Protocol Amendment 2

Study ID: 214468

Official Title of Study: Triple thErapy in paTients With COPD Under Real lIve Setting (the TETRIS Study)

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NON-INTERVENTIONAL STUDY PROTOCOL

UNIQUE IDENTIFIER	214468
TITLE	Triple thErapy in paTients with COPD under Real lIve Setting (the TETRIS study)
STUDY ACCOUNTABLE PERSON	Dr. med. PPD GSK
CONTRIBUTING AUTHORS	Dr. PPD Medical Advisor, GSK Dr. PPD Medical Advisor, IDS **Steering Committee:** Prof. Dr. med PPD University Hannover (MHH, Hannover) Prof. Dr. med. PPD for Internal Medicine Center of Pulmonology, University Medical Center Marburg PD. Dr. med. PPD Research Institute (PRI) at LungenClinic Großhansdorf PD. Dr. med. PPD PPD insaf Respiratory Research Institute, Wiesbaden PD. Dr. med. PPD settled pulmonologist, Frankfurt

ASSET ID	GSK2834425
GSK ASSET	Fixed-dose combination of fluticasone furoate / umeclidinium / vilanterol (Trelegy Ellipta)
INDICATION	Moderate to severe chronic obstructive pulmonary disease (COPD)
PHASE OF DEVELOPMENT	Post-launch

REVISION CHRONOLOGY

Date	Version	Change(s) since last version
25-Aug-2020	Version 1.0 final	N/A
08-Dec-2020	Version 1.1 final	Various specifications in Section 6.4 (Adverse Event, Pregnancy Exposure and Incident Reporting) Addition of appendix 4 and 5 Number of patients were changed from 2300 to 2050 in total Removal of physical activity tracking by fitness wristband
29-July-2021	Version 1.2 final	Extension of SITT or MITT treatment period prior to enrolment from 6-18 weeks to at least 6 but not longer than 48 weeks (inclusion criterion) Extension of the maximum study population per study site to 50
14-Feb-2022	Version 2.0 final	Extension of SITT or MITT treatment period prior to enrolment from 6-48 weeks to at least 2 but not longer than 48 weeks (inclusion criterion) Sample size was changed from 2050 to 1100 in total Extension of the maximum study population per study site to 100 Removal of Cohort C (patients from outpatient lung centres) and total patient number per physician group Revision and adaptation of chapters: 3.5, (3.6), 4 and 9

SPONSOR SIGNATORY

Dr. med. Moritz Meissner

Digital unterschrieben von Dr. med. Moritz Meissner
Datum: 2022.02.16 12:19:28 +01'00'

Senior Line Manager | Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:

PPD

Investigator Signature | Date (DD-MMM-YYYY)

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Abbreviations

AE	Adverse Event
AMG	German Medicines Act (Deutsches Arzneimittelgesetz)
BMI	Body Mass Index
CAT	COPD Assessment Test
COPD	Chronic Obstructive Pulmonary Disease
COPD*	COPD with or without comorbid comorbid asthma
CRO	Contract Research Organisation
CT	Computed Tomography
DLCO	Diffusing capacity of lung for carbon monoxide
DR	Dropout Rate
eCRF	Electronic Case Report Form
EOS	Eosinophils
EQ-5D / VAS	European Quality of Life 5 Dimensions / Visual Analogue Scale
FeNO	Fraction Exspiratory Nitric Oxide
FEV1	Forced Expiratory Volume in 1 second
FF/UMEC/VI	Fluticasone Furoate / Umeclidinium / Vilanterol
FSA	Voluntary self-control of pharmaceutical industry (freiwillige Selbstkontrolle der Arzneimittelindustrie)
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
HCP	Healthcare Professional
HRQoL	Health-related Quality of Life
HRU	Healthcare Resource Utilisation
hsCRP	High-sensitivity C-reactive protein
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
ICU	Intensive Care Unit
IHD	Individual Human Data
LABA	Long-Acting Beta 2 Agonist
LAMA	Long-Acting Muscarinic Antagonist

MITT	Multiple Inhaler Triple Therapy
OCS	Oral Corticosteroids
PROs	Patient-Reported Outcomes
QoL	Quality of Life
SAP	Statistical Analysis Plan
SAE	Serious Adverse Events
SD	Standard Deviation
SITT	Single-Inhaler Triple Therapy
WBC count	White Blood Cell count
WBC differential	White Blood Cell Count differential test
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

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1. BACKGROUND AND RATIONALE

Burden of chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a disabling respiratory disease characterised by airflow obstruction and associated symptoms, including breathing difficulties caused by shortness of breath and wheezing, airway hyperactivity, chronic cough, sputum production, exercise intolerance, and poor quality of life [Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020]. The main risk factor for COPD is tobacco smoking but other environmental exposures such as biomass fuel exposure and air pollution may contribute. Besides exposures, host factors predispose individuals to develop COPD. These include genetic abnormalities, abnormal lung development and accelerated aging [GOLD 2020].

According to [World Health Organization (WHO)] over 251 million people worldwide suffer from COPD [WHO 2016]. According to prevalence estimates, in Germany ten to twelve percent of adults older than 40 years are affected by COPD [Umweltbundesamt 2020]. While in 2010, 6.8 million people suffered from COPD in Germany, this number is expected to increase up to 7.9 million by 2030 [Umweltbundesamt 2020].

COPD is currently the third leading cause of death worldwide [Lozano 2012], with over 3 million reported deaths in 2016 (5.4% of all global deaths) [WHO 2016]. In contrast to coronary heart disease and stroke, it is the only leading cause of death with still increasing number [May 2015]. COPD is moreover, the second leading cause of (avoidable) hospitalizations: The admission rates are expected to exceed that of ischemic heart diseases within the next five years [Khakban 2017]. This underlines the unmet medical need for early COPD diagnosis and treatment optimisation. It is therefore of paramount importance to provide these patients with effective and safe medication to control symptoms and improve quality of life. It is also crucial to slow down the progression of the disease by preventing exacerbations and hospital stays, thereby reducing mortality rate [GOLD 2020].

The mainstay of pharmacological therapy for COPD is bronchodilation with a long-acting muscarinic antagonist (LAMA), a long-acting beta 2 agonist (LABA), or a combination of both, depending on the severity of breathlessness and the patient's risk of exacerbations [GOLD 2020]. Combinations of inhaled corticosteroids (ICS), long-acting beta 2 agonists (LABAs), and long-acting muscarinic antagonists (LAMAs) are also recommended for COPD maintenance therapy [GOLD 2020].

GOLD recommendations for triple therapy

At least 50% of patients with COPD fails to achieve adequate control of symptoms or exacerbation risk reduction while receiving only a single long-acting bronchodilator, such as a LAMA or LABA[Dransfield 2011]. Escalation to multiple bronchodilators with or without an inhaled corticosteroid (ICS) will depend on the patient's symptom burden (including dyspnoea, cough, sputum production as assessed by the COPD assessment test or modified Medical Research Council breathlessness scores) and risk of exacerbations [GOLD 2020]. Fixed-dose LAMA/LABA is relatively new to the market and the LAMA/LABA treatment recommendation was included in the GOLD report from 2017 onwards [Bogart 2018, GOLD 2020]. Current treatment guidelines recommend the use of triple therapy with an ICS/LAMA/LABA for

patients currently on bronchodilators with persistent symptoms and/or at risk for future exacerbations [Bogart 2018, GOLD 2020].

In addition to multiple inhaler triple therapy (MITT) with multiple inhalers, single inhaler triple therapy (SITT) is currently available. The first SITT product for the treatment of COPD (Trimbow, a twice-daily SITT) was approved in the European Union in July 2017, followed by Trelegy Ellipta (a once-daily SITT) in November 2017. The approval of another SITT product (Breztri Aerosphere) is expected in the near future.

Several recent studies have demonstrated the efficacy of SITT for the treatment of COPD patients with moderate-to-severe exacerbations [Ferguson 2018, Lipson 2017, Lipson 2018, Singh 2016, Vestbo 2017]. COPD exacerbations are common occurrences that cause a major burden of illness [GOLD 2020, Halpin 2017, McDonald 2019 (b)]. They are associated with impaired health status, decrease in lung function, hospitalization and increased risk of death. Exacerbation avoidance is therefore a major priority [GOLD 2020, McDonald 2019 (b)].

The use of SITT resulted in reduced rates of moderate-to-severe exacerbations compared with monotherapy [Vestbo 2017] and dual therapy [Lipson 2017, Singh 2016]. The IMPACT study evaluated the effects of SITT in comparison to therapy with either a LAMA/LABA or an ICS/LABA in symptomatic patients with risk of exacerbations. The results of this study demonstrated that SITT significantly reduced the rate of moderate-to-severe exacerbations, improved lung function and health-related quality of life scores, when compared with both dual therapies at 52 weeks timepoint [Lipson 2018]. A secondary analysis from the IMPACT trial proved that treatment of symptomatic patients with COPD and a history of exacerbation with a once-daily SITT significantly reduced the risk of all-cause mortality compared with a dual bronchodilator (LAMA/LABA) combination [Lipson 2020].

Triple therapy forCOPD in routine clinical practice

The GOLD recommendations suggest escalation to triple therapy for patients with a high symptom burden and high exacerbation risk, who develop further exacerbations while being treated with maximum bronchodilator therapy [GOLD 2020]. However, prescription behavior is not always aligned with these recommendations [Visentin 2016]. Treatment decisions in routine clinical practice may be different and can deviate from treatment recommendations. A retrospective survey in clinical routine found that approximately 10% of patients received triple therapy without prior bronchodilator use or exacerbation history [Bogart 2018]. Possible rationales could have been based on persistent symptoms reported by the patients, mild or unobserved exacerbations, or spirometry results [Bogart 2018].

A retrospective German study from 2018 revealed that treatment of COPD patients by experienced lung specialists seemed also to diverge from GOLD recommendations, probably leading to widespread under-treatment [Greulich et al., GSK data on file]. A significant number of patients under triple therapy received five or more different COPD medications during one year of treatment. Furthermore, data from this trial revealed that de-escalation of triple therapy in symptomatic COPD patients with a recent history of exacerbations via step-down to LAMA/LABA or ICS/LABA was common practice by many lung specialists [Greulich et al., data on file].

So far, limited data is available on how decisions regarding escalation to triple and de- or re-escalation are actually taken in COPD treatment reality in Germany and based on which rationale.

For further treatment optimisation, it is crucial to evaluate which patients with their individual disease characteristics particularly benefit from an escalation or de-escalation of therapy. This requires long-term data, which needs to last beyond a one-year observation period that is often chosen in controlled clinical trials.

Individualising COPD therapy: phenotyping and treatable traits

Obstructive lung diseases such as COPD and asthma have diverse aetiology and disease mechanisms, and manifest with a range of symptoms. The impact of each disease on individual patients is also heterogeneous. This heterogeneity and complexity have led to the recognition that treatment approaches cannot be 'one size fits all', but individualised treatment regimens are needed for chronic airway diseases [McDonald 2019 (a)]. Chronic bronchitis versus predominant emphysema as well as COPD with concomitant asthma are well recognized phenotypes in COPD [GOLD 2020]. GOLD does not longer refer to asthma & COPD overlap (ACO), instead it is emphasized that asthma and COPD are different disorders, although they may share common traits and clinical features (e.g., increase in eosinophilia level) [GOLD 2020].

A concept of treatable traits has developed over the last decade following recognition that chronic airway diseases are complex syndromes which require individualised assessment, investigation and treatment [Agusti 2016, Gibson 2010, Fingleton 2018]. Treatable traits are disease characteristics that are clinically relevant, identifiable and modifiable [McDonald 2019 (a)]. The treatable trait strategy was initially proposed in 2016 [Agusti 2016], building on previous work that proposed multidimensional assessment and treatment approaches for individual respiratory diseases [Gibson 2010]. Subsequent international workshops have been convened to seek expert consensus on how to apply and progress a treatable traits strategy for clinical management [Agusti 2017, McDonald 2019 (b)].

The treatable traits strategy incorporates a number of elements. Inherent to its approach is a multidimensional assessment of each individual patient to determine which traits exist in that patient. Multidimensional assessment can be used to identify the range of traits within an individual and involves a clinical history and examination, an evaluation of risk factors, and measurement of spirometry and blood eosinophils. The treatable traits strategy aims to support an individualised and targeted treatment approach [McDonald (a)]. Some of the treatable traits in COPD include airflow limitation, cachexia, reduced mobility, smoking, and eosinophilic airway inflammation [Sin 2020].

Poor mobility and impaired physical activity are major concerns in COPD patients, and reduced mobility is an underestimated clinical feature of COPD [Sin 2020]. Smoking is related to a rapid decline in lung function in COPD patients [Sin 2020]. Increased concentrations of blood eosinophils (EOS) in patients with COPD have been associated with increased frequency of exacerbation and reduction in lung function [Bafadhel 2011]. There is substantial evidence that a raised blood EOS count could be a biomarker for predicting patient response to inhaled corticosteroids (ICS) in COPD [DiSantostefano 2016, Zysman 2017]. In a clinical trial, a greater

decline in forced expiratory volume in 1 second (FEV_1) was observed in COPD patients with high blood EOS counts who were not treated with ICS [Barnes 2016].

Scientific Rationale for the TETRIS study

In accordance with the GOLD recommendations, it is important to assess the characteristics and treatment patterns of patients prior to triple therapy initiation, in order to determine adherence to these guidelines and understand how patients progress to triple therapy. Despite a clearly defined guidance from GOLD treatment recommendations for the initiation and maintenance of triple therapy, treatment changes in Germany, including de-escalation, are often seen in treatment reality. The TETRIS study is intended to provide information on how many COPD patients remain continuously on triple therapy in Germany. The reasons for treatment changes are hardly known, as are possible clinical consequences. Therefore, this observational study will also retrospectively capture the reasons in Germany to put the patients on MITT or SITT considering existing treatment recommendations. When evaluating all information that is collected about the therapy and patient environment, SITTs and MITTs will be looked at both separately and combined.

TETRIS will observe patients with COPD with or without comorbid asthma (hereinafter summarized as COPD*) who are on an existing combined treatment of LAMA, LABA and ICS. The study is intended to gain a better understanding of what influences the treatment decision of German physicians in primary and secondary care under real life conditions. TETRIS is also designed to elicit the reasons for treatment changes and to describe long-term outcomes with patients initiated on triple therapy over a period of two years. Another goal is to describe the temporal dynamics of treatment pattern and to unravel potentially complex patient journeys[§] in different German regions. Research investigating the patient journey is required to better understand the individualized treatment regime of a patient over time with COPD* in Germany and to address the limitations faced by health care professionals when aiming to optimise treatment according to current GOLD COPD recommendations.

A further aim of TETRIS is to identify and follow-up a variety of ‘treatable traits’ in COPD patients, which - when modified - may lead to improved health outcomes. Therefore, COPD patients with signs of asthma or an asthma history will also be included to gain a better understanding of this phenotype. Recognition of certain patient characteristics may already be directly or indirectly linked to treatment decisions and therefore are of particular interest to be further explored in clinical practice.

In order to be able to map treatment reality in Germany as comprehensively as possible, the TETRIS study will collect all relevant data. The results may guide the medical community to provide a more targeted medical education approach of the unmet medical need in COPD. The data will enable the medical community to ensure that patients receive optimised therapy for their COPD by driving better informed treatment decisions. In addition, analysis comparing patient characteristics in the event of maintenance or interruption of triple therapy could provide further valuable insights that contribute to an understanding of the treatment reality in Germany.

[§] *Patient journey means the ongoing sequence of care events which a patient follows from the point of access into the health system, continuing towards diagnosis and care and ending in outpatient care.*

2. OBJECTIVES

This section provides an overview of the study goals and objectives. **Details on related variables and times of documentation are tabulated in Section 3.2** (Table 1) **and Section 3.5 (**Table 2**).** Questionnaires referred to can be found in Appendix 2, together with references and comments on validation.

When evaluating the information gathered for primary and secondary objectives, SITTs and MITTs will be looked at both separately and combined.

2.1. Primary Objectives

The primary objective is to describe the percentage of participants with diagnosed COPD with or without comorbid asthma (hereinafter summarized as COPD*) who continuously receive triple therapy for 6, 12 and 24 months after study enrolment.

2.2. Secondary Objectives

Secondary objectives are to (for details see Table 2**)**:

- Describe profiles of COPD* patients who initiated or are on triple therapy (LAMA/LABA/ICS) in Germany, for example
  - patient and disease characteristics when initiating triple therapy
- Describe the distribution and frequency of combined treatable traits in COPD* patients.
- Describe the percentage of participants with at least one switch from triple therapy to LAMA/LABA or to ICS/LABA after 6, 12 and 24 months
- Describe COPD* treatment decisions of German physicians who have either initiated patients on triple or decided to change actual therapy, for example
  - distribution and frequency of prespecified reasons† to initiate or change triple therapy
- Describe clinical outcomes in COPD* patients initiated on triple therapy, for example
  - annual rate of moderate and/or severe exacerbations
- Describe the patient journey§ of COPD* patients initiated on triple therapy, for example
  - annual rate of COPD* related primary and secondary care contacts
- Describe safety with focus on pneumonia and cardiovascular events

† *The prespecified reasons were defined by leading medical experts within the Steering Committee.A drop-down list will be offered to the investigator including but not limited to:*

- patient is continuous symptomatic under current maintenance treatment
- patient asked for help because of disease worsening
- patient asked to change medication or device

- patient experienced 2 or more exacerbations treated with antibiotics and/or OCS
- patient was hospitalized for a severe exacerbation / others (including freetext windows)

[§] *Patient journey means the ongoing sequence of care events which a patient follows from the point of access into the health system, continuing towards diagnosis and care and ending in outpatient care.*

3. RESEARCH METHODOLOGY

3.1. Study Design

This study is a multi-centre, prospective observational cohort study. Participants with COPD* have already been treated with triple therapy for at least 2 but not longer than 48 weeks will be enrolled into two cohorts:

- *Cohort A:* treatment by settled general practitioners ("GPs", primary care, practitioner / registered doctor)
- *Cohort B*: treatment by settled pulmonologists ("specialists", primary or secondary care)

The involvement of these two German physician groups is an important basis to ensure that real everyday treatment conditions will be depicted for this observational cohort study.

About 30-35% of COPD drugs in Germany are prescribed through primary care physicians (mostly GPs). About 55-60% are prescribed by settled pneumologists and the remainder from outpatient lung centres. .

In general there is a high level of standardization in the education of HCPs (pneumologists, generalists)and in the processes in the private practices (treatment, documentation, visits, diagnostic methods). Thus, a generalizability of patient recruitment and study conduct can be assumed. The site feasibility performed in line with the study and the site managment processes also assure comparable patient recruitment and study conduct. General practitioners (GPs) usually serve as primary care sites, settled pneumologists as secondary care specialists. Nevertheless there is considerable interchangeability since GPs often serve as secondary care centre after hospitalizations due to severe exacerbations and patient with moderate/advanced disease may directly be referred to pneumonologists depending on the region in Germany.

As this is a non-interventional study, the protocol will not interfere with the physicians' management of the patients, i.e. this study does not include treatment interventions. Participants will continue to use medication prescribed by their regular treating physician. Data collection follows routine clinical practice, i.e. the study does not require additional visits to the physician.

Data will be collected at patients' routine visits and only questionnaires recommended in guidelines and questions used in daily practice will be applied. Participants' regular treating physician will be informed of the results of study assessments following each of the four main on-study visits.

Non-interventional studies shall not have the potential to incentivise physicians to prescribe any specific product. For this reason, the TETRIS study includes only patients who have been treated with triple therapy for at least 2 weeks. TETRIS does not intend to confirm the efficacy and tolerability of Trelegy in comparison to a control group, as efficacy and tolerability have already been well established in the clinical development programme [Lipson 2017, Lipson 2018, Lipson 2020].

The data collection in the study includes two parts (see Figure 1 below):

Part 1 involves the cross-sectional phenotyping of participating COPD* patients at study enrolment (hereinafter referred to as "visit 1").

Part 2 involves a two-year longitudinal follow-up period to monitor / document all visits of the study participants during the 24-months observation period. The goal is to understand how physicians assess and treat patients with COPD* in clinical practice in Germany. The study assumes that most COPD* patients see their doctor every 3 months (at least to get a new prescription). Further data should therefore be provided in the clinical routine after approximately 6 (-3/+2) months (hereinafter referred to as "visit 2"), 12 (-3/+5) months (hereinafter referred to as "visit 3") and for the last visit after approximately 24 (-6/no upper limit) months (hereinafter referred to as "visit 4"). There should be a minimum interval of 3 months between each of these visits, otherwise the visit is counted as an interim visit.

For each additional patient visit to the treatment centre between study visits 1 and 4, safety data, exacerbations, hospital stays as well as treatment changes and reasons for this are recorded. Patients will participate in the study for approximately two years from enrolment to the last study contact (visit 4).

Two interim analyses are planned:

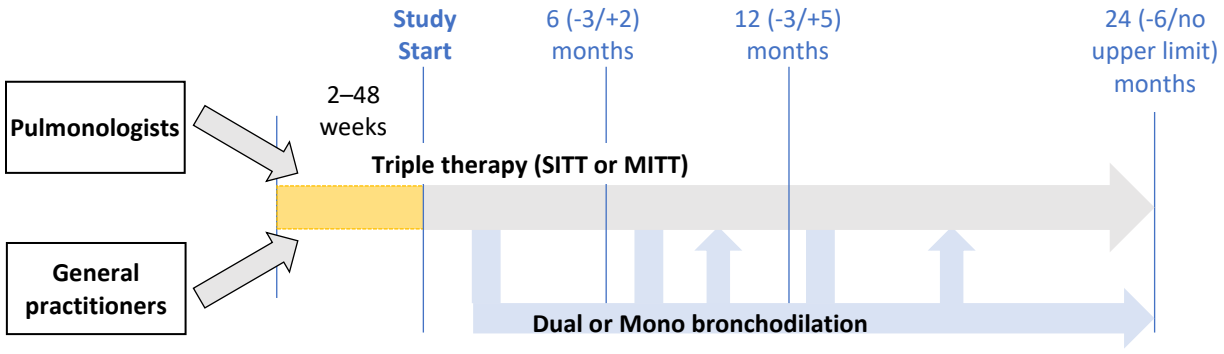
- The first interim analysis is intended to collect and analyse cross-sectional data / baseline characteristics and is planned after at least 825 patients (~75%) of the total study population have been recruited.
- The second interim analysis is intended to include 6 and 12 months data for a subset of the study population and is planned after full recruitment or after 2 years from study start, whatever occurs earlier.

The final analysis will be performed after a 24-month follow-up from study enrolment for all patients. Participants may be withdrawn from the study if they become pregnant or enrol in another study with treatment intervention. Furthermore, patients may discontinue study participation – with or without formal withdrawal of their informed consent and with or without giving reasons – at any time during the study.

- It is essential for the study objectives to obtain as complete follow-up of patients as is possible in a non-interventional study. An example in the patient journey where a patient may get lost to follow-up could be:Patients may move to another outpatient care physician for personal reasons.

A supporting concept with mitigation measures will be provided to avoid loss of patients at the risk points above. The concept provides that physicians as well as patients can refer to a change of doctor via a central homepage. The new supervising physician has the opportunity to also participate in the study. With these measures we expect to be able to reduce the dropout rate to 5-10%.

Figure 1: Assessment and follow-up study schematic



3.2. Data Source / Data Collection

The prospective observation period is scheduled for 24 months from study enrolment. This period is required to obtain information on the long-term maintenance of triple therapy, the long-term development of treatable traits and to meet clinical endpoints. So far, there has been limited data available that go beyond a one-year observation period for patients treated with single inhaler triple therapy for COPD with or without comorbid asthma (COPD*). Long-term data that provide information over a period of at least two years are therefore of great clinical interest.

As this is a non-interventional study, the protocol will not interfere with the physicians' management of the patients.

For each additional patient visit to the treatment centre between study visits 1 and 4, safety data, exacerbations, hospital stays, deaths and treatment changes and reasons for this are recorded. Patients will participate in the study for approximately two years from enrolment to the last study contact (visit 4).

Data will be collected in electronic case report forms (eCRFs). Table 1 (see below) illustrates data collection over time. Three eCRF variants will be used for the data collection, depending on the study visits (visit 1, visits 2-4, on-site visits at any time in between):

- An extended eCRF ("extended eCRF part 1") will be used for part 1 of study data collection. The extended eCRF part 1 documents the cross-sectional phenotyping of participants at study enrolment, including the recording of socio-demographic and comorbidity data.
- Another extended eCRF that is based on the extended eCRF part 1 ("extended eCRF part 2") will be used for part 2 of the study. The extended eCRF part 2 will document a two-year longitudinal follow-up consisting of three study visits (visits 2 to 4) during routine clinical practice. These are scheduled after approximately 6, 12 and 24 months. The

extended eCRF part 2 largely corresponds to the extended eCRF part 1 but does not involve the baseline questions on demographic data and comorbidities.

- For each additional patient visit to the treatment centre between study visits 1 and 4, safety data, events[3] including exacerbations, hospital stays as well as treatment changes and reasons for this will be recorded on a short eCRF ("short eCRF").

All information relevant for the study is expected to be routinely documented in the patients' charts, which will serve as source data. However, questionnaires collect information in a specific, unified and validated structure and with specified response options, which may differ not in extent, but in details from routine practice in study centres. Thus, the patients' charts may not be suitable source data for questionnaires, especially HRQoL and symptoms questionnaires, and the questionnaires themselves or suitable worksheets will serve as source data here and be stored with the patients' charts. For centre related information collected in this study, the eCRF itself will serve as source data, and an electronic copy or printout will be provided for the investigator site files.

Since an eCRF is used, all the patient has to do is complete the EQ-5D/VAS questionnaire remotely. All other data can be recorded by the attending doctor or nurse. In the case of telemedicine visits, the attending physician is asked to collect the completed questionnaire from the patients in order to transfer the data into the eCRF form.

Patients will participate in the study for approximately two years from enrolment to the last study contact (visit 4).

Data will be used in anonymized form conforming to data protection regulations (General Data Protection Regulation of the European Union and related German law on data protection).

[3] *Event includes: unstable COPD, cold requiring antibiotics, and exacerbation*

Table 1: Data collection schedule (data will be collected as per clinical routine). EW: Early withdrawal.

Procedure	**Screening (up to 14 days before visit 1)**	**Part 1**	**Part 2**						**EW**
		Visit 1: Month 0	**Intermediate visits**	**Visit 2[§]: Month 6 (-3/+2)**	**Intermediate visits**	**Visit 3[§]: Month 12 (-3/+5)**	**Intermediate visits**	**Visit 4[§]: Month 24 (-6/no upper limit)**	
Informed consent	X								
Inclusion and exclusion criteria	X								
Patient's sociodemo-graphic characteristics	X								
Height, weight, BMI		X		X		X		X	X
Medical history and comorbidities	X	X							
COPD* medication history before initiating triple therapy		X							
Maintenance medication for COPD*	X	X		X		X		X	X
Concomitant COPD* medication		X		X		X		X	X
Reasons for initiating triple therapy		X							
Reasons for changing maintenance medication for COPD*				X		X		X	X
Smoking status		X	X	X	X	X	X	X	X
Narratives of any lung CT scans[a)]		X		X		X		X	X
Spirometry testing (FEV_1, FVC, FEV_1/FVC ratio) (if routinely collected)	X	X		X		X		X	X
Body-plethysmo-graphie (if performed routinely)		X		X		X		X	
D_{LCO} (if routinely collected)		X		X		X		X	
FeNO (if routinely collected)		X		X		X		X	
Eosinophils (EOS) in blood (if routinely collected)	X	X		X		X		X	X
WBC count (if routinely collected)		X		X		X		X	X
WBC differential (if routinely collected)		X		X		X		X	X
hsCRP (if routinely collected)		X		X		X		X	X

Procedure	**Screening (up to 14 days before visit 1)**	**Part 1**	**Part 2**						**EW**
		Visit 1: Month 0	**Intermediate visits**	**Visit 2[§]: Month 6 (-3/+2)**	**Intermediate visits**	**Visit 3[§]: Month 12 (-3/+5)**	**Intermediate visits**	**Visit 4[§]: Month 24 (-6/no upper limit)**	
Healthcare resource utilisation (HRU)[c)]		X		X		X		X	X
Events[b)] during study			X	X	X	X	X	X	X
CAT	X	X		X		X		X	X
EQ-5D (incl. VAS)		X		X		X		X	X
AE/SAE review		X		X		X		X	X
The eCRF will additionally capture surrogate markers for compliance (e.g. "Did the patient regularly/every 3 months ask for a new prescription?").									

§ There should be a minimum interval of 3 months between each of the visits (visit 2, 3, 4), otherwise the visit is counted as an interim visit.

AE: adverse event; BMI: body mass index; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; COPD*: COPD with or without comorbid asthma; CT: computed tomography; D_{LCO}: diffusing capacity; EOS, eosinophils; EQ-5D, European Quality of Life 5 Dimensions; EW: early withdrawal; FeNO, Fraction Exspiratory Nitric Oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; hsCRP, high-sensitivity C-reactive protein; HRU, healthcare resource utilisation; SAE: serious adverse event; VAS, Visual Analogue Scale; WBC, white blood cell; WOCBP: woman of child bearing potential.

a. The radiologist's narrative will be collected for any historical lung CT scans performed in the year prior to the study or any lung CT scans performed as part of routine clinical management during the study.
b. Event includes: unstable COPD, cold requiring antibiotics, exacerbation and hospitalizations.
c. HRU includes: hospitalization, hospitalization in intensive care unit, number of physicians treating the patient (primary and secondary care), number of physician goups treating the patient (2 groups), change of treating physician, returning from secondary care to primary care physician, returning from acute care to primary or secondary care

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Patient characteristics can be identified in a number of ways. Determination of blood eosinophils and hsCRP may aid identification in the same way that D_{LCO} measurements and CT images can help detect persistent lung inflation. Sputum secretion, dry cough, or FeNO determinations can also help identify important patient characteristics. The detection of "rapid declines" (loss of> 100 ml lung volume per year) may be another important patient characteristic.

3.3. Study Population

This study plans to recruit a population of approximately 1100 patients with moderate to severe COPD with or without comorbid asthma (COPD*) who have been on triple therapy for at least 2 and for a maximum of 48 weeks (see sample size estimation in Section 3.6).

The TETRIS study participants will be enrolled by two different physician groups covering all German regions: a) settled general practitioners ("GPs", primary care) and b) settled

pulmonologists ("specialists", primary or secondary care. This is in order to get a better representation of the treatment reality in Germany. The patients will be recruited from the following physician groups:

- COPD* patients should be included by settled pulmonologists ("specialists", primary or secondary care). Depending on the regional distribution of the centres, patients within each centre of cohort B who meet the inclusion criteria will be considered. If a single centre has recruited the maximum number of patients, the study management will decide whether further patients may be recruited (up to a maximum of 100 patients).
- COPD* patients should be included by settled general practitioners ("GPs", primary care). Depending on the regional distribution of GPs, patients who meet the inclusion criteria will be considered within each centre of cohort A. If a single centre has recruited the maximum number of patients, the study management will decide whether further patients may be recruited (up to a maximum of 100 patients).

It is assumed that around 15% of the study population were hospitalized for exacerbations.

Continous crossfunctional recruitment management (lead by the CRO and the GSK study head) will be a key element to ensure proper regional distribution of centres and patients enrollment.

3.4. Eligibility Criteria

3.4.1. Inclusion Criteria

Study participants may be male or female. Participants are only eligible to be included in the TETRIS study if all of the following criteria apply:

- Participant is at least 18 years of age at the time of signing the informed consent
- Participant is on a single or multiple inhaler triple therapy (SITT or MITT) for treatment of an obstructive respiratory disease for a period of 2 to 48 weeks prior enrolment with a combination of inhaled LAMA, LABA and ICS either on
  - a triple maintenance treatment or
  - an intermediate triple therapy regime (ICS "on/off" or LAMA "on/off")
- *Only applies to Cohort A* (treatment by settled general practitioners): Participants are treated according to a physicians diagnosis of COPD*.
- *Only applies to Cohorts B* (treatment by settled pulmonologists): Participants have a confirmed physician's diagnosis (diagnosis based on spirometry or body plethysmography) of COPD*.
- Participants need to give and be capable of giving signed informed consent (ICF) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

3.4.2. Exclusion Criteria

Participants are ineligible to be included in the study if any of the following criteria apply:

- Participant has a diagnosis of pure asthma, without clinical features of COPD
- Participant has a current diagnosis of lung cancer or lung metastasis
- Participant has a current primary diagnosis of diffuse pan-bronchiolitis, or a primary diagnosis of bronchiectasis or pulmonary fibrosis or cystic fibrosis or other significant respiratory disorders
- Participant is currently enrolled or has participated in a study within the last 90 days before signing of consent involving investigational study treatment intervention. If, while enrolled in the present study, the participant enrols in another study involving investigational study treatment intervention, he/she will be withdrawn from the present study
- Recent (≤ 3 months) major cardiac or pulmonary event (e.g. myocardial infarction, pulmonary embolism)

3.5. Endpoints

Endpoints of the study are outlined in Table 2 below, with associated objectives.

The non-interventional concept of this study does not demand visits or examinations outside of clinical routine. The Statistical Analysis Plan (SAP) will define the allocation of data to time points of analysis, if required and non-obvious ("time windows").

Table 2: Listing of objectives and associated endpoints

Objective	Endpoints
Evaluate the percentage of patients who continuously receive triple therapy	• Patients who continuously receive triple therapy for 6, 12 and 24 months (including stratification by SITT vs. MITT) • Time to stop triple therapy
Describe profiles of COPD patients who initiated or are on triple therapy (LAMA/ LABA/ICS) in Germany	Patient and disease characteristics when initiating triple therapy: • Percentage of COPD patients with diagnosis of asthma at the age of <40 years • Percentage of patients with peripheral blood EOS of <100 cells/µl, 100-200 cells/µl, 200-300 cells/µl and > 300 cells/µl • Percentage of participants with a physician's diagnosis of COPD by site localization and physician´s group • Percentage of participants with different symptom and risk classes (GOLD) • Medications received by COPD patients (including OCS), split by physician group and site localization • Time on triple therapy before study start (<3 months / 3 - <6 months / >=6 months)
Describe the distribution and frequency of combined treatable traits in COPD patients	• Percentage of patients presenting with a smoking history (when initiating triple therapy and at different time points during a 24-month observation period) • Percentage of patients with a non-smoking history when initiating triple therapy

Objective	Endpoints
	• Percentage of patients with a FEV1/FVC ratio <0.7 at study enrolment and at a 6, 12 and 24 months documentation • Percentage of patients with any moderate/severe exacerbation in the 24 months prior to study enrolment or 3 months prior to each subsequent on-study visit during a 24-month observation period • Percentage of patients with a CAT score ≤10 / 11-19 / ≥20 at baseline and at a 6, 12 and 24 months documentation • Percentage of patients with peripheral blood eosinophil (EOS) count ≥100 cells/µl at baseline and at a 6, 12 and 24 months documentation • Percentage of patients with chronic bronchitis phenotype
Describe the percentage of participants with at least one switch from triple therapy to LAMA/LABA or to ICS/LABA after 6, 12 and 24 months	• Patients with at least one switch from triple therapy to LAMA/LABA after 6, 12 and 24 months • Patients with at least one switch from triple therapy to ICS/LABA after 6, 12 and 24 months
Describe COPD treatment decisions of German physicians who have initiated patients on triple therapy	• Distribution (by physician group) and frequency of prespecified reasons to initiate triple therapy (either MITT or SITT) • Percentage of patients changing from triple to dual therapy and back to triple therapy (re-escalation) during a 24-month observation period after study enrolment (split by SITT and MITT and split by LAMA/LABA and ICS/LABA) • Percentage of patients with at least one re-escalation from LAMA/LABA or ICS/LABA or LAMA to triple therapy during the 24-month observation period • Percentage of patients with at least one change from MITT to SITT or SITT to MITT during a 24-month observation period • Percentage of patients with at least one change from SITT to SITT or MITT to MITT during a 24-month observation period • Percentage of patients changing from once daily to twice daily medication or vice versa or between different inhaler types • Percentage of patients changing between different inhaler types • Distribution (by physician group) and frequency of prespecified reasons to change a triple therapy (either MITT or SITT) • Distribution and frequency of prespecified reasons to change triple therapy to another triple therapy • Distribution and frequency of prespecified reasons† to change triple therapy to therapy de-escalation • Distribution and frequency of prespecified reasons to change de-escalataed therapy back to triple therapy (re-escalation)
Describe clinical outcomes in COPD patients initiated on triple therapy	• Mean annual rate of moderate and/or severe exacerbations over a 24-month observation period (including subgroup analysis by peripheral blood eosinophil count, smoking status and asthma history) • Mean annual rate of hospitalizations due to severe exacerbations • Change of lung function parameters during a 24-month observation period (including subgroup analysis by peripheral blood eosinophil count, smoking status and asthma history) • Change of COPD symptoms during a 24-month observation period • Change in HRQoL during a 24-month observation period • Percentage of COPD patients experiencing a clinically important deterioration2 during a 24-month observation period

Objective	Endpoints
	• Time to first moderate or severe exacerbation during a 24-month observation period • Time to first hospitalization / hospitalization during a 24-month observation period • Time to death during a 24-months observation period
Describe the patient journey of COPD patients initiated on triple therapy	• Mean annual rate of COPD related primary and secondary care contacts • Number of different documenting physicians per patient during a 24-month observation period (also split by patients with a severe or moderate or severe exacerbation and split by site localization) • Mean number of treating physicians per patient over a 24-month observation period (also split by site localization and diagnosis) • Percentage of patients treated by 1, 2 or all 3 physician groups addressed in the study (settled general practitioners, settled pulmonologists, outpatient lung centres)
Describe safety with triple therapy	• Safety with focus on pneumonia and cardiovascular events • Benefit-harm profiles for single-inhaler triple therapies (SITTs, including Trelegy, Trimbow and Breztri) • Benefit-harm profiles for major multiple inhaler triple therapy (MITT) combinations • Benefit-harm profiles for triple therapies interrupted by ICS and/or LAMA “off/on” periods • Benefit-harm profiles for triple therapies switching between SITT and MITT

3.6. Sample Size / Power Calculations

See Appendix 1 for further details and various scenarios.

In order to obtain information about the long-term maintenance of triple therapy, a total observation period of 24 months was chosen for this non-interventional study. Within the co-primary endpoint “description of the percentage of participants with a physician's diagnosis of COPD* who continuously receive triple therapy for 6, 12 and 24 months after study enrolment”, we therefore focused on the percentage of patients on a continuous triple therapy regime for 24 months.

The sample size calculation is based on the precision of the estimate for this endpoint. Based on research data we assume the rate of patients continuously being on triple therapy of around 35% of all patients two years after study enrolment on triple therapy. With a target width of 7%, the corresponding 95% confidence interval ranges from 31.6% to 38.65% for a sample size of 740 patients. As for this planned analysis data are necessary for two years, we determine the sample size to a total of approximately 1,100 patients to consider about 30% study drop-outs.

Based on the current market mix of MITTs and SITTs and including the anticipated market dynamics towards more SITT usage during the next two years in Germany it is expected to enrol around 50 up to 60% of patients with COPD* on SITT (with shares of Trelegy/Trimbow/Breztri of approximately 2:2:1).

4. DATA ANALYSIS CONSIDERATIONS

This is a descriptive study which is designed to estimate the primary endpoint with a specific precision. The study is not powered to detect differences and no formal statistical hypothesis testing will be performed for any of the endpoints.

Two interim analyses are planned (see also Section 3.1):

- The first interim analysis is intended to collect and analyse cross-sectional data/ baseline characteristics and is planned when at least 825 patients (~75%) of the total study population have been recruited.
- The second interim analysis is intended to include 6 and 12 months data for a subset of the study population and is planned after full recruitment or after 2 years from study start, whatever occurs earlier.

The final analysis will be performed after a 24-month follow-up from study enrolment for all patients. Participants may be withdrawn from the study if they become pregnant or enrol in another study with treatment intervention. Furthermore, patients may discontinue study participation – with or without formal withdrawal of their informed consent and with or without giving reasons – at any time during the study.

In order to get a more detailed idea of how therapy and outcome parameters develop during the 24-month observation period, the following subgroups will be investigated separately:

- triple therapy once daily vs. twice daily
- SITT vs. MITT and SITT vs. SITT
- continuous vs. interrupted triple therapy
- physician cohorts
- COPD vs. COPD with asthma

further exploratory subgroups (i.e. by exacerbation history / by ± ICS containing pre-treatment / by smoking status) before study start.

The population enrolled in the data analysis will include all participants who sign the ICF and who complete both the screening visit and visit 1. This population will be the primary analysis population for all endpoints, including safety data.

Missing Data / Sensitivity analysis

Analyses will be based on available data. Missing data will not be imputed and will be displayed as a separate category. The number of dropouts will be analysed descriptively and their impact on the primary endpoint will be investigated.

If a variable is completely or systematically missing, it is excluded from the analyses. If a variable is missing for only some of the patients or arbitrarily missing, a missing data

category will be added and used in the analyses. However in case of a considerable amount of missing data (1/3 or more) for one variable, the impact of this missing data will be investigated by conducting the analysis without the corresponding variable – as a sensitivity analysis. If a variable is missing but equivalent information can be inferred using available variables, the corresponding information will be used instead.

According to the descriptive study design all endpoints will be analysed descriptively. Endpoints with continuous measures will be analysed by mean, median, minimum, maximum and standard deviation [SD], discrete and categorical endpoints by frequencies and percentages and event/survival-endpoints counts will be analysed by providing event rates per participant-year and Kaplan-Meier estimates). Full details including a list of exploratory endpoints will be provided in the SAP as an additional document to this study protocol.

5. LIMITATIONS

This is a real-life, prospective, non-interventional study. Availability of data for collected variables may be limited due to the non-interventional character of the study, and variables may not be comprehensively recorded for all patients. Therefore, availability of data for collected variables may not be complete, which can lead to a bias due to missing data.

There may be an enrolment bias, though sites will be expected to enrol all eligible patients that present at their site and maintain screening logs of all patients meeting eligibility criteria, along with reasons for non-enrolment of otherwise eligible patients.

Because of recruitment strategies in this study (recruitment from “GPs”and “specialists; accessibility limitations to GPs) there may also be a potential bias in generalizing to overall patient population in Germany.

There are different inclusion/exclusion criteria for cohort A (physician diagnosis) vs. cohort B (confirmed diagnosis). This potential selection bias is unavoidable since general practitioners do not always use spirometry or body plethysmography to diagnose COPD.

Selecting patients who have received triple therapy for at least 2 weeks may limit the population to adherent patients and those who do not experience significant AEs after initiating triple therapy. This can limit the generalizability of the collected data.

There also may be inconsistent interpretation of eCRF by participating centres. Therefore, all centres/sites will undergo standardised training and utilise standardised documentation for completing of case report forms at enrolment and for each assessment during the observation period.

By participating in a study, the investigators may feel more obliged to follow treatment recommendations. Therefore, there may be deviations from “real world” treatment when making therapy decisions (Hawthorne effect).

Another point to consider is that patients can drop out in follow-up care for various reasons. To mitigate this risk, a supporting concept to follow-up patients (see 3.1.) will be provided as an additional document to this study protocol.

Furthermore, non-interventional studies and studies without a control group can only describe correlations but cannot establish causality.

6. STUDY CONDUCT, MANAGEMENT & ETHICS

The study is intended to provide insights into the use of an authorized medicinal products. It is therefore a non-interventional study ("Anwendungsbeobachtung", observational study) according to § 4 (23) and § 67 (6) of the German Medicines Act (AMG). The study considers the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices of 2015. To the extent relevant, the study also submits to the principles set out in the current version of the Declaration of Helsinki of the World Medical Association.

Prior to its launch, this study will be registered to the relevant authorities and professional and payers' associations and entered in a publicly accessible study register. The study register will disclose consenting centres, and the study will be conducted in accordance with the codex of the “freiwillige Selbstkontrolle der Arzneimittelindustrie” (FSA Codex, German voluntary self-control of pharmaceutical industry). Fees paid to centres and investigators will be reported to authorities and professional and payers' associations in accordance with the AMG. Authorities may publish information received within the framework of the AMG. Centres may only participate, if required permissions are obtained, e.g. of hospital operators.

The study will be submitted to the ethics committee of the Hannover Medical School (Medizinische Hochschule Hannover, MHH) for professional advice. It will only start, after queries have been resolved and the ethics committee has issued a positive vote. Subsequent changes to the protocol will be communicated to the ethics committee. Any changes that affect the Informed Consent Form (ICF) beyond editorial aspects or the scientific value of the project or relevantly increase the amount of data collected, will be submitted to the ethics committee as an amendment. Like the original protocol and ICF, amendments may only be installed, after the ethics committee has issued a positive vote. Locally responsible ethics committees of centres are involved as required by the local investigator's professional code (Ärztliche Berufsordnung).

An ICF must be signed by the participant before his or her participation in the study. The medical file for each participant must document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICF must be provided to the participant.

The ICF must be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the participant to participate. For any updated or revised ICFs, the medical file for each participant must document the informed consent process and that written informed consent was obtained for the updated/revised ICF for continued participation in the study.

In order to maintain participant confidentiality, each participant will be assigned a unique participant identifier upon study enrolment. This participant identifier will be used in place of participant name for the purpose of data analysis and reporting. Medical record number or other local reference identifiers are not collected as part of the study database.

All parties will ensure protection of participant personal data and will not include participant names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in Germany, participants will be informed about data handling procedures and asked for their consent.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. Every effort will be made to protect participant confidentiality in compliance with Safe Harbour privacy principles, if data are transferred to countries outside the European Union.

The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of the International Conference on Harmonisation (ICH) guideline E6R2 regarding electronic study data handling and is available for audit upon request.

This study will comply with all applicable laws regarding subject privacy. No direct subject contact or primary collection of individual human subject data will occur. Study results will be in tabular form and aggregate analyses that omits subject identification, therefore informed consent, ethics committee or IRB approval are not required. Any publications and reports will not include subject identifiers.

6.1. Legal Basis for Processing Individual Human Data

The authors confirm that study data is Individual Human Data (IHD) owned by GSK and that:

- The proposed use of the IHD is Study Use* as outlined in the patient consent.
- The research participants consented to their IHD being processed for Further Research and have NOT submitted an Individual Rights Management (IRM) request that limits the use of their IHD

* Study Use means - the use of IHD is as stated in the original study protocol and/or aligned with the informed consent form to answer the study objectives and satisfy regulatory requirements and learn more about the *product* studied and the disease/condition studied. This includes bringing the *product* to market or maintaining market access which includes working with government agencies, insurers or health care payers and aiding GSK's understanding of clinical efficacy, safety, or effectiveness of the product.

6.2. Monitoring & Data Quality

To ensure high data quality, it is planned to perform a source data check in 10% of all enrolled sites. Sites and patients will be selected through a risk-based algorithm. Details will be described in the project plan or the monitoring plan.

Before receiving access to the electronic case report form (eCRF) system for data entry, participating physicians and/or their study nurses need to participate in a study specific training. Furthermore, data entered to the eCRF will undergo data validation at data entry and entries violating validation rules will be rejected immediately to be corrected or explained. This assures high ad hoc data quality. Further data checks as well as medical reviews of data entered will be performed regularly at database level, with incomplete, inconsistent or ambiguous entries returned to the sites for clarification.

6.3. Study discontinuation

Patients may discontinue study participation – with or without formal withdrawal of their informed consent and with or without giving reasons – at any time without any detrimental effect on their treatment and physician-patient relationship. However, patients discontinuing shall be asked to consent to a final data collection ("early withdrawal observation"; see Table 1). Patients shall also be asked to consent to the further use of their data collected until study discontinuation, and this decision shall be documented. If patients do not consent to the further use of their data, these data will be deleted or used only in anonymized form conforming to data protection regulations (General Data Protection Regulation of the European Union and related German law on data protection).

Furthermore, physicians may also discontinue data collection for specific patients at their own discretion, e.g. in cases of non-compliance with treatment or visit schedules agreed upon outside the study. For these patients, the physician should fill in all available information to the "early withdrawal" forms.

6.4. Adverse Event (AE), Pregnancy Exposure, and Incident Reporting

All clinical safety data will be collected as outlined in the eCRF. Under ICH GCP and all applicable local regulations and legal requirements, the Sponsor, is responsible for, and undertakes to, assess all clinical safety information arising during the Study (including, but not limited to, that set out in the Definition 6.4.1 in order to generate all safety reports as required.

Definition and reporting of incidents are described in the form "Medical device or combination product with device deficiency/incident report form - Investigator Instructions" that can be found in the Investigator Site File (ISF).

6.4.1. Definition of adverse events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medication, whether or not related to the medication.

An adverse drug reaction (ADR) is defined as a noxious and unintended response to a medication related to any dose that has at least a reasonable possibility of relationship, with facts, evidence and/or arguments that suggest a causal relationship.

A serious adverse event (SAE) shall mean any adverse event which meets the following criteria:

- fatal
- life threatening
- disabling or incapacitating
- requires unplanned in-patient treatment or prolongs existing hospitalization (i.e., hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE)
- is a congenital anomaly in the offspring of a subject
- medically significant or which may require intervention to prevent the previously stated outcomes

In addition, all occurrences of possible drug-induced liver injury that meet Hy's law criteria must be reported as an SAE. These criteria are the following: ALT or AST increase of ≥ 3 x the ULN, total bilirubin increase of ≥ 2 x the ULN with absence of initial findings of cholestasis (i.e., no AP increase of ≥ 2 x the ULN) and without other explanation for the observed abnormalities.

For the purposes of this agreement, all ADRs and SAEs will be captured in the eCRF and reported to the sponsor as defined in Sections 6.4.2, 6.4.3, and 6.4.4.

6.4.2. Data collected for adverse events

Investigator completes all data fields of the AE form in the eCRF and sends it to the GSK email address below within 24 hours of becoming aware of the event. The address is embedded in the EDC system. In case investigator does not actively send AEs fulfilling the minimum case criteria, the EDC system will transmit information automatically within 24 hours of entry (see also 6.4.4).

6.4.3. Reporting of AEs and timelines

The study investigator involved is obliged to collect and report from the time of informed consent to study termination, all ADRs and SAES, COVID-19 cases, pregnancy exposures, and incidents identified as explicitly attributed to any GSK product (including products not covered in the specific study objective).

All ADRs and SAEs will be reported to GSK global safety case management (**OAX37649@gsk.com**) in the form of an electronic safety report within 24 hours of documentation via an automated process.

The safety-related information will be processed according to the legal requirements and country specific regulations to the competent authorities. The recording and reporting of safety data is in a pseudo anonymous format.

A study specific Pharmacovigilance Plan (sPVP) has been approved and provide detailed information on the study specific pharmacovigilance processes and procedures.

6.4.4. Reporting of COVID-19 cases

COVID-19 cases will be reported based on the WHO criteria using the following categories: suspected, probable, and confirmed cases. A COVID-19 form that can also be found in the ISF will be used to capture additional COVID case details. COVID-19 infection related SAEs will be documented and followed as described in sections 6.4.2 and 6.4.3.

6.4.5. Reporting of pregnancy exposures

To ensure subject safety, each pregnancy must be reported to the sponsor within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, which must also be reported to the sponsor. Pregnancy complications and elective terminations for medical reasons must be reported.

Investigators will be provided with necessary "pregnancy exposure" and "pregnancy follow up" forms and supported by CRA and/or GSK medical affairs in complying with pregnancy reporting procedures.

7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Based on the objectives and the different timelines of data availability, analyses will be performed, and results presented (abstract/poster, full publication).

Two interim analyses are planned (first interim analysis when at least 825 patients (~75%) of the total study population have been recruited, ; second interim analysis after full recruitment or after 2 years from study start, whatever occurs earlier). The final analysis will be performed after a 24-month follow-up from study enrolment for all patients.

1. The results of the first interim analysis are planned to be published after all study centres have been recruited and all participating patients have completed study visit 1. The analysis will describe cross-sectional data of COPD* patients initiated on triple therapy in Germany and reasons for initiating triple therapy.

2. The results of the second interim analysis should be published if the data are available. This analysis will focus on the 6 and 12 months data for a subset of the study population, covering primarily treatment patterns and reasons for treatment changes as well as evolution and patient journey§ of COPD* patients initiated on triple therapy in Germany.

3. The final publication is planned to use data collected until the end of the 24-month follow-up. It will concentrate primarily on long-term treatment patterns as well as evolution and patient journey of COPD* patients who have initiated triple therapy in Germany.

Any publication of the results from this study will be consistent with GSK's publication policy and guided by the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (ICMJE 2018).

[§] *Patient journey means the ongoing sequence of care events which a patient follows from the point of access into the health system, continuing towards diagnosis and care and ending in outpatient care.*

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APPENDIX 1: SAMPLE SIZE CALCULATION

This is the original output of the sample size calculation software, in which several scenarios for the actual proportion of the primary endpoint (ranging from 0,1 to 0,5) were investigated. Finally the sample size was selected based on a proportion of 0,35

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Confidence Intervals for One Proportion

Numeric Results for Two-Sided Confidence Intervals for One Proportion

Confidence Interval Formula: Exact (Clopper-Pearson)

Confidence Level	Sample Size (N)	Target Width	Actual Width	Proportion (P)	Lower Limit	Upper Limit	Width if P = 0.5
0,950	310	0,070	0,070	0,100	0,069	0,139	0,114
0,950	427	0,070	0,070	0,150	0,117	0,187	0,097
0,950	529	0,070	0,070	0,200	0,167	0,237	0,087
0,950	615	0,070	0,070	0,250	0,216	0,286	0,080
0,950	685	0,070	0,070	0,300	0,266	0,336	0,076
0,950	740	0,070	0,070	0,350	0,316	0,386	0,073
0,950	779	0,070	0,070	0,400	0,365	0,435	0,071
0,950	803	0,070	0,070	0,450	0,415	0,485	0,070
0,950	810	0,070	0,070	0,500	0,465	0,535	0,070

References

Fleiss, J. L., Levin, B., Paik, M.C. 2003. Statistical Methods for Rates and Proportions. Third Edition. John
Wiley & Sons. New York.
Newcombe, R. G. 1998. 'Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods.'
Statistics in Medicine, 17, pp. 857-872.

Report Definitions

Confidence level is the proportion of confidence intervals (constructed with this same confidence level, sample size, etc.) that would contain the population proportion.
N is the size of the sample drawn from the population.
Width is the distance from the lower limit to the upper limit.
Target Width is the value of the width that is entered into the procedure.
Actual Width is the value of the width that is obtained from the procedure.
Proportion (P) is the assumed sample proportion.
Lower Limit is the lower limit of the confidence interval.
Upper Limit is the upper limit of the confidence interval.
Width if P = 0.5 is the maximum width for a confidence interval with sample size N.

Summary Statements

A sample size of 310 produces a two-sided 95% confidence interval with a width equal to 0,070 when the sample proportion is 0,100.

Confidence Intervals for One Proportion

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
30%	310	443	133
30%	427	610	183
30%	529	756	227
30%	615	879	264
30%	685	979	294
30%	740	1058	318
30%	779	1113	334
30%	803	1148	345
30%	810	1158	348

Definitions

Dropout Rate (DR) is the percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e. will be treated as "missing").

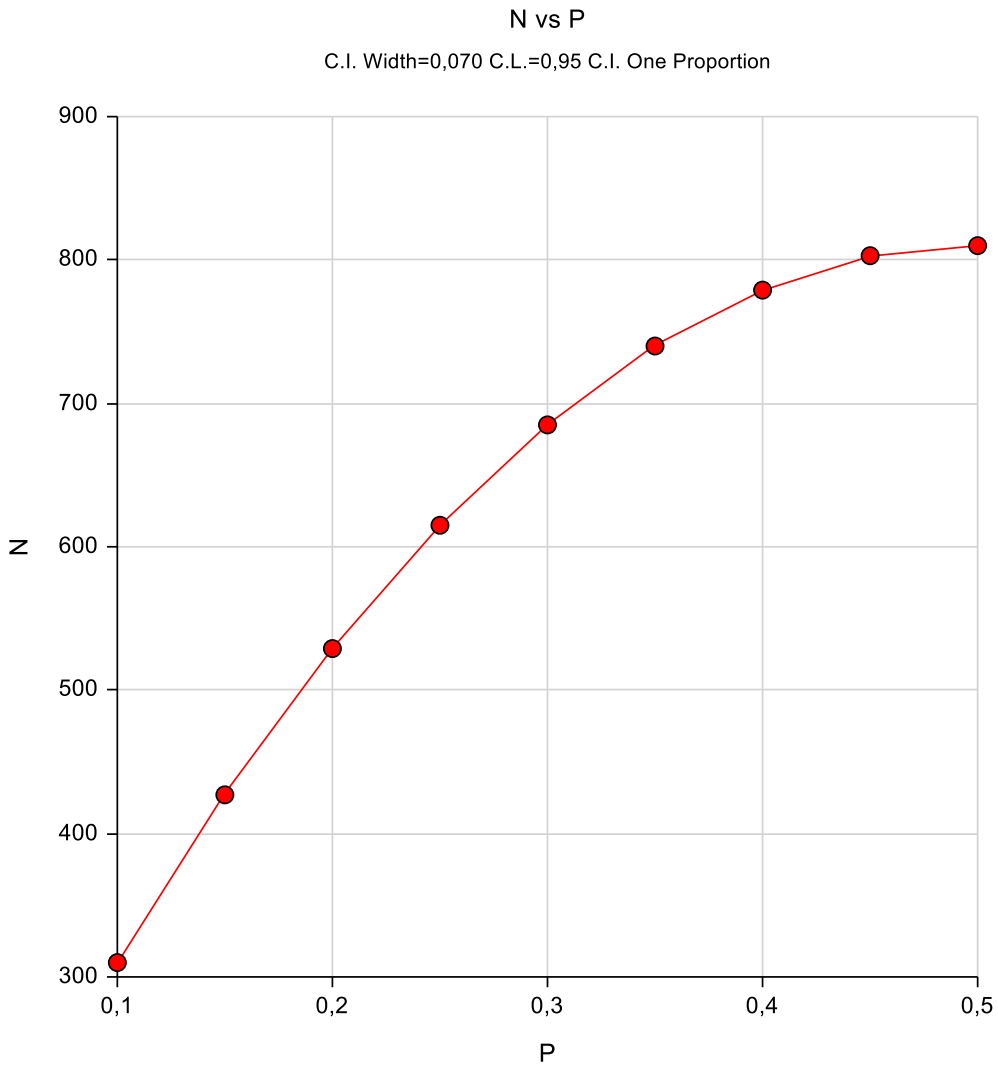
N is the evaluable sample size at which the confidence interval is computed. If N subjects are evaluated out of the N' subjects that are enrolled in the study, the design will achieve the stated confidence interval.

N' is the total number of subjects that should be enrolled in the study in order to end up with N evaluable subjects, based on the assumed dropout rate. After solving for N, N' is calculated by inflating N using the formula N' = N / (1 - DR), with N' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.)

D is the expected number of dropouts. D = N' - N.

Confidence Intervals for One Proportion

Chart Section

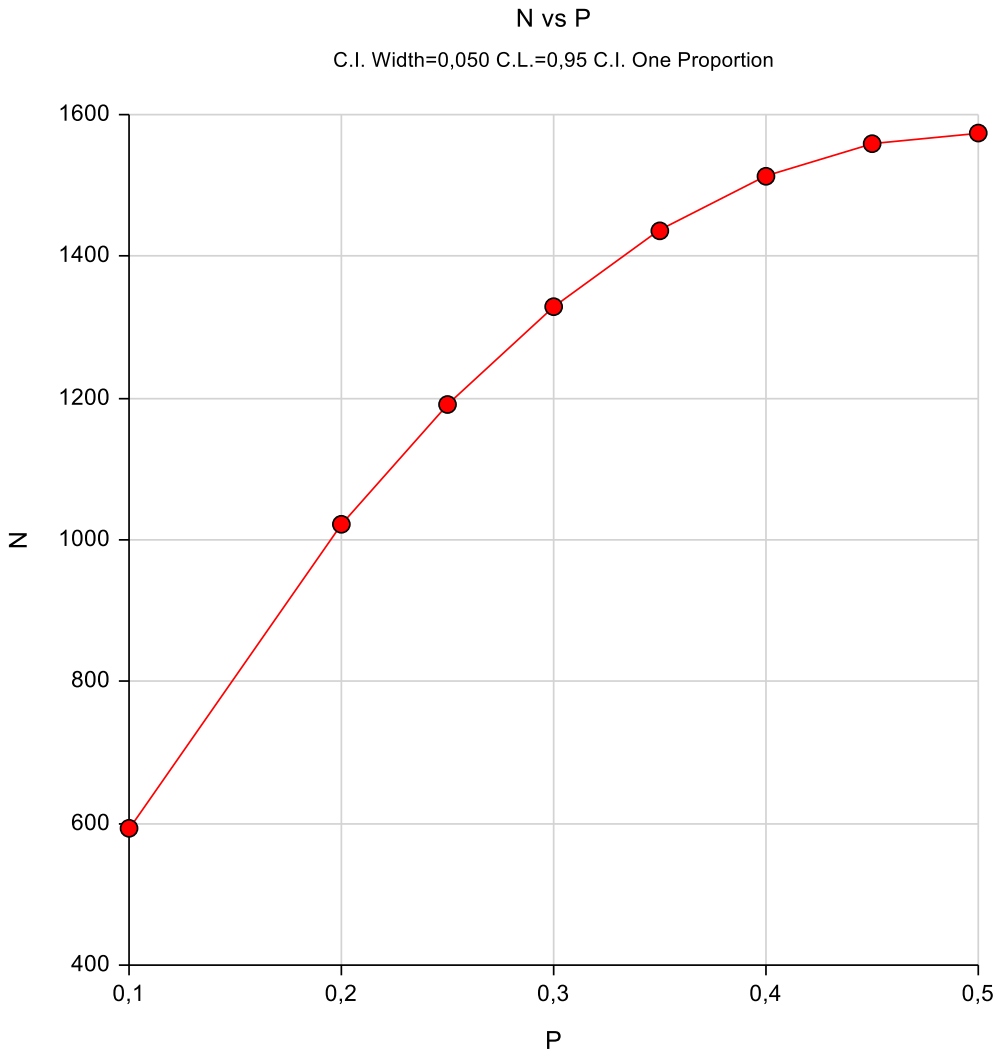


Confidence Intervals for One Proportion

Procedure Input Settings

Design Tab

Solve For:	Sample Size
Confidence Interval Formula:	Exact (Clopper-Pearson)
Interval Type:	Two-Sided
Confidence Level (1 - Alpha):	0,95
Confidence Interval Width (Two-Sided):	0,07
P (Proportion):	0,1 to 0,5 by 0,05



APPENDIX 2: CODE LISTS

Patient-Reported Outcomes (PROs)

COPD Assessment Test (CAT)

The CAT is a validated measure of health status in COPD. The CAT is an 8-item, patient-completed instrument that covers symptoms such as cough, phlegm, chest tightness and breathlessness, and disease impacts including physical activity, confidence, sleep and energy. The CAT asks patients to score each item according to their current experience; there is no specific recall period. Items are scored on a 6-point response scale, with a score of 0 representing the patient not experiencing the symptom or the impact at all and a score of 5 representing a maximal symptom or impact. All items have equal weighting and so the total score is simply the sum of all scores and can range from 0 to a maximum of 40, with higher scores indicating a worse health state [Jones 2009 (a); Jones et al. 2009 (b)]. A decrease in score indicates an improvement in health status and the minimum clinically important difference (MCID) is estimated to be between 1.2 to 2.8 units [Jones 2012, Kon 2014].

The CAT has been translated into many languages including Japanese and has been shown to be easy to understand and to complete by patients in many countries worldwide.

The CAT has been used previously to compare health-related quality of life (HRQoL) and severity of airflow limitation in patients with asthma, ACO and COPD [Kurashima 2016].

Example of the COPD Assessment Test (CAT) (in the TETRIS study, a German language version will be provided):

Your name:

Today's date:

CAT
COPD Assessment Test™

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	**I cough all the time**	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	**My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	0 1 2 3 4 5	**My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	**When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	0 1 2 3 4 5	**I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	**I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	0 1 2 3 4 5	**I don't sleep soundly because of my lung condition**	
I have lots of energy	0 1 2 3 4 5	**I have no energy at all**	
		TOTAL SCORE	

CCI

[redacted]


CCI

APPENDIX 3: TABLES AND FIGURES

Table 1 (see also Section 3.2):

SCHEDULE OF ACTIVITIES

Table 1: Data collection schedule (data will be collected as per clinical routine). EW: Early withdrawal.

Procedure	**Screening (up to 14 days before visit 1)**	**Part 1**	**Part 2**						**EW**
		Visit 1: Month 0	**Intermediate visits**	**Visit 2[§]: Month 6 (-3/+2)**	**Intermediate visits**	**Visit 3[§]: Month 12 (-3/+5)**	**Intermediate visits**	**Visit 4[§]: Month 24 (-6/no upper limit)**	
Informed consent	X								
Inclusion and exclusion criteria	X								
Patient's sociodemo-graphic characteristics	X								
Height, weight, BMI		X		X		X		X	X
Medical history and comorbidities	X	X							
COPD* medication history before initiating triple therapy		X							
Maintenance medication for COPD*	X	X		X		X		X	X
Concomitant COPD* medication		X		X		X		X	X
Reasons for initiating triple therapy		X							
Reasons for changing maintenance medication for COPD*				X		X		X	X
Smoking status		X	X	X	X	X	X	X	X
Narratives of any lung CT scans[a)]		X		X		X		X	X
Spirometry testing (FEV_1, FVC, FEV_1/FVC ratio) (if routinely collected)	X	X		X		X		X	X
Body-plethysmo-graphie (if performed routinely)		X		X		X		X	
D_{LCO} (if routinely collected)		X		X		X		X	
FeNO (if routinely collected)		X		X		X		X	

Procedure	**Screening (up to 14 days before visit 1)**	**Part 1**	**Part 2**						**EW**
		Visit 1: Month 0	**Intermediate visits**	**Visit 2[§]: Month 6 (-3/+2)**	**Intermediate visits**	**Visit 3[§]: Month 12 (-3/+5)**	**Intermediate visits**	**Visit 4[§]: Month 24 (-6/no upper limit)**	
Eosinophils (EOS) in blood (if routinely collected)	X	X		X		X		X	X
WBC count (if routinely collected)		X		X		X		X	X
WBC differential (if routinely collected)		X		X		X		X	X
hsCRP (if routinely collected)		X		X		X		X	X
Healthcare resource utilisation (HRU)[c)]		X		X		X		X	X
Events[b)] during study			X	X	X	X	X	X	X
CAT	X	X		X		X		X	X
EQ-5D (incl. VAS)		X		X		X		X	X
AE/SAE review		X		X		X		X	X
The eCRF will additionally capture surrogate markers for compliance (e.g. "Did the patient regularly/every 3 months ask for a new prescription?").									

§ There should be a minimum interval of 3 months between each of the visits (visit 2, 3, 4), otherwise the visit is counted as an interim visit.

AE: adverse event; BMI: body mass index; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; COPD*: COPD with or without comorbid asthma; CT: computed tomography; D_{LCO}: diffusing capacity; EOS, eosinophils; EQ-5D, European Quality of Life 5 Dimensions; EW: early withdrawal; FeNO, Fraction Exspiratory Nitric Oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; hsCRP, high-sensitivity C-reactive protein; HRU, healthcare resource utilisation; SAE: serious adverse event; VAS, Visual Analogue Scale; WBC, white blood cell; WOCBP: woman of child bearing potential.

a. The radiologist's narrative will be collected for any historical lung CT scans performed in the year prior to the study or any lung CT scans performed as part of routine clinical management during the study.
b. Event includes: unstable COPD, cold requiring antibiotics, exacerbation and hospitalizations.
c. HRU includes: hospitalization, hospitalization in intensive care unit, number of physicians treating the patient (primary and secondary care), number of physician goups treating the patient (2 groups), change of treating physician, returning from secondary care to primary care physician, returning from acute care to primary or secondary care

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Patient characteristics can be identified in a number of ways. Determination of blood eosinophils and hsCRP may aid identification in the same way that D_{LCO} measurements and CT images can help detect persistent lung inflation. Sputum secretion, dry cough, or FeNO determinations can also help identify important patient characteristics. The detection of "rapid declines" (loss of> 100 ml lung volume per year) may be another important patient characteristic.

Table 2 (see also Section 3.5):

LISTING OF OBJECTIVES AND ASSOCIATED ENDPOINTS

Objective	Endpoints
Evaluate the percentage of patients who continuously receive triple therapy	• Patients who continuously receive triple therapy for 6, 12 and 24 months (including stratification by SITT vs. MITT) • Time to stop triple therapy
Describe profiles of COPD patients who initiated or are on triple therapy (LAMA/ LABA/ICS) in Germany	Patient and disease characteristics when initiating triple therapy: • Percentage of COPD patients with diagnosis of asthma at the age of <40 years • Percentage of patients with peripheral blood EOS of <100 cells/µl, 100-200 cells/µl, 200-300 cells/µl and > 300 cells/µl • Percentage of participants with a physician's diagnosis of COPD by site localization and physician´s group • Percentage of participants with different symptom and risk classes (GOLD) • Medications received by COPD patients (including OCS), split by physician group and site localization • Time on triple therapy before study start (<3 months / 3 - <6 months / >=6 months)
Describe the distribution and frequency of combined treatable traits in COPD patients	• Percentage of patients presenting with a smoking history (when initiating triple therapy and at different time points during a 24-month observation period) • Percentage of patients with a non-smoking history when initiating triple therapy • Percentage of patients with a FEV1/FVC ratio <0.7 at study enrolment and at a 6, 12 and 24 months documentation • Percentage of patients with any moderate/severe exacerbation in the 24 months prior to study enrolment or 3 months prior to each subsequent on-study visit during a 24-month observation period • Percentage of patients with a CAT score ≤10 / 11-19 / ≥20 at baseline and at a 6, 12 and 24 months documentation • Percentage of patients with peripheral blood eosinophil (EOS) count ≥100 cells/µl at baseline and at a 6, 12 and 24 months documentation • Percentage of patients with chronic bronchitis phenotype
Describe the percentage of participants with at least one switch from triple therapy to LAMA/LABA or to ICS/LABA after 6, 12 and 24 months	• Patients with at least one switch from triple therapy to LAMA/LABA after 6, 12 and 24 months • Patients with at least one switch from triple therapy to ICS/LABA after 6, 12 and 24 months
Describe COPD treatment decisions of German physicians who have initiated patients on triple therapy	• Distribution (by physician group) and frequency of prespecified reasons to initiate triple therapy (either MITT or SITT) • Percentage of patients changing from triple to dual therapy and back to triple therapy (re-escalation) during a 24-month observation period after study enrolment (split by SITT and MITT and split by LAMA/LABA and ICS/LABA) • Percentage of patients with at least one re-escalation from LAMA/LABA or ICS/LABA or LAMA to triple therapy during the 24-month observation period • Percentage of patients with at least one change from MITT to SITT or SITT to MITT during a 24-month observation period

Objective	Endpoints
	• Percentage of patients with at least one change from SITT to SITT or MITT to MITT during a 24-month observation period • Percentage of patients changing from once daily to twice daily medication or vice versa or between different inhaler types • Percentage of patients changing between different inhaler types • Distribution (by physician group) and frequency of prespecified reasons to change a triple therapy (either MITT or SITT) • Distribution and frequency of prespecified reasons to change triple therapy to another triple therapy • Distribution and frequency of prespecified reasons† to change triple therapy to therapy de-escalation • Distribution and frequency of prespecified reasons to change de-escalataed therapy back to triple therapy (re-escalation)
Describe clinical outcomes in COPD patients initiated on triple therapy	• Mean annual rate of moderate and/or severe exacerbations over a 24-month observation period (including subgroup analysis by peripheral blood eosinophil count, smoking status and asthma history) • Mean annual rate of hospitalizations due to severe exacerbations • Change of lung function parameters during a 24-month observation period (including subgroup analysis by peripheral blood eosinophil count, smoking status and asthma history) • Change of COPD symptoms during a 24-month observation period • Change in HRQoL during a 24-month observation period • Percentage of COPD patients experiencing a clinically important deterioration2 during a 24-month observation period • Time to first moderate or severe exacerbation during a 24-month observation period • Time to first hospitalization / hospitalization during a 24-month observation period • Time to death during a 24-months observation period
Describe the patient journey of COPD patients initiated on triple therapy	• Mean annual rate of COPD related primary and secondary care contacts • Number of different documenting physicians per patient during a 24-month observation period (also split by patients with a severe or moderate or severe exacerbation and split by site localization) • Mean number of treating physicians per patient over a 24-month observation period (also split by site localization and diagnosis) • Percentage of patients treated by 1, 2 or all 3 physician groups addressed in the study (settled general practitioners, settled pulmonologists, outpatient lung centres)
Describe safety with triple therapy	• Safety with focus on pneumonia and cardiovascular events • Benefit-harm profiles for single-inhaler triple therapies (SITTs, including Trelegy, Trimbow and Breztri) • Benefit-harm profiles for major multiple inhaler triple therapy (MITT) combinations • Benefit-harm profiles for triple therapies interrupted by ICS and/or LAMA “off/on” periods • Benefit-harm profiles for triple therapies switching between SITT and MITT