructive pulmonary disease; SE = standard error; CI = confidence interval.

Figure 10-1 Kaplan-Meier curve for time until worsening of COPD (per protocol V4 set)



Source: Figure 2.1-1

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; COPD = chronic obstructive pulmonary disease.

Table 10-7 Cumulative number (percentage) of patients experiencing a worsening of COPD by visit based on CAT only, and median time to worsening (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Cumulative number (percentages) of patients experiencing a worsening of COPD based on CAT by visit			
Visit 1 after 3 months	32 (11.0)	149 (22.1)	181 (18.7)
Visit 2 after 6 months	46 (15.8)	213 (31.6)	259 (26.8)
Visit 3 after 9 months	54 (18.5)	258 (38.2)	312 (32.3)
Visit 4 after 12 months	63 (21.6)	290 (43.0)	353 (36.5)

Cox regression model, LABA/LAMA fixed vs. LABA+LAMA+ICS

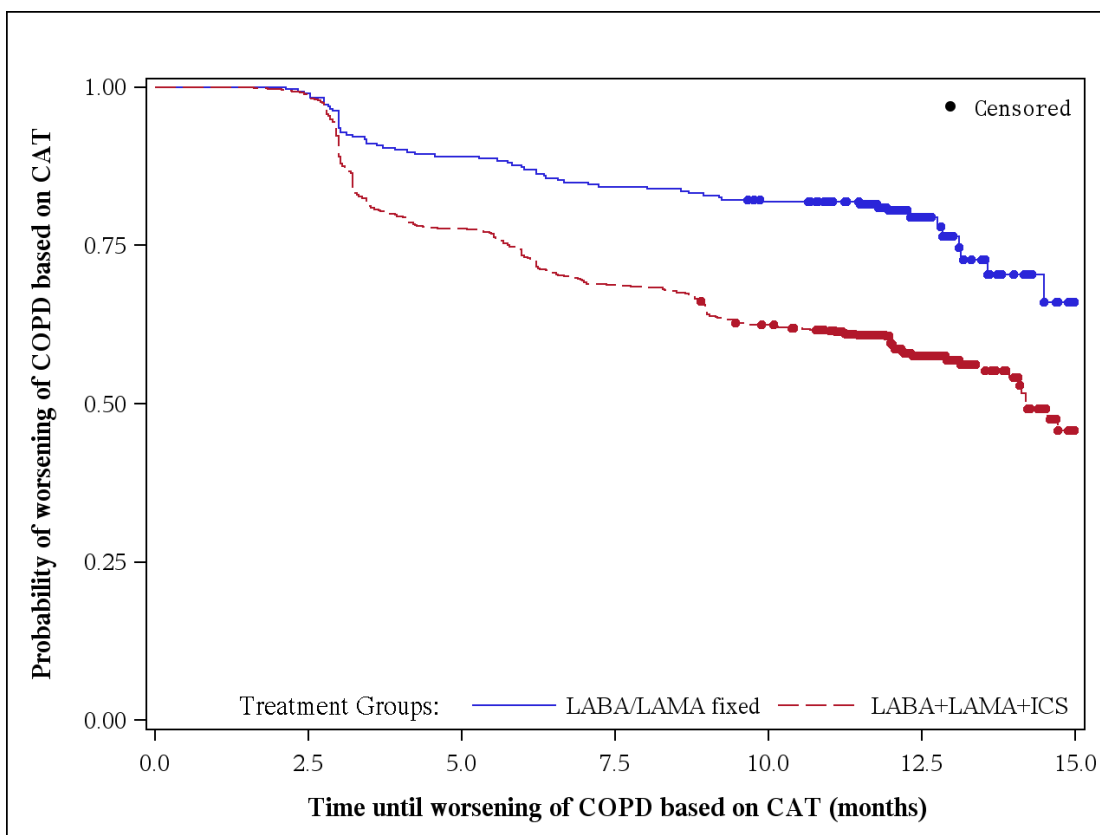
Estimate (SE) 0.799 (0.139)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
p value		<.001	
Hazard ratio [95% CI]		2.223 [1.692; 2.921]	
Median time until worsening of COPD [95% CI] in months	- [-; -]	14.23 [13.93; -]	- [14.23; -]

Source: Tables 2.1-2.3 (cumulative number), 2.1-2.1 (Cox regression) and 2.1-2.4 (time until worsening)

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; COPD = chronic obstructive pulmonary disease; CAT = COPD Assessment Test; SE = standard error; CI = confidence interval.

Figure 10-2 Kaplan-Meier curve for time until worsening of COPD (per protocol V4 set)



Source: Figure 2.1-2

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; COPD = chronic obstructive pulmonary disease.

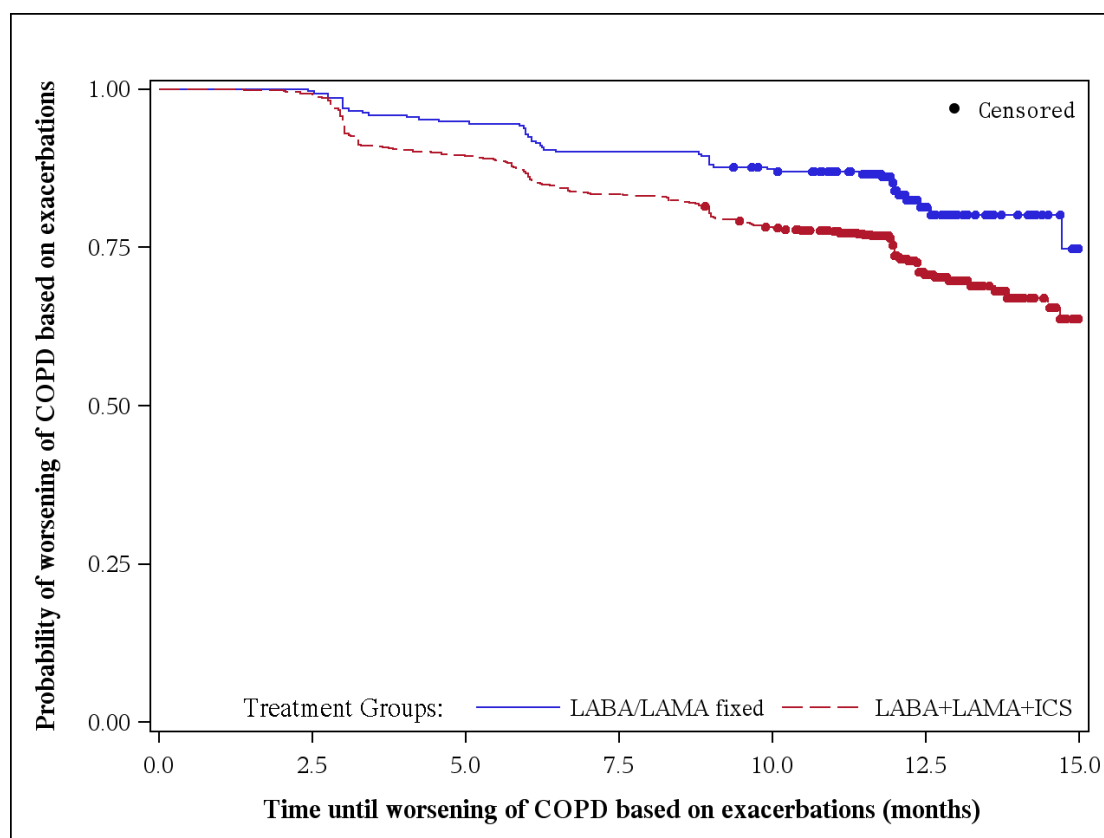
Table 10-8 Cumulative number (percentage) of patients experiencing a worsening of COPD by visit, and median time to worsening (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Cumulative number (percentages) of patients experiencing a worsening of COPD based on exacerbations by visit			
Visit 1 after 3 months	15 (5.1)	70 (10.4)	85 (8.8)
Visit 2 after 6 months	27 (9.2)	113 (16.7)	140 (14.5)
Visit 3 after 9 months	39 (13.4)	151 (22.4)	190 (19.6)
Visit 4 after 12 months	49 (16.8)	190 (28.1)	239 (24.7)
Cox regression model, LABA/LAMA fixed vs. LABA+LAMA+ICS			
Estimate (SE)	0.544 (0.161)		
p value	<.001		
Hazard ratio	1.723		
[95% CI]	[1.258; 2.360]		
Median time until worsening of COPD	-	-	-
[95% CI] in months	[-; -]	[-; -]	[-; -]

Source: Tables 2.1-2.7 (cumulative number), 2.1-2.5 (Cox regression) and 2.1-2.8 (time until worsening)

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; COPD = chronic obstructive pulmonary disease; SE = standard error; CI = confidence interval.

Figure 10-3 Kaplan-Meier curve for time until worsening of COPD (per protocol V4 set)



Source: Figure 2.1-2

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; COPD = chronic obstructive pulmonary disease.

10.4.2 Exacerbations

At baseline, the proportion of patients who had experienced at least one exacerbation in the previous 12 months was not significantly different between the two groups, although was numerically lower in the LABA/LAMA FDC group (Table 10-9). Consistent with the data presented in Section 10.4.1, the percentage of patients exacerbating during the study was lower at each visit in the LABA/LAMA FDC group than the triple therapy group, although not significantly so at the 6 month visit.

Table 10-9 Percentage of patients with exacerbations (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)	p-Value
Baseline visit (exacerbations during the previous 12 months)				
no	165 (56.5)	345 (51.1)	510 (52.7)	0.123 *
yes	127 (43.5)	330 (48.9)	457 (47.3)	

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)	p-Value
Year 1				
no	231 (79.1)	449 (66.5)	680 (70.3)	<0.001 *
yes	54 (18.5)	194 (28.7)	248 (25.6)	
missing values	7 (2.4)	32 (4.7)	39 (4.0)	
Visit 1 after 3 months				
no	274 (93.8)	590 (87.4)	864 (89.3)	0.012 *
yes	17 (5.8)	73 (10.8)	90 (9.3)	
missing values	1 (0.3)	12 (1.8)	13 (1.3)	
Visit 2 after 6 months				
no	273 (93.5)	605 (89.6)	878 (90.8)	0.060 *
yes	15 (5.1)	58 (8.6)	73 (7.5)	
missing values	4 (1.4)	12 (1.8)	16 (1.7)	
Visit 3 after 9 months				
no	272 (93.2)	580 (85.9)	852 (88.1)	0.004 *
yes	14 (4.8)	69 (10.2)	83 (8.6)	
missing values	6 (2.1)	26 (3.9)	32 (3.3)	
Visit 4 after 12 months				
no	276 (94.5)	599 (88.7)	875 (90.5)	0.005 *
yes	16 (5.5)	76 (11.3)	92 (9.5)	

Source: Table 2.2.1

Data are number of patients (%). *Chi-square test. During Year 1 a patient is displayed as 'yes' if they have exacerbations in at least one visit during the study year, and displayed as 'no' if the question on exacerbations was answered with 'no' on all four visits of the study year. The Visit 1 to 4 data are for the three months prior to the visit. LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid

Consistent with the percentages, the annualized exacerbation rate was lower in the LABA/LAMA FDC group than the triple therapy group (as indicated by non-overlapping 95% confidence intervals; [Table 10-10](#)). When the data were analyzed according to exacerbations during the 12 months prior to entry, the rates in all three groups were highest in patients who had exacerbated prior to entry (especially those with a history of ≥ 2 exacerbations).

Table 10-10 Annualized exacerbation rates (per protocol V4 set)

	LABA/LAMA fixed (N=292)		LABA+LAMA+ICS (N=675)		Total (N=967)	
	n	Annualized exacerbation rate (95% confidence limit)	n	Annualized exacerbation rate (95% confidence limit)	n	Annualized exacerbation rate (95% confidence limit)
All patients						
missings	281	0.207	625	0.432	906	0.362
excluded		(0.158, 0.271)		(0.368, 0.506)		(0.315, 0.416)
missings=0	292	0.212	675	0.436	967	0.369
		(0.164, 0.274)		(0.375, 0.507)		(0.323, 0.421)
Patients without exacerbations within 12 months prior to baseline						
missings	156	0.121	314	0.207	470	0.178
excluded		(0.074, 0.198)		(0.151, 0.284)		(0.136, 0.234)
missings=0	165	0.131	345	0.221	510	0.192
		(0.084, 0.206)		(0.167, 0.294)		(0.151, 0.245)
Patients with exacerbations within 12 months prior to baseline						
missings	125	0.315	311	0.659	436	0.560
excluded		(0.231, 0.429)		(0.553, 0.784)		(0.479, 0.655)
missings=0	127	0.317	330	0.661	457	0.565
		(0.234, 0.430)*		(0.558, 0.783)		(0.485, 0.659)
Patients with ≥2 exacerbations within 12 months prior to baseline						
missings	19	0.435	111	0.894	130	0.827
excluded		(0.233, 0.815)*		(0.690, 1.159)		(0.646, 1.058)
missings=0	19	0.435	116	0.918	135	0.850
		(0.233, 0.815)*		(0.713, 1.181)		(0.668, 1.081)

Source: Table 2.2.3.2

Data are mean (95% confidence limit). *The validity of the model fit is questionable. Exacerbation rate was estimated as overall using a negative binomial regression model with annualized numbers of exacerbation as dependent variable and no independent variable. Estimates are only presented if N>1, if at least one patient had exacerbations in the study year and if model assumptions are valid. LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

Patients in the LABA/LAMA FDC group were less likely to require hospitalization due to an exacerbation, both during the 12 months prior to entry and throughout the study (Table 10-11). There were no other consistent patterns in the treatment or action taken for exacerbations in the two groups (Table 10-12).

Table 10-11 Percentage of patients with hospital stay due to exacerbations (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Baseline visit			
Percent base	127	330	457
No	120 (94.5)	274 (83.0)	394 (86.2)
Yes	7 (5.5)	56 (17.0)	63 (13.8)
Year 1			
Percent base	54	194	248
No/Unknown/missing	52 (96.3)	157 (80.9)	209 (84.3)
Yes	2 (3.7)	37 (19.1)	39 (15.7)
Visit 1 after 3 months			
Percent base	17	73	90
No	17 (100.0)	61 (83.6)	78 (86.7)
Yes	0 (0.0)	12 (16.4)	12 (13.3)
Visit 2 after 6 months			
Percent base	15	58	73
No	15 (100.0)	51 (87.9)	66 (90.4)
Yes	0 (0.0)	7 (12.1)	7 (9.6)
Visit 3 after 9 months			
Percent base	14	69	83
No	12 (85.7)	57 (82.6)	69 (83.1)
Yes	2 (14.3)	12 (17.4)	14 (16.9)
Visit 4 after 12 months			
Percent base	16	76	92
No	16 (100.0)	64 (84.2)	80 (87.0)
Yes	0 (0.0)	12 (15.8)	12 (13.0)

Source: Table 2.2.4

Data are number of patients (%). *100% are patients with exacerbations during the last 12 months (baseline) / 3 months (other visits) during the last 3 months. In Year 1 a patient is displayed as 'yes' if he has a hospital stay in at least one visit with exacerbation(s) during the respective year, and displayed as 'no/unknown/missing' otherwise. LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

Table 10-12 Course of treatment of or action taken for exacerbations (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Baseline visit			
Systemic steroids	69 (23.6)	228 (33.8)	297 (30.7)
Antibiotics	111 (38.0)	234 (34.7)	345 (35.7)
Other treatment	4 (1.4)	35 (5.2)	39 (4.0)
Hospitalization	7 (2.4)	56 (8.3)	63 (6.5)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Patients with systemic steroids + antibiotics	54 (18.5)	141 (20.9)	195 (20.2)
no/missing exacerbation	165 (56.5)	345 (51.1)	510 (52.7)
Visit 1 after 3 months			
Systemic steroids	13 (4.5)	44 (6.5)	57 (5.9)
Antibiotics	6 (2.1)	48 (7.1)	54 (5.6)
Other treatment	3 (1.0)	11 (1.6)	14 (1.4)
Hospitalization	0 (0.0)	12 (1.8)	12 (1.2)
Patients with systemic steroids + antibiotics	4 (1.4)	27 (4.0)	31 (3.2)
no/missing exacerbation	275 (94.2)	602 (89.2)	877 (90.7)
Visit 2 after 6 months			
Systemic steroids	6 (2.1)	40 (5.9)	46 (4.8)
Antibiotics	11 (3.8)	33 (4.9)	44 (4.6)
Other treatment	2 (0.7)	6 (0.9)	8 (0.8)
Hospitalization	0 (0.0)	7 (1.0)	7 (0.7)
Patients with systemic steroids + antibiotics	4 (1.4)	19 (2.8)	23 (2.4)
no/missing exacerbation	277 (94.9)	617 (91.4)	894 (92.5)
Visit 3 after 9 months			
Systemic steroids	10 (3.4)	50 (7.4)	60 (6.2)
Antibiotics	7 (2.4)	38 (5.6)	45 (4.7)
Other treatment	2 (0.7)	7 (1.0)	9 (0.9)
Hospitalization	2 (0.7)	12 (1.8)	14 (1.4)
Patients with systemic steroids + antibiotics	4 (1.4)	28 (4.1)	32 (3.3)
no/missing exacerbation	278 (95.2)	606 (89.8)	884 (91.4)
Visit 4 after 12 months			
Systemic steroids	11 (3.8)	55 (8.1)	66 (6.8)
Antibiotics	9 (3.1)	47 (7.0)	56 (5.8)
Other treatment	2 (0.7)	4 (0.6)	6 (0.6)
Hospitalization	0 (0.0)	12 (1.8)	12 (1.2)
Patients with systemic steroids + antibiotics	6 (2.1)	32 (4.7)	38 (3.9)
no/missing exacerbation	276 (94.5)	599 (88.7)	875 (90.5)

Source: Table 2.3

Data are number of patients (%). A patient may have more than one treatment/action. LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

One of the secondary objectives was the time to next exacerbation. The exact date of the onset of exacerbations was not recorded, and so this analysis was not possible.

10.4.3 COPD Assessment Test

At baseline, the median CAT total score was slightly higher (i.e., worse) in the LABA/LAMA FDC group, with the difference reaching statistical significance, although the 1st and 3rd quartiles were both lower (Table 10-13). This inconsistency was likely due to the distribution of the scores, given a higher proportion of patients in the LABA/LAMA FDC group were in the high impact category, and yet higher proportions of patients in this group were also in the low and normal impact categories. At the end of the year, the median total score improved from baseline in both groups, although this improvement was clinically meaningful (i.e., ≥ 2 unit decrease) only in the LABA/LAMA FDC group, with a statistically difference in the median scores between the two groups. Further, a significantly higher proportion of patients in the LABA/LAMA FDC group had a clinically relevant improvement from baseline in CAT total score (i.e., decrease ≥ 2 unit).

Table 10-13 Course of COPD Assessment Test score (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)	p-Value
Median CAT score (1st, 3rd quartile)				
Baseline visit	21.0 (13.0, 23.0)	20.0 (15.0, 25.0)	20.0 (14.0, 24.0)	0.008 *
N	292	675	967	
Visit 1 after 3 months	19.0 (12.0, 22.0)	20.0 (14.0, 24.0)	20.0 (14.0, 23.0)	0.001 *
N	291	663	954	
Visit 2 after 6 months	18.0 (10.5, 21.0)	19.0 (14.0, 24.0)	18.0 (13.0, 23.0)	<0.001 *
N	288	663	951	
Visit 3 after 9 months	17.0 (11.0, 21.0)	19.0 (13.0, 23.0)	18.0 (13.0, 22.0)	<0.001 *
N	286	649	935	
Visit 4 after 12 months	17.0 (10.0, 21.5)	19.0 (13.0, 23.0)	18.0 (12.0, 22.0)	<0.001 *
N	292	675	967	
Median CAT score, absolute difference to baseline (1st, 3rd quartile)				
Visit 1 after 3 months	-1.0 (-3.0 to 0.0)	-1.0 (-3.0 to 1.0)	-1.0 (-3.0 to 1.0)	0.028 *
N	291	663	954	
Visit 2 after 6 months	-2.0 (-4.0 to 0.0)	-1.0 (-4.0 to 1.0)	-1.0 (-4.0 to 1.0)	0.002 *
N	288	663	951	
Visit 3 after 9 months	-2.0 (-4.0 to 0.0)	-1.0 (-4.0 to 2.0)	-2.0 (-4.0 to 1.0)	0.004 *
N	286	649	935	
Visit 4 after 12 months	-2.0 (-5.0 to 0.0)	-1.0 (-4.0 to 2.0)	-2.0 (-5.0 to 1.0)	0.003 *
N	292	675	967	

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)	p-Value
CAT score impact level, n (%)				
Baseline visit, n (%)				
very high	4 (1.4)	48 (7.1)	52 (5.4)	
high	143 (49.0)	284 (42.1)	427 (44.2)	
medium	103 (35.3)	281 (41.6)	384 (39.7)	
low	31 (10.6)	44 (6.5)	75 (7.8)	
normal / healthy non-smokers	11 (3.8)	18 (2.7)	29 (3.0)	
Visit 1 after 3 months, n (%)				
very high	6 (2.1)	42 (6.2)	48 (5.0)	
high	95 (32.5)	256 (37.9)	351 (36.3)	
medium	139 (47.6)	295 (43.7)	434 (44.9)	
low	33 (11.3)	42 (6.2)	75 (7.8)	
normal / healthy non-smokers	18 (6.2)	28 (4.1)	46 (4.8)	
missing values	1 (0.3)	12 (1.8)	13 (1.3)	
Visit 2 after 6 months, n (%)				
very high	3 (1.0)	35 (5.2)	38 (3.9)	
high	82 (28.1)	245 (36.3)	327 (33.8)	
medium	146 (50.0)	312 (46.2)	458 (47.4)	
low	33 (11.3)	43 (6.4)	76 (7.9)	
normal / healthy non-smokers	24 (8.2)	28 (4.1)	52 (5.4)	
missing values	4 (1.4)	12 (1.8)	16 (1.7)	
Visit 3 after 9 months, n (%)				
very high	2 (0.7)	42 (6.2)	44 (4.6)	
high	83 (28.4)	217 (32.1)	300 (31.0)	
medium	143 (49.0)	313 (46.4)	456 (47.2)	
low	40 (13.7)	48 (7.1)	88 (9.1)	
normal / healthy non-smokers	18 (6.2)	29 (4.3)	47 (4.9)	
missing values	6 (2.1)	26 (3.9)	32 (3.3)	
Visit 4 after 12 months, n (%)				
very high	3 (1.0)	50 (7.4)	53 (5.5)	
high	86 (29.5)	227 (33.6)	313 (32.4)	
medium	142 (48.6)	304 (45.0)	446 (46.1)	
low	40 (13.7)	64 (9.5)	104 (10.8)	
normal / healthy non-smokers	21 (7.2)	30 (4.4)	51 (5.3)	

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)	p-Value
CAT score responders				
Visit 1 after 3 months, n (%)				
MCID+	124 (42.5)	250 (37.0)	374 (38.7)	<0.001 **
MCID-	32 (11.0)	149 (22.1)	181 (18.7)	
no minimum clinically important difference	135 (46.2)	264 (39.1)	399 (41.3)	
missing values	1 (0.3)	12 (1.8)	13 (1.3)	
Visit 2 after 6 months, n (%)				
MCID+	156 (53.4)	304 (45.0)	460 (47.6)	<0.001 **
MCID-	32 (11.0)	155 (23.0)	187 (19.3)	
no minimum clinically important difference	100 (34.2)	204 (30.2)	304 (31.4)	
missing values	4 (1.4)	12 (1.8)	16 (1.7)	
Visit 3 after 9 months, n (%)				
MCID+	166 (56.8)	313 (46.4)	479 (49.5)	<0.001 **
MCID-	34 (11.6)	173 (25.6)	207 (21.4)	
no minimum clinically important difference	86 (29.5)	163 (24.1)	249 (25.7)	
missing values	6 (2.1)	26 (3.9)	32 (3.3)	
Visit 4 after 12 months, n (%)				
MCID+	170 (58.2)	330 (48.9)	500 (51.7)	<0.001 **
MCID-	40 (13.7)	172 (25.5)	212 (21.9)	
no minimum clinically important difference	82 (28.1)	173 (25.6)	255 (26.4)	

Source: Table 2.5

*Wilcoxon test; **Chi-square test. MCID+ is defined as a reduction in CAT of at least two points; MCID- is defined as an increase in CAT of at least two points. LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; MCID, minimum clinically important difference.

10.4.4 Pulmonary function

Pulmonary function (in terms of mean percent predicted FEV₁) was slightly higher at baseline and after 12 months in the LABA/LAMA FDC group (although the mean FEV₁ and FVC values were similar in the two groups; [Table 10-14](#)). The annualized rates of FEV₁ and FVC decline were small in both groups. Note, however, that given this was a non-interventional study, pulmonary function assessments were performed without requiring washout (or standardization of time post-dose) of maintenance medication, and the data were not formally compared between groups.

Table 10-14 Change in FEV₁ and FVC over time (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
FEV ₁ (liters)			
Baseline visit	1.7 (0.6)	1.5 (0.6)	1.6 (0.6)
N	292	675	967
Visit 4 after 12 months	1.7 (0.6)	1.5 (0.6)	1.5 (0.6)
N	290	653	943
FEV ₁ predicted			
Baseline visit	67.2 (22.7)	58.0 (21.8)	60.7 (22.5)
N	292	675	967
Visit 4 after 12 months	68.1 (24.0)	57.7 (22.3)	60.9 (23.3)
N	290	653	943
FVC (liters)			
Baseline visit	2.5 (0.8)	2.4 (0.8)	2.5 (0.8)
N	292	675	967
Visit 4 after 12 months	2.5 (0.8)	2.4 (0.8)	2.4 (0.8)
N	290	653	943
Annualized rate of FEV ₁ decline (liters/year)	-0.00 (0.29)	-0.03 (0.26)	-0.02 (0.27)
N	289	653	942
Annualized rate of FVC decline (liters/year)	-0.01 (0.47)	-0.04 (0.46)	-0.03 (0.46)
N	289	653	942

Source: Tables 2.7.1 and 2.7.2

Data are mean (standard deviation). LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; FEV₁ = forced expiratory volume in 1 sec; FVC = forced vital capacity.

10.4.5 Predictive value of blood eosinophil count

At baseline, the mean blood eosinophil count was slightly lower in the LABA/LAMA FDC group than the triple therapy group (Table 10-15). Over the follow-up period, mean values decreased from baseline in the LABA/LAMA FDC group and increased in the triple therapy group, although post-baseline data were from small numbers of patients.

Table 10-15 Course of blood eosinophil values (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Baseline visit	222.5 (201.9)	259.7 (237.9)	248.5 (228.2)
N	287	668	955
Visit 1 after 3 months	205.8 (115.4)	388.1 (200.5)	306.2 (190.3)
N	66	81	147
Visit 2 after 6 months	209.2 (109.9)	386.4 (201.9)	311.5 (190.2)
N	63	86	149

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Visit 3 after 9 months	213.2 (138.0)	381.6 (211.6)	308.6 (201.1)
N	65	85	150
Visit 4 after 12 months	195.7 (102.8)	332.9 (192.8)	272.4 (173.2)
N	90	114	204

Source: Table 2.6.1

Data are mean (standard deviation). LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

When subgrouped by change from baseline in CAT total score, the mean blood eosinophil counts were consistently numerically lower in the LABA/LAMA FDC group than in the triple therapy group (Table 10-16). In the LABA/LAMA FDC group there was no obvious trend of mean eosinophil count across the CAT subgroups at either baseline or Visit 4; in the triple therapy group, there was a slight increase in baseline eosinophil count from CAT worsening, through CAT unchanged, to CAT improved (although not in the Visit 4 values). However, differences were small, with wide variability around the mean, and overall the correlation coefficients indicated negligible correlations (<0.1). The strongest correlation coefficient was between change from baseline in eosinophil values and change from baseline in CAT – but even then this was only 0.109.

Table 10-16 Correlation between eosinophil values and CAT total score (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Baseline visit, mean (standard deviation), cells/ μ L			
CAT worsening	211.9 (149.9)	236.9 (233.4)	232.2 (220.0)
N	40	172	212
CAT unchanged	242.6 (278.1)	254.3 (232.5)	250.7 (247.0)
N	77	171	248
CAT improvement	215.9 (169.7)	274.6 (242.6)	254.5 (221.9)
N	170	325	495
Visit 4 after 12 months, mean (standard deviation), cells/ μ L			
CAT worsening	174.9 (106.7)	240.2 (159.5)	225.7 (149.1)
N	4	14	18
CAT unchanged	228.7 (141.9)	366.8 (245.1)	318.3 (222.6)
N	13	24	37
CAT improvement	191.0 (94.8)	339.2 (176.6)	266.6 (160.3)
N	73	76	149

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Correlation coefficient, baseline eosinophils value and CAT			
CAT at baseline			0.034
N			955
CAT at Visit 4			-0.037
N			955
CAT change baseline to Visit 4			-0.093
N			955
Correlation coefficient, eosinophil change from baseline at Visit 4 and CAT			
CAT at Visit 4			-0.064
N			204
CAT change baseline to Visit 4			0.109
N			204

Source: Tables 2.6.4 (CAT subgroups), and 2.6.2 and 2.6.3 (correlation coefficients)

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease.

Similarly, when grouped by in-study exacerbation occurrence mean eosinophil counts were again lower in the LABA/LAMA FDC group than the triple therapy group for all exacerbation categories. However, there were no consistent trends, although in the LABA/LAMA FDC group the mean baseline eosinophil value decreased slightly with increasing exacerbation occurrence (Table 10-17).

Table 10-17 Correlation between eosinophil values and in-study exacerbation occurrence (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Baseline visit			
0 exacerbations	230.9 (215.4)	257.7 (240.8)	248.8 (232.8)
N	238	478	716
1 exacerbation	184.4 (109.2)	277.3 (234.5)	254.4 (214.1)
N	41	125	166
2 exacerbations	167.8 (113.7)	249.6 (230.3)	236.8 (217.4)
N	8	43	51
3 exacerbations	-	212.5 (250.1)	212.5 (250.1)
N	-	12	12
>3 exacerbations	-	233.7 (174.2)	233.7 (174.2)
N	-	10	10

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Visit 4 after 12 months			
0 exacerbations	196.3 (106.0)	319.1 (193.3)	253.7 (164.5)
N	75	66	141
1 exacerbation	193.0 (88.4)	368.3 (188.1)	315.7 (182.7)
N	15	35	50
2 exacerbations	-	373.0 (182.0)	373.0 (182.0)
N	-	10	10
3 exacerbations	-	32.3 (45.7)	32.3 (45.7)
N	-	2	2
>3 exacerbations	-	200.0 (-)	200.0 (-)
N	-	1	1

Source: Table 2.6.5

Data are mean (standard deviation) cells/ μ L. LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

Finally, in both treatment groups the mean eosinophil counts were lower at baseline (although not at Visit 4) in patients who had a worsening of COPD than in those who had an improvement – although again there was high variability around the means (Table 10-18).

Table 10-18 Correlation between eosinophil values and worsening of COPD (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Baseline visit			
Worsening: no	240.2 (227.3)	274.3 (244.5)	260.8 (238.2)
N	192	292	484
Worsening: yes	186.7 (131.0)	248.4 (232.3)	235.9 (217.0)
N	95	376	471
Visit 4 after 12 months			
Worsening: no	195.2 (108.0)	334.2 (198.6)	256.5 (168.8)
N	71	56	127
Worsening: yes	197.5 (83.1)	331.5 (188.8)	298.5 (178.2)
N	19	58	77

Source: Table 2.6.6

Data are mean (standard deviation) cells/ μ L. LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; COPD = chronic obstructive pulmonary disease.

10.4.6 COPD symptoms

At baseline, all patients had at least one COPD symptom – most commonly exertional dyspnea (Table 10-19). At the end of the year, the proportion of patients with dyspnea had reduced, but all patients still had at least one COPD symptom.

Table 10-19 Course of COPD symptoms (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Baseline visit			
None	0 (0.0)	0 (0.0)	0 (0.0)
Exertional dyspnea	267 (91.4)	644 (95.4)	911 (94.2)
Dyspnea at rest	70 (24.0)	149 (22.1)	219 (22.6)
Chest tightness / chest pain	123 (42.1)	271 (40.1)	394 (40.7)
Cough	251 (86.0)	561 (83.1)	812 (84.0)
Wheezing or grunting	80 (27.4)	220 (32.6)	300 (31.0)
Prolonged expiration	102 (34.9)	205 (30.4)	307 (31.7)
Restricted exercise tolerance	219 (75.0)	553 (81.9)	772 (79.8)
missing values	4 (1.4)	6 (0.9)	10 (1.0)
Visit 4 after 12 months			
None	0 (0.0)	0 (0.0)	0 (0.0)
Exertional dyspnea	246 (84.2)	623 (92.3)	869 (89.9)
Dyspnea at rest	26 (8.9)	112 (16.6)	138 (14.3)
Chest tightness / chest pain	55 (18.8)	189 (28.0)	244 (25.2)
Cough	237 (81.2)	495 (73.3)	732 (75.7)
Wheezing or grunting	23 (7.9)	141 (20.9)	164 (17.0)
Prolonged expiration	47 (16.1)	151 (22.4)	198 (20.5)
Restricted exercise tolerance	187 (64.0)	499 (73.9)	686 (70.9)
missing values	6 (2.1)	18 (2.7)	24 (2.5)

Source: Table 2.9

Data are number of patients (%). *More than one symptom possible per patient. LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; COPD = chronic obstructive pulmonary disease.

10.4.7 Frequency of regimen change

Persistence (in terms of maintenance of regimen) was high in both groups, with just under 90% of not having changed therapy regimen by the end of the year (Table 10-20).

Table 10-20 Treatment persistence (per protocol V4 set)

	LABA/LAMA fixed (N=292)	LABA+LAMA+ICS (N=675)	Total (N=967)
Regimen change			
never changed	256 (87.7)	603 (89.3)	859 (88.8)
changed	7 (2.4)	15 (2.2)	22 (2.3)
returned	29 (9.9)	57 (8.4)	86 (8.9)

Source: Table 2.10

Data are number of patients (%). LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

10.5 Other analyses

Not applicable.

10.6 Adverse events/adverse reactions

10.6.1 Adverse events

10.6.1.1 Display of adverse events

A lower proportion of patients in the LABA/LAMA FDC group reported non-serious AEs overall and for the majority of MedDRA system organ classes, with the most commonly reported system organ class in both groups being respiratory, thoracic and mediastinal, followed by infections and infestations (Table 10-21). The event rate was also lower for the LABA/LAMA FDC group.

Table 10-21 Non-serious adverse events (by patients and overall event rates) - overall and by MedDRA system organ class (safety set)

	LABA/LAMA fixed (N=340) n (%)	LABA+LAMA+ICS (N=784) n (%)	Total (N=1124) n (%)
Number (%) of patients with at least one event	44 (12.9)	118 (15.1)	162 (14.4)
Event rates per 100 patient-years	19.943	26.355	
Blood and lymphatic system disorders	0	1 (0.1)	1 (<0.1)
Endocrine disorders	0	1 (0.1)	1 (<0.1)
Gastrointestinal disorders	3 (0.9)	3 (0.4)	6 (0.5)
General disorders and administration site conditions	5 (1.5)	13 (1.7)	18 (1.6)
Immune system disorders	0	6 (0.8)	6 (0.5)
Infections and infestations	11 (3.2)	29 (3.7)	40 (3.6)
Injury, poisoning and procedural complications	0	4 (0.5)	4 (0.4)
Investigations	4 (1.2)	14 (1.8)	18 (1.6)
Metabolism and nutrition disorders	1 (0.3)	3 (0.4)	4 (0.4)
Musculoskeletal and connective tissue disorders	3 (0.9)	7 (0.9)	10 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.1)	1 (<0.1)
Nervous system disorders	4 (1.2)	9 (1.1)	13 (1.2)
Product issues	0	1 (0.1)	1 (<0.1)
Psychiatric disorders	2 (0.6)	2 (0.3)	4 (0.4)
Respiratory, thoracic and mediastinal disorders	18 (5.3)	59 (7.5)	77 (6.9)

	LABA/LAMA fixed (N=340) n (%)	LABA+LAMA+ICS (N=784) n (%)	Total (N=1124) n (%)
Skin and subcutaneous tissue disorders	1 (0.3)	4 (0.5)	5 (0.4)
Vascular disorders	1 (0.3)	0	1 (<0.1)

Source: Tables 3.1-2.1.3 and 3.1-2.4 (event rates)

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

10.6.1.2 Analysis of adverse events

The most frequent non-serious AEs by preferred term in both groups were related to COPD – most commonly COPD (i.e., exacerbations or worsening) (Table 10-22).

Table 10-22 Non-serious adverse events (by patients and event rates) - overall and most common preferred term ($\geq 0.5\%$ in either group) (safety set)

	LABA/LAMA fixed (N=340)		LABA+LAMA+ICS (N=784)		Total (N=1124)
	n (%)	Event rate per 100 pt- yrs	n (%)	Event rate per 100 pt- yrs	n (%)
Number (%) of patients with at least one event	44 (12.9)	19.943	118 (15.1)	26.355	162 (14.4)
Chronic obstructive pulmonary disease	10 (2.9)	3.989	32 (4.1)	5.803	42 (3.7)
Nasopharyngitis	4 (1.2)	1.140	16 (2.0)	2.055	20 (1.8)
Forced expiratory volume decreased	4 (1.2)	1.140	8 (1.0)	0.967	12 (1.1)
Dyspnea	4 (1.2)	1.140	6 (0.8)	0.725	10 (0.9)
Cough	3 (0.9)	1.140	5 (0.6)	0.604	8 (0.7)
Gastroenteritis	3 (0.9)	0.855	2 (0.3)	0.242	5 (0.4)
Sciatica	2 (0.6)	0.570	4 (0.5)	0.604	6 (0.5)
Drug ineffective	2 (0.6)	0.570	2 (0.3)	0.242	4 (0.4)
Adverse drug reaction	2 (0.6)	0.570	0		2 (0.2)
Chest discomfort	1 (0.3)	0.285	9 (1.1)	1.088	10 (0.9)
Chest pain	1 (0.3)	0.285	9 (1.1)	1.088	10 (0.9)
Grunting	1 (0.3)	0.285	7 (0.9)	0.846	8 (0.7)
Wheezing	1 (0.3)	0.285	7 (0.9)	0.846	8 (0.7)
Seasonal allergy	0		6 (0.8)	0.725	6 (0.5)
Dyspnea exertional	0		4 (0.5)	0.484	4 (0.4)
Exercise tolerance decreased	0		4 (0.5)	0.484	4 (0.4)
Productive cough	0		4 (0.5)	0.484	4 (0.4)

Sources: Tables 3.1-2.1.3 (numbers and percentages) and 3.1-2.5 (event rates)

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

10.6.1.3 Suspected relationship of non-serious adverse events to the study

Very few patients had non-serious AEs that were considered study related. As with the overall experience of non-serious AEs, fewer patients in the LABA/LAMA FDC group had non-serious AEs that were considered related to the study than in the triple therapy group ([Table 10-23](#)).

Table 10-23 Non-serious adverse events suspected study-related or relationship not assigned - overall and most common preferred term ($\geq 0.5\%$ in either group) (safety set)

	LABA/LAMA fixed (N=340) n (%)	LABA+LAMA+ICS (N=784) n (%)	Total (N=1124) n (%)
Number (%) of patients with at least one event	12 (3.5)	49 (6.3)	61 (5.4)
Forced expiratory volume decreased	3 (0.9)	5 (0.6)	8 (0.7)
Nasopharyngitis	2 (0.6)	4 (0.5)	6 (0.5)
Cough	2 (0.6)	2 (0.3)	4 (0.4)
Dyspnea	2 (0.6)	0	2 (0.2)
Chronic obstructive pulmonary disease	1 (0.3)	13 (1.7)	14 (1.2)
Chest discomfort	1 (0.3)	7 (0.9)	8 (0.7)
Chest pain	1 (0.3)	7 (0.9)	8 (0.7)
Seasonal allergy	0	4 (0.5)	4 (0.4)

Source: Table 3.1-2.1.2

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

10.6.1.4 Outcome of non-serious adverse events

Given the non-interventional nature of the study, data on the outcome of the non-serious AEs is missing from many cases. Where data are available, the majority of patients in both groups recovered ([Table 10-24](#)).

Table 10-24 Outcome of non-serious adverse events (by patients) (safety set)

	LABA/LAMA fixed (N=340) n (%)	LABA+LAMA+ICS (N=784) n (%)	Total (N=1124) n (%)
Number (%) of patients with at least one event	44 (12.9)	118 (15.1)	162 (14.4)
Recovered	26 (7.6)	51 (6.5)	77 (6.9)
Condition improved	7 (2.1)	18 (2.3)	25 (2.2)
Not recovered	6 (1.8)	14 (1.8)	20 (1.8)
Unknown	2 (0.6)	13 (1.7)	15 (1.3)
not reported	1 (0.3)	1 (0.1)	2 (0.2)

	LABA/LAMA fixed (N=340) n (%)	LABA+LAMA+ICS (N=784) n (%)	Total (N=1124) n (%)
missing values	5 (1.5)	33 (4.2)	38 (3.4)

Source: Table 3.1-2.2.2.3

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

10.6.1.5 Non-serious adverse events of special interest

There were no non-serious AEs of special interest as specified for Ultibro[®] Breezhaler[®] or glycopyrronium.

10.6.2 Serious adverse events

10.6.2.1 Display of serious adverse events

The proportion of patients with an SAE was lower in the LABA/LAMA FDC group than the triple therapy group (Table 10-25). The most commonly-reported MedDRA system organ class in both groups was respiratory, thoracic and mediastinal.

Table 10-25 Serious adverse events (by patients and overall event rates) - overall and by MedDRA system organ class (safety set)

	LABA/LAMA fixed (N=340) n (%)	LABA+LAMA+ICS (N=784) n (%)	Total (N=1124) n (%)
Number (%) of patients with at least one event	27 (7.9)	108 (13.8)	135 (12.0)
Event rates per 100 patient-years	12.251	35.543	
Cardiac disorders	3 (0.9)	19 (2.4)	22 (2.0)
Ear and labyrinth disorders	0	1 (0.1)	1 (<0.1)
Eye disorders	0	1 (0.1)	1 (<0.1)
Gastrointestinal disorders	0	4 (0.5)	4 (0.4)
General disorders and administration site conditions	5 (1.5)	23 (2.9)	28 (2.5)
Hepatobiliary disorders	0	1 (0.1)	1 (<0.1)
Immune system disorders	0	2 (0.3)	2 (0.2)
Infections and infestations	12 (3.5)	25 (3.2)	37 (3.3)
Injury, poisoning and procedural complications	0	4 (0.5)	4 (0.4)
Investigations	0	10 (1.3)	10 (0.9)
Metabolism and nutrition disorders	0	2 (0.3)	2 (0.2)
Musculoskeletal and connective tissue disorders	0	2 (0.3)	2 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.6)	4 (0.5)	6 (0.5)

	LABA/LAMA fixed (N=340) n (%)	LABA+LAMA+ICS (N=784) n (%)	Total (N=1124) n (%)
Nervous system disorders	1 (0.3)	2 (0.3)	3 (0.3)
Psychiatric disorders	0	2 (0.3)	2 (0.2)
Renal and urinary disorders	0	4 (0.5)	4 (0.4)
Respiratory, thoracic and mediastinal disorders	11 (3.2)	66 (8.4)	77 (6.9)
Skin and subcutaneous tissue disorders	0	2 (0.3)	2 (0.2)
Surgical and medical procedures	1 (0.3)	2 (0.3)	3 (0.3)
Vascular disorders	1 (0.3)	8 (1.0)	9 (0.8)

Sources: Tables 3.1-3.1.3 (numbers and percentages) and 3.1-3.4 (event rate)

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

10.6.2.2 Analysis of serious adverse events

As with the non-serious AEs, the most frequently reported SAEs by preferred term were those related to the underlying condition – with the most common being COPD (worsening or exacerbation) (Table 10-26).

Table 10-26 Serious adverse events (by patients and event rates) - overall and most common preferred term ($\geq 0.5\%$ in either group) (safety set)

	LABA/LAMA fixed (N=340)		LABA+LAMA+ICS (N=784)		Total (N=1124)
	n (%)	Event rate per 100 pt- yrs	n (%)	Event rate per 100 pt- yrs	n (%)
Number (%) of patients with at least one event	27 (7.9)	12.251	108 (13.8)	35.543	135 (12.0)
Chronic obstructive pulmonary disease	6 (1.8)	1.994	55 (7.0)	10.881	61 (5.4)
Infective exacerbation of chronic obstructive airways disease	6 (1.8)	1.994	7 (0.9)	1.088	13 (1.2)
Pneumonia	4 (1.2)	1.425	7 (0.9)	0.967	11 (1.0)
Dyspnea at rest	2 (0.6)	0.570	15 (1.9)	1.934	17 (1.5)
Death	2 (0.6)	0.570	8 (1.0)	0.967	10 (0.9)
Dyspnea	2 (0.6)	0.570	3 (0.4)	0.363	5 (0.4)
Cardiac failure	1 (0.3)	0.285	9 (1.1)	1.088	10 (0.9)
Forced expiratory volume decreased	0		7 (0.9)	0.967	7 (0.6)
Adverse event	0		4 (0.5)	0.604	4 (0.4)
Chest discomfort	0		4 (0.5)	0.604	4 (0.4)

Source: Tables 3.1-3.1.3 (numbers and percentages), and 3.1-3.5 (event rates)

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

10.6.2.3 Suspected relationship of serious adverse events to the study

The majority of events were not considered study related. Of those that were considered related, the percentage of patients with at least one SAE was lower in the LABA/LAMA FDC group (Table 10-27).

Table 10-27 Most common ($\geq 0.3\%$ in either group) serious adverse events suspected related to the study or relationship not assigned - overall and by preferred term (safety set)

	LABA/LAMA fixed (N=340) n (%)	LABA+LAMA+ICS (N=784) n (%)	Total (N=1124) n (%)
Number (%) of patients with at least one event	5 (1.5)	31 (4.0)	36 (3.2)
Chronic obstructive pulmonary disease	1 (0.3)	15 (1.9)	16 (1.4)
Drug ineffective	1 (0.3)	2 (0.3)	3 (0.3)
Sinobronchitis	1 (0.3)	1 (0.1)	2 (0.2)
Acute coronary syndrome	1 (0.3)	0	1 (<0.1)
Pneumonia	1 (0.3)	0	1 (<0.1)
Cholecystectomy	1 (0.3)	0	1 (<0.1)
Dyspnea at rest	0	6 (0.8)	6 (0.5)
Death	0	3 (0.4)	3 (0.3)
Forced expiratory volume decreased	0	2 (0.3)	2 (0.2)
Respiratory tract infection	0	1 (0.1)	1 (<0.1)

Source: Table 3.1-3.1.2

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

10.6.2.4 Outcome of serious adverse events

As mentioned in Section 10.6.1.4, the non-interventional nature of this study means that outcomes data are missing for many of the AEs. Where data are available, the majority of patients recovered following a SAE (Table 10-28).

Table 10-28 Serious adverse events (by patients) - outcomes (safety set)

	LABA/LAMA fixed (N=340) n (%)	LABA+LAMA+ICS (N=784) n (%)	Total (N=1124) n (%)
Number (%) of patients with at least one event	5 (1.5)	31 (4.0)	36 (3.2)
Recovered	18 (5.3)	62 (7.9)	80 (7.1)
Recovered with sequelae	-	4 (0.5)	4 (0.4)
Condition improved	1 (0.3)	28 (3.6)	29 (2.6)
Not recovered	2 (0.6)	15 (1.9)	17 (1.5)
Condition worsened	-	6 (0.8)	6 (0.5)
Fatal	3 (0.9)	18 (2.3)	21 (1.9)
Unknown	2 (0.6)	7 (0.9)	9 (0.8)
not reported	-	3 (0.4)	3 (0.3)
missing values	3 (0.9)	16 (2.0)	19 (1.7)

Source: Table 3.1-3.2.2.3

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

10.6.2.5 Deaths

A total of 21 patients died during the study, with a lower proportion of patients in the LABA/LAMA FDC dying than in the triple therapy group (Table 10-29). The MedDRA system organ class and preferred terms for the SAEs with a fatal outcome are shown in Table 10-29. Note that this table lists the events with a fatal outcome, not necessarily the cause of death. Furthermore, five patients in the triple therapy group (and none in the LABA/LAMA FDC group) had fatal events that were considered related to the study (Table 10-30).

Table 10-29 Fatal serious adverse events (by patients) – overall, by MedDRA system organ class and preferred term (safety set)

	LABA/LAMA fixed (N=340) n (%)	LABA+LAMA+ICS (N=784) n (%)	Total (N=1124) n (%)
Number (%) of patients with at least one fatal SAE	3 (0.9)	18 (2.3)	21 (1.9)
Event rates per 100 patient-years	1.994	2.781	
Cardiac disorders	0	3 (0.4)	3 (0.3)
Cardiac failure	0	1 (0.1)	1 (0.1)
Myocardial infarction	0	1 (0.1)	1 (0.1)
Right ventricular failure	0	1 (0.1)	1 (0.1)

	LABA/LAMA fixed (N=340) n (%)	LABA+LAMA+ICS (N=784) n (%)	Total (N=1124) n (%)
General disorders and administration site conditions	2 (0.6)	12 (1.5)	14 (1.2)
Adverse event	0	4 (0.5)	4 (0.4)
Death	2 (0.6)	8 (1.0)	10 (0.9)
Infections and infestations	1 (0.3)	1 (0.1)	2 (0.2)
Infective exacerbation of chronic obstructive airways disease	0	1 (0.1)	1 (0.1)
Pneumonia	1 (0.3)	1 (0.1)	2 (0.2)
Sepsis	1 (0.3)	1 (0.1)	2 (0.2)
Septic shock	1 (0.3)	0	1 (0.1)
Injury, poisoning and procedural complications	0	1 (0.1)	1 (0.1)
Fall	0	1 (0.1)	1 (0.1)
Renal and urinary disorders	0	1 (0.1)	1 (0.1)
Renal failure	0	1 (0.1)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	1 (0.1)	2 (0.2)
Acute respiratory distress syndrome	1 (0.3)	0	1 (0.1)
Dyspnea	0	1 (0.1)	1 (0.1)
Surgical and medical procedures	0	1 (0.1)	1 (0.1)
Hospitalization	0	1 (0.1)	1 (0.1)

Source: Tables 3.1-3.2.2.3 (numbers and percentages), and 3.1-4.2 (event rates)

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

Table 10-30 Study-related fatal serious adverse events (by patients) – overall, by MedDRA system organ class and preferred term (safety set)

	LABA/LAMA fixed (N=340) n (%)	LABA+LAMA+ICS (N=784) n (%)	Total (N=1124) n (%)
Number (%) of patients with at least one fatal SAE	0	5 (0.6)	5 (0.4)
Cardiac disorders	0	2 (0.3)	2 (0.2)
Cardiac failure	0	1 (0.1)	1 (0.1)
Myocardial infarction	0	1 (0.1)	1 (0.1)
General disorders and administration site conditions	0	3 (0.4)	3 (0.3)
Death	0	3 (0.4)	3 (0.3)
Injury, poisoning and procedural complications	0	1 (0.1)	1 (0.1)
Fall	0	1 (0.1)	1 (0.1)

Source: Table 3.1-3.2.2.2

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

10.6.2.6 Serious adverse events of special interest

The only SAEs of special interest for glycopyrronium bromide that occurred during the study in a patient receiving glycopyrronium bromide was supraventricular tachycardia, which was not considered study related ([Table 10-31](#)).

Table 10-31 Serious adverse events of special interest (for glycopyrronium bromide) (by patients) - overall, and by MedDRA class and preferred term (safety set, subset of patients receiving glycopyrronium bromide at any time during the observation period)

	LABA/LAMA fixed (N=1) n (%)	LABA+LAMA+ICS (N=57) n (%)	Total (N=58) n (%)
Number (%) of patients with at least one event	0	1 (1.8)	1 (1.7)
Tachyarrhythmias	0	1 (1.8)	1 (1.7)
Supraventricular Tachycardia	0	1 (1.8)	1 (1.7)

Source: Table 3.1-3.3.3

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

SAEs of special interest for Ultibro Breezhaler occurring during the study in patients receiving Ultibro Breezhaler are shown in [Table 10-32](#). A higher proportion of patients receiving ICS in addition to Ultibro Breezhaler (the triple therapy group) reported these events than those only receiving Ultibro Breezhaler (the LABA/LAMA FDC group). Only three patients had events that were considered study related: Acute coronary syndrome in a patient in the LABA/LAMA FDC group; and cardiac failure (one of the patients) and myocardial infarction in the triple therapy group.

Table 10-32 Serious adverse events of special interest (for Ultibro Breezhaler) (by patients) - overall, and by MedDRA class and preferred term (safety set, subset of patients receiving Ultibro Breezhaler at any time during the observation period)

	LABA/LAMA fixed (N=246) n (%)	LABA+LAMA+ICS (N=193) n (%)	Total (N=439) n (%)
Number (%) of patients with at least one event	3 (1.2)	5 (2.6)	8 (1.8)
Atrial fibrillation	0	1 (0.5)	1 (0.2)
Atrial fibrillation	0	1 (0.5)	1 (0.2)
Cardiac failure	1 (0.4)	3 (1.6)	4 (0.9)
Cardiac failure	1 (0.4)	2 (1.0)	3 (0.7)
Right ventricular failure	0	1 (0.5)	1 (0.2)

	LABA/LAMA fixed (N=246) n (%)	LABA+LAMA+ICS (N=193) n (%)	Total (N=439) n (%)
Cerebrovascular events	1 (0.4)	0	1 (0.2)
Ischemic cerebral infarction	1 (0.4)	0	1 (0.2)
Ischemic heart disease	0	1 (0.5)	1 (0.2)
Angina pectoris	0	1 (0.5)	1 (0.2)
Myocardial infarction	1 (0.4)	1 (0.5)	2 (0.5)
Acute coronary syndrome	1 (0.4)	0	1 (0.2)
Myocardial infarction	0	1 (0.5)	1 (0.2)
Tachyarrhythmias	0	1 (0.5)	1 (0.2)
Atrial fibrillation	0	1 (0.5)	1 (0.2)

Source: Table 3.1-3.3.2

LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

11 Discussion

11.1 Key results

The overall aim of Recruitment Phase 3 of DACCORD was to evaluate effectiveness and safety over 1 year in patients with COPD who were switching from inhaled triple therapy to a LABA/LAMA FDC, in comparison to those who continued inhaled triple therapy. Importantly, the study was non-interventional (with treatment decisions not influenced by study participation), and patients received standard clinical care at primary and secondary practices throughout Germany.

Given slower than anticipated recruitment, fewer patients were recruited than originally planned, and there was an imbalance in the number in each group (363 in the LABA/LAMA FDC group and 829 in the triple therapy group). However, these lower numbers were considered sufficient to address the overall study aim. The majority of the baseline demographics were similar between the two groups, although patients in the LABA/LAMA FDC group were more likely to be female, and a higher proportion were aged >75 years (though the mean ages were similar). Disease characteristics were also similar in the two groups. All patients were symptomatic on entry, and 47.3% had experienced at least one COPD exacerbation in the previous year, suggesting that those included in this recruitment phase had a higher disease burden than those recruited into Recruitment Phases 1 and 2. Unfortunately the most common reason selected for switching a patient from inhaled triple therapy to LABA/LAMA FDC was 'other', so the exact reasons are unclear.

During the 1-year follow-up period, patients switched to a LABA/LAMA FDC had overall better outcomes than those who continued inhaled triple therapy, with a lower percentage having a worsening of COPD (in terms of the overall analysis and the two components [CAT and exacerbations]), an extension to the time to worsening of COPD, a reduction in exacerbation occurrence, and an improvement in health-related quality of life (CAT total score). There were, however, minimal differences between groups in terms of lung function and symptoms – although this could have been influenced by the non-interventional nature of the study (there

was no requirement for timing of the visits, so patients may have taken their medication before or after visits) or that the symptoms questionnaire was only administered at the visits.

Eosinophil data were collected for all patients at baseline, potentially from samples taken up to 12 months prior to study entry. This was intended to evaluate the predictive value of blood eosinophil count for subsequent outcomes. There was high variability in these counts, and a resultant negligible correlation between baseline blood eosinophil count and subsequent change in CAT total score, and no consistent trends in blood eosinophil count across exacerbation categories. In patients who had a worsening in COPD, the baseline eosinophil count was lower than in those who had an improvement – although again there was high variability in these eosinophil values. This suggests that, in this population at least, eosinophil values have limited utility in predicting subsequent outcomes. Further, mean eosinophil values changed little over the follow-up period (although data were only available for a small subset of patients at Visits 1 to 4, and it is possible that the data came from different patients at each visit). Previous analyses have suggested that ICS-containing therapy (including inhaled triple therapy) is most useful in patients with COPD who have higher blood eosinophil counts (especially consistently high values ([Chapman 2018](#))), with a cut-point of 300 cells/ μ L suggested in GOLD for initiation of ICS ([GOLD 2021](#)). Although the DACCORD analyses are not consistent with this, it is always challenging to compare studies of contrasting designs (especially non-interventional vs. RCT), when differences in patient characteristics can influence the results (a much higher percentage of patients entering this phase of DACCORD had an exacerbation history than entering SUNSET ([Chapman 2018](#))), and we analyzed the correlations in all patients, so effectively ignoring the ICS effect.

Overall, the safety and tolerability profile of the LABA/LAMA FDC group was better than that of the triple therapy group, with a lower proportion of patients experiencing non-serious AEs, SAEs or fatal adverse events in the LABA/LAMA FDC group. Few patients in either treatment group were considered to have events considered related to the study.

Recruitment into this phase of DACCORD was not limited to specific molecules. A total of 58 patients in the safety set were receiving glycopyrronium bromide (one and 57 in the LABA/LAMA FDC and triple therapy groups, respectively) and 439 were receiving Ultibro Breezhaler (246 and 193, respectively). When analyzed in these patients, the occurrence of SAEs of special interest for glycopyrronium bromide or Ultibro Breezhaler were low, and almost all events were considered not study related. The results therefore do not change the overall risk-benefit profile of either Ultibro Breezhaler or Seebri Breezhaler.

11.2 Limitations

The study recruited a broad population from study centers across Germany. However, to be eligible all patients had to be previously receiving inhaled triple therapy, and to either continue that therapy or switch to a LABA/LAMA FDC; the results therefore apply only to this population. In addition, as a non-interventional, observational study, the data available are only those collected from standard clinic visits, with a limited opportunity to follow-up on missing or implausible data. Finally, consistent with the non-interventional status of the study, all data are collected from the study centers' own equipment and laboratories. In contrast, an interventional study would typically use dedicated spirometry equipment (of all one make and

model), potentially with a central over-read, and a centralized laboratory to process, for example, the eosinophil data.

11.3 Interpretation

Overall, Recruitment Phase 3 of DACCORD confirmed that withdrawal of ICS in patients receiving inhaled triple therapy can be achieved by switching to a LABA/LAMA FDC, supporting and extending the results of WISDOM ([Magnussen 2014](#)) and SUNSET ([Chapman 2018](#)). These previous studies were conducted as RCTs; in contrast, the non-interventional nature of DACCORD means that the decision to de-escalate therapy was left to the investigator (presumably in discussion with the patient, given the need for informed consent on entry). The reason for therapy change or continuation was captured, and it was hoped that this would provide interesting information on standard care. In the event, the inclusion of an 'other' option limits the conclusions that can be drawn on the reasons for stepping down therapy, but the similarity of the demographics and disease characteristics at baseline between the two groups suggest that physicians are making the decision on the basis of criteria other than purely these parameters. In particular, the decision was not based on symptoms or exacerbation history.

The two previous RCTs generally demonstrated that withdrawal of ICS from inhaled triple therapy did not lead to a marked worsening in patients' COPD. The results from these analyses of DACCORD not only suggest that there is no overall worsening in patients switched from triple therapy to LABA/LAMA FDC, but that LABA/LAMA FDC may be more effective than triple therapy. There are a number of potential reasons for this. First, many patients would presumably not just have the ICS withdrawn, but be switched to different LABA and LAMA molecules, since 72.4% of patients in the LABA/LAMA FDC group (246/340) were receiving the FDC of indacaterol and glycopyrronium bromide (at the time DACCORD was recruiting no indacaterol-containing ICS/LABA FDC was available, and the triple therapy combination of indacaterol, glycopyrronium and the ICS mometasone was only approved in 2020 – and then only for asthma). In contrast, many (if not all) patients in the comparator group would presumably continue with their prior triple therapy. Given none of the treatments were blinded, it is possible that the receipt of a new medication from such a change may explain a difference in subjective parameters (including health-related quality of life and symptoms). Lack of blinding is less likely to explain the improvement in the (presumably) more objective exacerbations-related endpoints. Another reason could be that adherence was improved by patients using a single LABA/LAMA FDC inhaler once-daily – almost all patients in the triple therapy arm were on a twice-daily regimen, with the vast majority using at least two different inhalers. This is important, as decreasing the number of daily doses and the number of different inhalers has the potential to improve medication adherence ([Toy 2011](#); [Yu 2011](#)). However, adherence was not captured in DACCORD – the only data available are the percentage of patients who completed the 1-year follow-up in both groups, and the proportion who completed with no therapy regimen change, neither of which suggest a difference between the two groups.

The safety and tolerability data also overall support the switch from inhaled triple therapy to LABA/LAMA FDC. The proportions of patients with one or more AE or SAE were lower in the LABA/LAMA FDC group than the triple therapy group, with the majority of the events reported being those associated with COPD itself. Importantly, very few patients had AEs or

SAEs that were considered related to the study, and only five patients (all in the triple therapy group) had fatal adverse events considered study related.

Overall, therefore, the results of this recruitment phase of DACCORD suggest that physicians are able to identify patients who can be ‘stepped down’ from inhaled triple therapy to a LABA/LAMA FDC (although not necessarily based on easily identifiable demographic or disease characteristics). When such patients have their therapy stepped down, there is no overall decline in their disease – and some patients may have a benefit in terms of exacerbations, health-related quality of life, or overall disease control.

11.4 Generalizability

Given this study recruited a broad, geographically diverse population from primary and secondary care, the results can be generalized to patients with COPD across Germany who are receiving inhaled triple therapy.

12 Other information

This study report presents the results of Recruitment Phase 3 of DACCORD. The results of Recruitment Phases 1 and 2 have been presented in a previous study report [\[Bernschneider. CNVA237ADE01 Non-Interventional Study Final Report \(Recruitment Phases 1 and 2\). 25 January 2019\]](#). The overall aim of these two phases were to evaluate the impact and progression of COPD in a population that was representative of patients in Germany. In Recruitment Phase 1, patients received either a regimen that included glycopyrronium bromide or a regimen of other anti-obstructive therapy (i.e., maintenance COPD therapy excluding glycopyrronium bromide). Recruitment Phase 2 was of patients receiving either a regimen that included a LABA/LAMA FDC, or a regimen of other anti-obstructive therapy. Unlike Recruitment Phase 3, all patients initiated or changed COPD maintenance medication on entry to Phases 1 and 2 of DACCORD (although the change could be within therapeutic class), and no formal statistical comparisons between treatment groups were prespecified. Further, patients were permitted to take any concomitant COPD maintenance therapy. For the previous study report, results of these two cohorts were combined, and were presented as three treatment groups: the glycopyrronium bromide group; the LABA/LAMA FDC group; and ‘other’.

The Recruitment Phase 1 and 2 population had a high symptom load (similar to Recruitment Phase 3), with a subset of patients also having an exacerbation history (interestingly, a higher proportion of patients in Recruitment Phase 3 had an exacerbation history, although direct comparison is difficult, as Phase 3 collected data for a full 12 months whereas Phases 1 and 2 only collected a 6-month history). A substantial proportion of patients also had comorbidities (more than half having cardiovascular disease, compared to approximately 60% in Recruitment Phase 3). The substantial use of concomitant COPD maintenance medication in Recruitment Phases 1 and 2 complicates the interpretation of the data, but the results overall demonstrated the benefits possible through switching medication (in particular with the use of a LABA/LAMA FDC).

The COVID-19 pandemic had minimal impact on Recruitment Phase 3, because at the start of the pandemic, 100% of patients had been enrolled (and the decision to cease further recruitment had already been taken), and around 70% had already completed the 1 year follow-up period.

It is likely that individual follow-up visits were postponed by either patients or physicians due to the pandemic, but as this was a non-interventional study the three-monthly interval for follow-up visits was only a suggestion from the start (in accordance with typical COPD management) and any delays would have had limited impact on data integrity.

13 Conclusion

Overall, DACCORD Recruitment Phase 3 builds on the results of Phases 1 and 2, providing useful data on the course of COPD in Germany, and supporting the potential benefit to selected patients in switching from triple therapy to a LABA/LAMA FDC. The safety data do not change the overall benefit-risk profile of glycopyrronium or the glycopyrronium/indacaterol FDC.

14 References

References are available upon request.

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Appendices

Annex 1 – List of stand-alone documents

1. Study investigators and other important participants.

Annex 1 List of investigators and other important participants in the study

1 Study investigators and other important participants

