Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

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Title:	Real-world treatment of newly diagnosed COPD patients: A retrospective German claims data analysis
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Product reference:	Not applicable
Procedure number:	Not applicable
Joint PASS:	No
Research question and objectives:	A. Description of the real-life drug treatment of patients with incident COPD, including description of treatment sequence/escalation in the first 12/24/36 months after incident diagnosis B. Comparison of initial drug treatment of incident COPD patients with two versions of German treatment guidelines (2012/2018) C. Description of exacerbation frequency (severe exacerbations associated with an inpatient hospitalization) of incident COPD patients in the first 12/24/36 months after incident diagnosis

	D. Description of health-care resource use (HCRU; including use of oxygen therapy) and direct treatment cost of incident COPD patients in the first 12/24/36 months after incident diagnosis [redacted]
Country(-ies) of study:	Germany
Author:	[redacted]
Marketing authorisation holder(s):	[redacted]
MAH contact person:	[redacted]
In case of PASS, add: **<EU-QPPV:>**	Not applicable
In case of PASS, add: <**Signature of EU-QPPV:>**	Not applicable
Date:	16 October 2019

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical / Defined Daily Dose Classification
BI	Boehringer Ingelheim
BMI	Body-Mass-Index
CAT	COPD Assessment Test
CCI	Charlson Comorbidity Index
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
CRO	Clinical Research Organization
DALYs	Disability-Adjusted Life Years
DDD	Defined Daily Dose
DMP	diseases management program
EBM	Einheitlicher Bewertungsmaßstab
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS (register)	European Union electronic Register of Post-Authorisation Studies
FEV(1)	Forced expiratory volume (in 1 second)
GLM	Generalized Linear Model
GOLD	Global initiative for chronic obstructive lung disease
GONr	Gebührenordnungs-Nr.
GP	General Practitioners
GPP	Good Pharmacoepidemiology practices
GVP	Good pharmacovigilance practices
HCRU	Health care resource use
HRQoL	Health-related quality of life
IC	Informed Consent
ICD	International Statistical Classification of Diseases and Related Health Problems
ICH-GCP	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
[redacted]	
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LOCF	Last observation carried forward

LTOT	Long-Term Oxygen Therapy
MedDRA	Medical Dictionary for Drug Regulatory Activities
mMRC	Modified Medical Research Council
NIS	Non-interventional study
OPS	Operationen- und Prozedurenschlüssel
PASS	Post-authorisation safety study
PhRMA	Pharmaceutical Research and Manufacturers Association
PY	Patient year
PZN	Pharmazentralnummer
QALYs	Quality added life years
SABA	Short-acting beta antagonist
SAMA	Short-acting muscarinic antagonist
SD	Standard Deviation
SI	Study Investigator
WHO	World-Health Organization

3. RESPONSIBLE PARTIES

Function	*Name*	*Affiliation*
Project Manager	[redacted]	[redacted]
Medical Project Member		
TCM		
Study Coordinator GPV		
Scientific advisor		
Scientific advisor		
Scientific advisor		
Scientific Lead		[redacted]
Main Project Management		
Claims Data Management		[redacted]
Study investigators / Study sites	*NA*	*NA*

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: COPD medication of any type			
Name of active ingredient: COPD medication of any type, ATC code R03			
Protocol date: 16 Oct 2019	**Study number:** 1237-0092	**Version/Revision:** 1.0	**Version/Revision date:** Not applicable
Title of study:	Real-world treatment of newly diagnosed COPD patients: A retrospective German claims data analysis		
Rationale and background:	In terms of COPD drug therapy, the current German COPD guideline (S2) [1, 2] recommends a treatment escalation procedure. For incident COPD patients (for the sake of simplicity, newly diagnosed and so far treatment naïve COPD patients will be referred to as "incident COPD patients" in the following), the German guideline recommends the following: • No treatment (low symptom burden) • SABA or SAMA • LABA or LAMA or LABA+LAMA. All other treatments, particularly combination treatments including ICS[1], are only recommended as escalation therapy. Currently, knowledge on real world treatment of incident COPD patients in Germany is sparse, in particular regarding the frequency of different drug therapy prescriptions and the frequency of early therapy escalation including ICS. This study aims to address this issue by reporting treatment of incident COPD patients in the real world. COPD and treatment associated outcomes, especially severe exacerbations (leading to hospitalization), health-care resource use, and early use of oxygen therapy, will be explored. In addition, real-world treatment of incident COPD patients will be compared to German guidelines, using current 2018 guidelines and 2012 guidelines as framework in two scenario calculations.		

[1] ICS is recommended by the guideline for COPD patients with an asthmatic component. Based on inclusion/exclusion criteria as applied in this study, these patients will be excluded from analysis.

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Research question and objectives:	A. Description of the real-life drug treatment of patients with incident COPD, including description of treatment sequence/escalation in the first 12/24/36 months after incident diagnosis B. Comparison of initial drug treatment of incident COPD patients with two versions of German treatment guidelines (2012/2018) C. Description of exacerbation frequency (severe exacerbations associated with an inpatient hospitalization) of incident COPD patients in the first 12/24/36 months after incident diagnosis D. Description of health-care resource use (HCRU; including use of oxygen therapy) and direct treatment cost of incident COPD patients in the first 12/24/36 months after incident diagnosis [redacted]		
Study design:	A retrospective analysis will be done based on a claims dataset delivered by a German sickness fund (so far, a cooperation with [redacted] (approximately 3.2 million insured persons) is planned; a second sickness fund might be included as well). The dataset will cover the period 01/01/2013-30/06/2018[2], and will only include patients who were continuously insured within the sickness fund between the entire period (death is the only exception)[3]. In selected analyses, incident COPD patients will be observed for an exact follow-up period of 12 months (in subgroup analyses: 24 and 36 months); censoring of patients will only be done in case a patient died during the respective follow-up period. [redacted]		

[2] If more data will be available until time of analysis start, further quarters (from 2018) will be included into the analysis. The Steering Board of the study will discuss whether it is meaningful to include additional date from 2010/2011/2012 taking into account that a ministry approval would be necessary in that case.
[3] Continuous insurance is necessary, to not accidently include patients twice in case they left the sickness fund intermediately and went back later on and are included within the dataset with two different pseudo numbers.

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Population:	The following inclusion criteria apply: • All patients who were continuously insured by the sickness fund for the entire period (01/01/2013-30/06/2018) or, in case a patient deceased after index date, for the time until death[4] • A patient will be included as an incident COPD patient if either a hospital documented at least one COPD diagnosis (ICD-10 J 44.-) or a specialist (pneumologist) documented at least 2 confirmed COPD diagnoses (above ICD-10 code) in two different quarters; the first of the above diagnoses is defined as index diagnosis; inclusion period is defined as lasting from 01/01/2014 until 30/06/2017[5] • Patients should not have received any COPD diagnosis (ICD-10 J44.-) or any COPD-associated medication (Suppl. Table 2[6]) in the 12 months pre-index period • Patient should have, at date of incident COPD diagnosis (index date), an age of at least 40 years In the planned analyses, different subpopulations with regard to follow-up time and availability of disease management program (DMP) data will be defined.		

[4] Patients censored due to their death will be included as well including reporting of their baseline characteristics.
[5] Please note: Based on all patients with at least one confirmed outpatient or inpatient COPD diagnosis (from specialists, GPs and/or hospitals), an attrition chart will show how many patients are subsequently excluded because of the applied inclusion/exclusion criteria.
[6] Prescription of systemic/oral corticosteroids (SCS/oral) will not be considered as exclusion criteria

<table>
<tr><td colspan="2">Name of company:
Boehringer Ingelheim</td><td rowspan="3"></td><td></td></tr>
<tr><td colspan="2">Name of finished medicinal product:
COPD medication of any type</td><td rowspan="2"></td></tr>
<tr><td colspan="2">Name of active ingredient:
COPD medication of any type, ATC code R03</td></tr>
<tr><td>Protocol date:

16 Oct 2019</td><td>Study number:
1237-0092</td><td>Version/Revision:

1.0</td><td>Version/Revision date:
Not applicable</td></tr>
<tr><td>Variables:</td><td colspan="3"><u>Baseline characteristics (referring either to index date = date of incident (first) diagnosis of COPD, or to 12 months pre-index period)</u>
• Age
• Gender
• Concomitant diseases /comorbidity level
o Most frequently observed 10 diseases, based on recorded ICD-10 codes up to 3rd level
o Charlson Comorbidity Index (CCI)
o Percentage of patients with at least one confirmed inpatient or two confirmed outpatient diagnoses in two different quarters of the following diseases:
▪ Asthma
▪ Bronchiectasis
▪ Bronchial carcinoma
▪ Diabetes mellitus
▪ Congestive heart failure
▪ Moderate to severe kidney disease
▪ Myocardial infarction
▪ Hypertension
▪ Peripheral vascular disease
▪ Cerebrovascular event or transient ischemic attack
▪ Hemiplegia
▪ Dementia
▪ Sleep apnoea
▪ Osteoporosis
o Percentage of patients with at least one confirmed inpatient or two confirmed outpatient diagnoses in two different quarters of the following respiratory diseases:
▪ ICD-10 codes J0-J99 (Top-5 diseases)</td></tr>
</table>

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- Previous drug treatment in the pre-index period, based on appropriate ATC group level
    - Percentage of patients who received specific treatments (most common 10 treatments as observable for above samples) with at least two prescriptions in the pre-index period.

<u>Documentation referring to the 12 months follow-up after index date (for patient subgroups: 24 months/36 months follow-up, or complete follow-up period)</u>

- For patients with available data resulting from a disease management program (DMP)
    - Weight [kg] (reported MIN, MAX and MEAN during follow-up period)
    - Height [cm]
    - Blood pressure (reported MIN, MAX and MEAN during follow-up period)
    - Non-drug treatment recommendations
    - Exacerbations (number and severity)
    - FEV_1 (reported MIN, MAX and MEAN during follow-up period)
    - Smoking status if applicable

- Drug treatment with long-acting bronchodilators (incl. separate reporting for respective agent classes beta-agonists, anticholinergics, methylxanthines)
- Drug treatment with short-acting agents
- Drug treatment with anti-inflammatory drugs (ICS, PDE-4, macrolides)
- Top-10 prescribed non-COPD drug therapies (based on ATC codes on appropriate level)

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	• Antibiotics for systemic use (based on ATC J02AA)
	• Antibiotics in combination with corticosteroids (based on ATC D07C)
	• Systemic/oral corticosteroids (SCS/OCS; based on ATC R01AD02; D07AA01; D10AA02; H02AB04)
	• All-cause hospitalizations
	  o Among them: hospitalizations with COPD as main diagnosis (ICD-10 J44.-)
	• Among them: hospitalizations with a COPD exacerbation as main diagnosis (ICD-10 J44.1)
	• Exacerbations as documented by outpatient pneumologists (ICD-10 J44.1)
	• GP visits and pneumologists' visits and visits to other specialists
	• Prescription of COPD-associated aids
	  o Oxygen therapy
	• Date of death, if patient died during follow-up period (for censoring and time to event analyses).		

Data sources:	This retrospective study is an analysis of an anonymized claims dataset provided by the [redacted] and potentially a second sickness fund (approval still pending).		
Study size:	Based on an initial feasibility assessment done by [redacted] **N>40,000** incident COPD patients meeting above inclusion/exclusion criteria can be expected. • Among them, about 26,000 (~65%) received at least one prescription of a long-acting bronchodilator in the 12 months follow-up period • Percentage of incident patients with at least one DMP documentation (providing more detailed information for additional analysis) is about 30%. Among the DMP patients, about 4,000 incident patients can be expected with at least one prescription of a long-acting bronchodilator in the 12 months follow-up period. It needs to be evaluated during the study whether the DMP data can be used for study purposes, which would require a start of DMP documentation early after the incident COPD diagnosis.		

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Data analysis:	• Descriptive statistics will mainly be applied in this study. For categorical (including dichotomous) variables, frequencies, percentages and 95% confidence intervals (CIs) will be reported, along with corresponding sample sizes. Continuous variables will be summarized using mean, standard deviation, median, ranges and 95% CIs along with corresponding sample sizes. • Statistical comparisons of socio-demographic and clinical characteristics will be conducted between different patient groups, e.g. patients with different comorbidity profile or therapy. Comparisons will be done based on appropriate tests, e.g. Chi-square tests, Fisher's exact tests, t-tests or a suitable non-parametric tests. • Time to event analyses will be done based on a Kaplan Meier (KM) methodology; comparisons between groups will be done using Log Rank tests. [redacted]		
Milestones:	[redacted]		

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	**Planned Date**
Draft of study protocol	[redacted]
First Steering Board Meeting	
Final study protocol & approval by [redacted]	
Start of data collection (Start of data access/ data validation)	
End of data collection (End of data analyisis)	
Final report of study results (Final Steering Board Meeting)	
Finalization of publication drafts	

7. RATIONALE AND BACKGROUND

In terms of chronic obstructive pulmonary disease (COPD) drug therapy, the current German COPD guideline (S2) [1] recommends a treatment escalation procedure (Figure 1). For incident COPD patients (for the sake of simplicity, newly diagnosed and so far treatment naïve COPD patients will be referred to as "incident COPD patients" in the following), the guideline recommends the following:

- No treatment (low symptom burden) or
- Short-acting beta antagonist (SABA) or short-acting muscarinic antagonist (SAMA) or
- Long-acting beta agonist (LABA) or long-acting muscarinic antagonist (LAMA) or LABA+LAMA.

All other treatments, particularly combination treatments including inhaled corticosteroids (ICS), are only recommended as escalation therapy. However, despite the increasing evidence (e.g. WISDOM study [3], FLAME study [4]), there might exist the view that early use of ICS in the treatment of COPD might be advisable, and might be prescribed in a substantial percentage of COPD-incident patients.

Figure 1 Treatment recommendations with regard to COPD stages, according to German 2018 S2 guideline [1]

<table>
<tr><th colspan="2">Medikamentöse Dauertherapie der COPD</th></tr>
<tr><td>Symptome - Ausmaß der Lungenfunktions-einschränkungen berücksichtigen</td><td>Medikamentöse Therapie</td></tr>
<tr><td>Wenig (z. B. CAT < 10)
GOLD Gruppe A</td><td>- Keine
- SABA + SAMA (initial)
- LABA oder LAMA</td></tr>
<tr><td>Viel (z. B. CAT ≥ 10)
GOLD Gruppe B</td><td>- LABA oder LAMA
- LABA + LAMA</td></tr>
<tr><td colspan="2">Exazerbationen > 1 oder Exazerbation mit Hospitalisierung GOLD Gruppen C und D</td></tr>
<tr><td>Nicht vorbehandelt</td><td>LAMA oder LAMA + LABA</td></tr>
<tr><td>Vorbehandelt</td><td>LAMA + LABA</td></tr>
<tr><td>Eskalation/Wechsel</td><td>⇄ ⇄</td></tr>
<tr><td></td><td>LABA + ICS → LAMA + LABA +ICS</td></tr>
<tr><td></td><td>± Roflumilast
(Phänotyp chronische Bronchitis)</td></tr>
</table>

Currently, knowledge on real world treatment of incident COPD patients in Germany is sparse, in particular regarding the frequency of different drug therapy prescriptions and the frequency of early therapy escalation including ICS. With the current analyses, we aim to emphasize the central role of LAMA/LABA therapy in COPD and importance of treatment guideline adherence.

This study aims to address the question of guideline adherence by reporting treatment of incident COPD patients as well as description of COPD-associated outcomes, especially severe exacerbations leading to hospitalization. In addition, real-world treatment of incident COPD patients will be compared to German guidelines, using current 2018 guidelines and 2012 guidelines as framework in two scenario calculations. The results of this study could serve as basis for the tailored development of managed care projects together with payers.

8. RESEARCH QUESTION AND OBJECTIVES

The main research questions of this study can be summarized as follows:

PRIMARY

- Description of the real-life drug treatment of patients with incident COPD, including description of treatment sequence/escalation in the first 12/24/36 months after incident diagnosis

SECONDARY

- Comparison of initial drug treatment of incident COPD patients with two versions of German treatment guidelines (2012/2018)
- Description of exacerbation frequency (severe exacerbations associated with an inpatient hospitalization) of incident COPD patients in the first 12/24/36 months after incident diagnosis
- Description of health-care resource use (HCRU; including use of long-term oxygen therapy (LTOT)) and direct treatment cost of incident COPD patients in the first 12/24/36 months after incident diagnosis

[redacted]

9. RESEARCH METHODS

9.1 STUDY DESIGN

A retrospective analysis will be done based on a claims dataset delivered by two German sickness funds (so far, a cooperation with [redacted] is planned, second sickness fund needs to be named yet). The dataset will cover the period 01/01/2013-30/06/2018[7]. In selected analyses, incident COPD patients will be observed for an exact follow-up period of 12 months (in subgroup analyses: 24 and 36 months); censoring of patients will only be done in case a patient died during the respective follow-up period. [redacted]

The data will be analyzed for a pre-index period (12 months before index diagnosis) and for a follow-up period of 12 months after index date. In subgroup analyses, longer follow-ups (24 and 36 months, and full observation time (up to 54 months[8])), are used. Death after index diagnosis during the follow-up is the only accepted exception from this rule. For a subsample of patients, disease management program (DMP) data might be available. These provide disease specifics such as forced expiratory volume in 1 second (FEV_1) values, specifics of prescribed therapy, and exacerbation frequency and severity.

The dataset contains available information on the sociodemographic characteristics of the patients, their treatment with prescription aids and medications, their outpatient and inpatient treatment, and COPD-specific clinical parameters for the patients who participated in a disease management program (DMP). A first overview of data generally available in claims data of a German sickness fund is given in Table 1. The study-specific data set (required data according to approved study protocol) needs to be approved by the respective sickness funds, based on the study objectives and the respective methodology as outlined in this protocol.

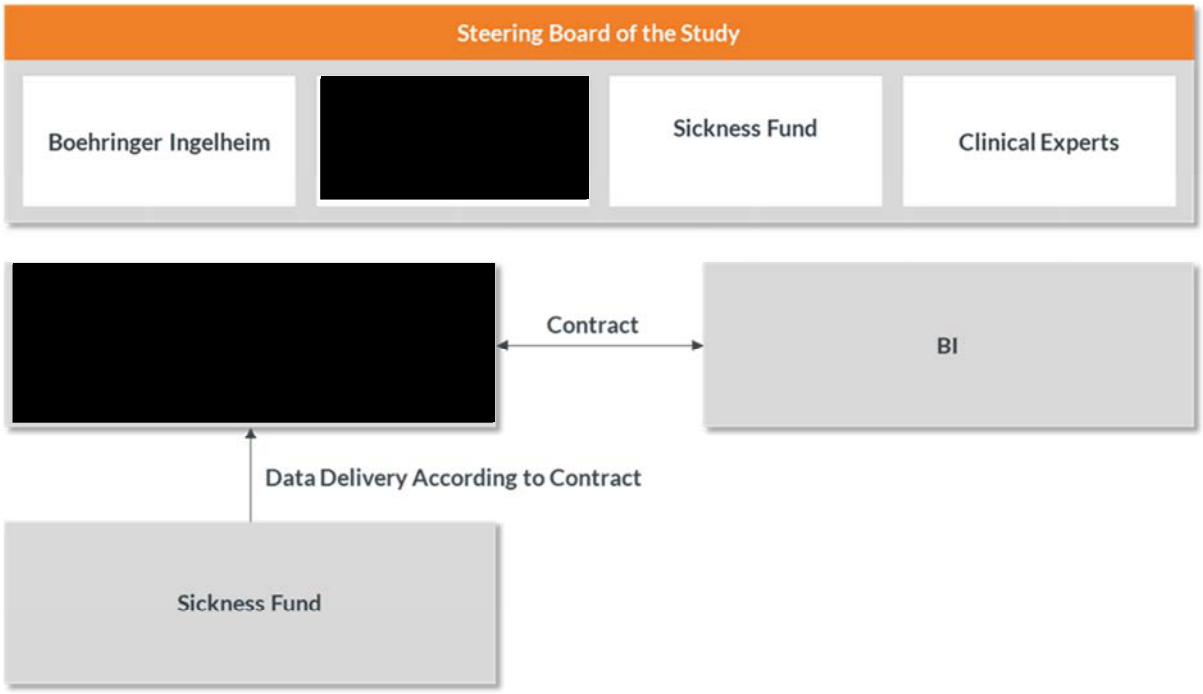
[7] If more data will be available until time of analysis start, further quarters (from 2018) will be included into the analysis.
[8] If more data will be available until time of analysis start, further quarters (from 2018) will be included into the analysis.

Table 1 Data generally available in the claims data set

Sociodemo-graphic characteristics	*Inpatient care*	*Outpatient care*	*Outpatient medication (prescriptions only)*	*Other data*
• *Age*	• *Data about initial diagnoses including day of admission*	• *All physicians' visits including type of physician (esp. GPs and specialists in different specialist groups)*	• *Type of medication (medication number – in Germany: PZN), ATC code, number of packs, dates of prescription and of dispensing pharmacy*	• *Costs for outpatient devices/other supportive measures* • *Outpatient surgeries*
• *Gender*	• *All documented diagnoses/ procedures*	• *Documentation of diagnoses/ measures (EBM, GONr, OPS)*	• *Prescribing physician*	• *Other services paid by the insurance, e.g. salary co-payments etc. and Costs of other diagnostic/ therapeutic measures*
• *Type of insurance*	• *Length of stay in days*	• *Description of "safety" of diagnoses*	• *Medication-specific data (DDD, other information)*	• *Outpatient/in-patient long-term care data*
• *Partly: Socioeconomic status*	• *Costs including specific DRG*	• *Dates (physician visits; all diagnostic/ therapeutic measures)*	• *Costs; indirectly by calculation: patients' co-payments*	• *Days absent from work*
• *Mortality*	• *Data about inpatient/ outpatient rehabilitation clinic stays/other follow-up measures*	• *Costs of outpatient care based on activity points documented by doctors*		• *Partly DMP data: FEV_1, need for COPD medication, exacerbations (Suppl. Table 1)*

For the claims data analysis, [redacted] will involve its university-affiliated partner, [redacted] has a longstanding experience in claims data analyses. [redacted] will close a contract with the cooperating sickness funds. This includes a detailed and mutually agreed list defining data extraction inclusion/exclusion criteria as well as all variables and formats to be used. Moreover, the contract outlines which data protection measures need to be implemented by [redacted] The sickness funds will participate in the Steering Board of the study as well as being a co-author of all future publications of study results. The general model of cooperation is shown in Figure 2.

Figure 2 General study organization



In a first meeting of the Steering board, the study protocol draft will be discussed and, finally, be approved. After the approval of the steering board, the protocol will be submitted to the cooperating sickness funds and BI for final approval.

9.2 SETTING

An anonymized dataset from the cooperating sickness funds, which includes all patients with at least one COPD diagnosis, who were insured by this sickness funds for the entire period (01/01/2013 - 30/06/2018) will be available.

A patient will be confirmed as being COPD-incident if specialists documented at least two confirmed outpatient COPD diagnoses (ICD J44.-) and/or at least one inpatient COPD diagnosis (ICD J44.-), without such diagnoses in the previous 12 months and without any COPD prescription in the previous 12 months (Suppl. Table 2).

Specific inclusion criteria can be described as follows:

- All patients should have been covered by the sickness fund for the entire period (01/01/2013-30/06/2018) or, in case a patient deceased after index date, for the time until death
- A patient will be included as an incident COPD patient if either a hospital documented at least one COPD diagnosis (ICD-10 J44.-) or a specialist (pneumologist) documented at least two confirmed COPD diagnoses (above ICD-10 code) in two different quarters; the first of the above diagnoses is defined as index diagnosis; inclusion period is defined as lasting from 01/01/2014 until 30/06/2017

- Patients should not have received any COPD diagnosis (ICD-10 J44.-) or any COPD-associated medication (Suppl. Table 2)[9] in the 12 months pre-index period
- Patient should have, at date of incident COPD diagnosis (index date), an age of at least 40 years

Patients who received at least one confirmed inpatient asthma diagnosis or two confirmed outpatient diagnoses of asthma (ICD-10: J45.-) by pneumologists after the incident COPD diagnosis (index diagnosis) will be separately observed.

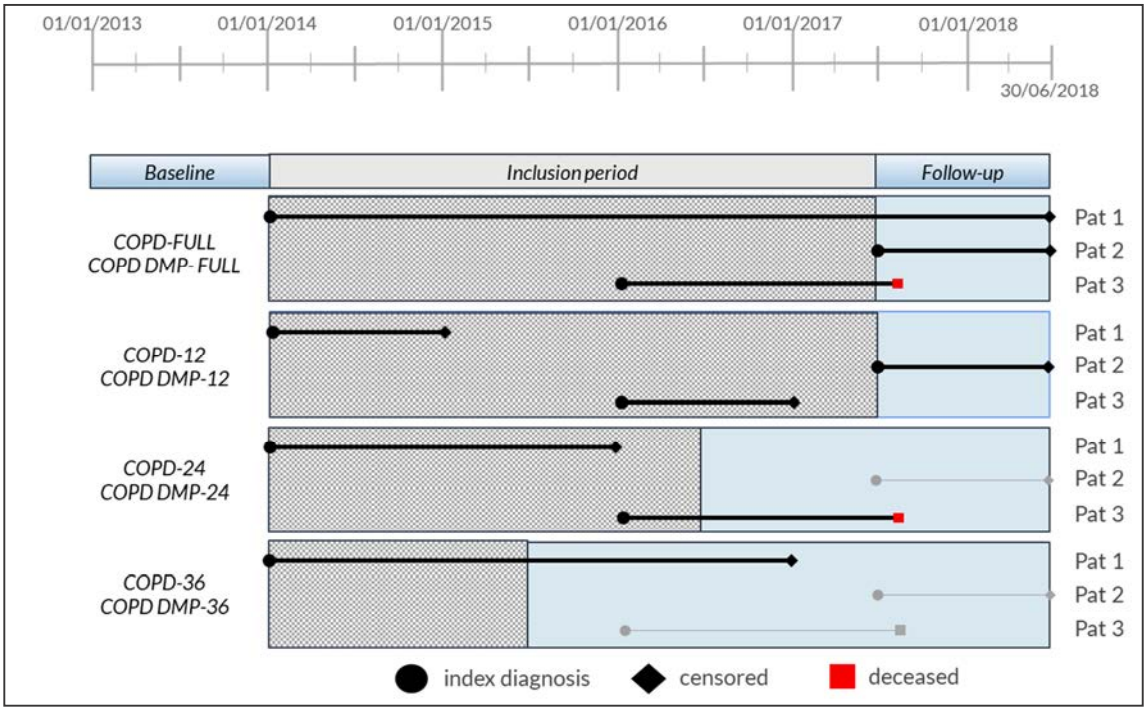
Based on these inclusion/exclusion criteria, the following data sets will be analyzed (Figure 3)[10]:

- COPD-FULL DATA: All incident COPD patients with a follow-up of up to 54 months
- COPD-12: All incident COPD patients with a follow-up[11] of 12 months since index date
- COPD-24: All incident COPD patients with a follow-up of 24 months since index date
- COPD-36: All incident COPD patients with a follow-up of 36 months since index date
- COPD DMP-FULL DATA: All incident COPD patients with available DMP data (at least one entry during 3 months after index date[12]) and a follow-up of up to 54 months.
- COPD DMP-12: All incident COPD patients with available DMP data (at least one entry during 3 months after index date) and a follow-up of 12 months since index date
- COPD DMP-24: All incident COPD patients with available DMP data (at least one entry during 3 months after index date) and a follow-up of 24 months since index date
- COPD DMP-36: All incident COPD patients with available DMP data (at least one entry during 3 months after index date) and a follow-up of 36 months since index date.

[9] Prescription of systemic/oral corticosteroids (SCS/OCS) will not be considered as exclusion criteria
[10] Please note that this samples will not include patients with at least one confirmed inpatient or two confirmed outpatient diagnoses of asthma (ICD-10: J45.-) by pneumologists after the incident COPD diagnosis (index diagnosis) during the follow-up period. Those patients will be described separately.
[11] Time since patient-individual index date until 30/06/2018; patients who died within this period will not be excluded from the analysis
[12] So far it is unknown how many patients were included in the DMP directly after incident diagnosis and for how many patients an entry in the first months after diagnosis will be available. Thus, depending on the pattern that will be observed in the data, the restriction „at least one entry during the 3 months after index date“ might be extended to „at least one entry during the 6/12 months after index date“.

Figure 3 Baseline period, inclusion period, follow-up period for different study samples

(note: for time to event analyses, COPD-full data sample (with full follow-up times) will be applied). DMP: disease management program (refers to the subsample of patients who participate in the COPD DMP and thus provide more detailed data)



9.3 VARIABLES

9.3.1 Exposures

For all above samples, baseline characteristics will be described. These refer either to index date (= date of incident (first) diagnosis of COPD) or to the 12-month pre-index period:

- Age
- Gender
- Concomitant diseases /comorbidity level
    - 10 most frequently documented diseases, based on recorded ICD-10 codes up to 3rd level
    - Charlson Comorbidity Index (CCI, see Suppl. Table 3)
    - Percentage of patients with at least one confirmed inpatient or two confirmed outpatient diagnoses in two different quarters of the following diseases:
        - Asthma (J45.)
        - Bronchiectasis (J47.)
        - Bronchial carcinoma (C34.)

- Diabetes mellitus (E10.-E14.)
- Congestive heart failure (I11., I50.)
- Kidney disease (N17.-N19.)
- Myocardial infarction (I21., I22.)
- Hypertension (I10.-I15.)
- Peripheral vascular disease (I73., I74., I77.)
- Cerebrovascular event or transient ischemic attack (I60.-I69., G45.)
- Hemiplegia (G81.)
- Dementia (F00.-F03.)
- Sleep apnoea (G47.3)
- Osteoporosis (M80., M81.)

o Percentage of patients with at least one confirmed inpatient or two confirmed outpatient diagnoses in two different quarters of the following respiratory diseases: ICD-10 codes J0-J99 (Top-5 diseases as observable for sample COPD-12 and COPD-FULL SAMPLE will be reported)

o Previous drug treatment in the pre-index period, based on appropriate ATC group level

- Percentage of patients who received specific treatments (most common 10 treatments as observable for above samples) with at least two prescriptions in the pre-index period

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary objective of this study is to describe the real-life drug treatment of patients with incident COPD, including description of treatment sequence/escalation in the first 12/24/36 months after incident diagnosis. This analysis will be based on the following samples:

- COPD-12: All incident COPD patients with a follow-up of 12 months since index date (analysis will be done for the first 12 months of observation)
- COPD-24: All incident COPD patients with a follow-up of 24 months since index date (analysis will be done for the first 24 months of observation)
- COPD-36: All incident COPD patients with a follow-up of 36 months since index date (analysis will be done for the first 36 months of observation)
- COPD FULL DATA: All incident COPD patients. (analysis will be done for the full observation period)
- COPD DMP-12: All incident COPD patients with available DMP data (at least one entry after index date) and a follow-up of 12 months since index date (analysis will be done for the first 12 months of observation)

In this analysis, baseline treatment as well as treatment cascades including mean duration of treatment in the pre-defined follow-up periods will be assessed. Results will be reported as follows:

- Mean number of different agents an observed patient received (per patient year)[13]
- List of most frequently prescribed agents (based on Suppl. Table 2) including percentage of patients who received these agents
- Longitudinal analysis of treatment patterns/cascades with long-acting bronchodilators and ICS, as described in Table 2. Here, proportion of observed patients whose treatment can be described by the pre-defined treatment patterns will be assessed.

Table 2 Description of treatment patterns/cascades (template for reported outcomes)[14,15]
(please note: below table might not show all theoretically possible treatment patterns. In the analysis, based on observed treatment patterns, all treatment pattern combinations that were observed in >5% of the patient population will be reported)

Therapy pattern after index date	1st line	2nd line	3rd line	4th line	N (%) of patients
Mono, no switch during follow-up period	LAMA	-	-	-	…
	LABA	-	-	-	…
	ICS	-	-	-	…
Mono, with switch	LAMA	LABA	-	-	…
	LAMA	ICS	-	-	…
	LABA	LAMA			
	LABA	ICS			
	ICS	LABA			
	ICS	LAMA			

[13] Even if this study is based on fixed follow-up periods, death of some patients during the follow-up period might lead to shorter follow-up periods than 12, 24, or 36 months in some patients. That is why above numbers will be reported per observed patient year.
[14] Analyses will be done for all three defined follow-up periods (12 months, 24 months, 36 months). For major treatment patterns, characteristics of respective patients will be described.
[15] Switching between different drugs of the same drug class (LAMA,LABA,ICS) will not be taken into account for this analysis.

Table 2 (cont'd) Description of treatment patterns/cascades (template for reported outcomes)
(please note: below table might not show all theoretically possible treatment patterns. In the analysis, based on observed treatment patterns, all treatment pattern combinations that were observed in >5% of the patient population will be reported)

Therapy pattern after index date	1st line	2nd line	3rd line	4th line	N (%) of patients
Mono, with switch to dual therapy	LAMA	LAMA+LABA	-	-	…
		LAMA+ICS			
		LABA+ICS			
	LABA	LAMA+LABA		-	
		LAMA+ICS			
		LABA+ ICS			
Mono, with switch to dual therapy and subsequent switch to another dual therapy	LAMA	LAMA+LABA	LAMA+ICS		
		LAMA+ICS	LAMA+LABA		
		LABA+ICS	LABA+ICS		
	LABA	LABA+LAMA	LABA+ICS		
		LABA+ ICS	LABA+LAMA		
		LAMA+ICS	LAMA+ICS		
Mono, with switch to dual therapy and subsequent triple therapy	LAMA	LAMA+LABA	LAMA+LABA+ICS	-	…
		LAMA+ICS	LAMA+LABA+ICS		
	LABA	LAMA+LABA	LAMA+LABA+ICS	-	
		LABA+ ICS	LAMA+LABA+ICS		
Mono, with switch to triple therapy	LAMA	LAMA+LABA+ICS			
	LABA	LAMA+LABA+ICS			

Table 2 (cont'd) Description of treatment patterns/cascades (template for reported outcomes)
(please note: below table might not show all theoretically possible treatment patterns. In the analysis, based on observed treatment patterns, all treatment pattern combinations that were observed in >5% of the patient population will be reported)

Therapy pattern after index date	1st line	2nd line	3rd line	4th line	N (%) of patients
Dual therapy, no switch during follow-up period	LAMA+LABA	-	-	-	…
	LABA+ICS	-	-	-	
	LAMA+ICS				
Dual therapy with switch to another dual therapy	LAMA+LABA	LAMA+ICS			
		LABA+ICS			
	LAMA+ICS	LAMA+LABA			
		LABA+ICS			
	LABA+ICS	LAMA+LABA			
		LAMA+ICS			
Dual therapy with switch to triple therapy	LAMA+LABA	LAMA+LABA+ ICS	-		
	LAMA+ICS				
	LABA +ICS	LAMA+LABA+ ICS			
		LAMA+LABA+ ICS			
Triple therapy, no switch during follow-up period	LAMA+LABA+ICS				

Table 2 (cont'd) Description of treatment patterns/cascades (template for reported outcomes)
(please note: below table might not show all theoretically possible treatment patterns. In the analysis, based on observed treatment patterns, all treatment pattern combinations that were observed in >5% of the patient population will be reported)

Therapy pattern after index date	1st line	2nd line	3rd line	4th line	N (%) of patients
Triple therapy, de-escalation during follow-up	LAMA+LABA+ICS	LAMA+LABA LAMA+ICS LABA+ICS LAMA+LABA			…
Dual therapy, any downgrading during follow-up	LABA+ICS LABA+ICS LAMA+ICS LAMA+ICS LABA+LAMA LABA+LAMA	LABA ICS LAMA ICS LABA LAMA			
Others					

For the most common Top-5 treatment cascades, duration of treatment of each line of therapy as well as characteristics of patients that could be assigned to the specific cascades will be reported.

Please note that a specific combination therapy will be assumed to have been prescribed if there was a prescription of a respective combination agent. In case separate agents were prescribed, two scenarios are applied: (1) A combination treatment is assumed to have been prescribed if the respective agents were prescribed at the same day or (2) a combination treatment is assumed to have been prescribed if the respective agents were prescribed within a 21 days window and a similar prescription behavior was repeated at least one additional time (example – assumed LABA+LAMA combination: LABA prescription day 1, LAMA day 10, LABA day 91, LAMA day 96). Coverage calculation (days covered by a respective treatment pattern) will be based on the defined daily dosage (DDD) of each prescription.

An agent will be considered as discontinued if a supply gap of at least 60 days (sensitivity analysis: 15/30/90 days) is observed.

In an additional Kaplan Meier analysis, time to start of a dual therapy (LAMA+LABA/LABA+ICS/LAMA+ICS) and time to start of a triple therapy (LAMA+LABA+ICS) will be assessed (days from incident diagnosis until first day of triple

therapy). This analysis will be based on the COPD full data sample, i.e. no fixed follow-up period but patient-specific follow-up periods (until end of observational period or until censoring or until date of event, whatever comes first) will be applied.

9.3.2.2 Secondary outcomes

First Secondary

Comparison of initial drug treatment with treatment guidelines

Comparison of real-world treatment of patients with guidelines will be done based on two samples: COPD-12 and COPD DMP-12. Assessment will generally be done for two time points:

- For all patients at index date (+ 4 weeks)
- For patients who received a triple combination (LABA+LAMA+ICS) at first day of triple therapy prescription.

Prescription patterns will be compared with German treatment guideline recommendations. Here, the 2018 S2 guideline [1] will be used (sensitivity analysis: 2012 guideline, which is an updated version of the 2006 guideline [2]). Obviously, as patients are only observed until mid of 2018, it cannot be expected that they were treated in line with the 2018 S2 guideline. However, this analysis describes potential needs to adapt the current treatment of the patients in the future, and is as such important for preparation of later initiatives to optimize the treatment of the patients.

Based on claims data only, assessment of the severity of the COPD disease for COPD patients is hardly possible. The reason is that neither FEV_1 data nor symptoms' data as measured by the COPD assessment test (CAT) or the Modified Medical Research Council (mMRC) are available in a claims dataset. So, for the comparison of the real-world treatment with 2018/2012 guideline recommendations, based on sample COPD-12, the following analyses will be done:

- COPD-12, at index date
    - Based on the inclusion criteria, an incident COPD patient did not experience any exacerbation in the previous 12 months, as no such diagnosis was documented. So, the initial treatment with long-acting bronchodilators should generally not include use of ICS (both guidelines). Moreover, based on the 2012 guideline, a therapy with long-acting bronchodilators should start with either a LAMA or a LABA, but not with a combination of them.

So, based on these criteria, the following percentages will be reported:

- Percentage of patients not treated in line with 2018 guideline
  - Therapy at index date includes ICS

- Percentage of patients not treated in line with 2012 guideline
  - Therapy at index date includes ICS or a LABA/LAMA combination or triple therapy of LABA+LAMA+ICS[16]

- COPD-12, at first date of an observed LABA+LAMA+ICS combination, which is not the index date

  - According to both guidelines mentioned above, a triple combination treatment LABA+LAMA+ICS should only be prescribed if a patient experienced at least two exacerbations or one severe exacerbation requiring an inpatient treatment in the history of the disease. Based on this, the following percentage will be reported:

    - Percentage of patients not treated in line with the 2012/2018 guideline

      - Only 1 or less confirmed outpatient diagnoses and no inpatient diagnosis of a COPD exacerbation (ICD-10 J44.1) before date of prescription of a triple therapy.

- COPD-12, for the whole follow-up period (12 months)

  - A treatment intensification (mono to dual therapy, mono to triple or dual to triple therapy) should generally be accompanied by a thorough application of recommended diagnostic measures, according to the 2012/2018 guidelines. For these, typically, general practitioners (GPs) do not have the necessary infrastructure. Based on this, the following percentage will be reported:

    - Percentage of patients who received a treatment intensification without any previous visit of a pneumologist or hospital (same quarter or previous quarter)

Sensitivity analysis

In a first sensitivity analysis, those of above patients will be included for whom at least one ICD-10 COPD code that provides information up to the 5th level is documented: These subcodes include information about FEV_1 level. For patients for whom such a subcode is available, in this analysis, disease severity will be defined based on this information, which is mainly important when applying the 2012 guideline.

[16] Of those patients starting with triple therapy of LABA+LAMA+ICS at time of incident COPD diagnosis, physician visits (separately of cardiologists, pneumologists) and measures of lung function (DMP-dataset only) before or at index date will be reported. Time since last physician visits to a cardiologist or a pneumologist will be reported too.

In a second sensitivity analysis, the sample COPD DMP-12 will be analyzed. In the DMP data set, additional documentation about exacerbation history and FEV_1 is available. Based on these data, the following analyses are planned:

- COPD DMP-12, at index date: no additional analysis, as DMP data will not be available for the pre-index period

- COPD DMP-12, at first date of an observed LABA+LAMA+ICS combination, which is not the index date; patients for whom at least one DMP entry before date of prescription of above combination will be included
    - According to both above guidelines, a triple combination treatment LABA+LAMA+ICS should only be prescribed if a patient experienced at least 2 exacerbations or one severe exacerbation requiring an inpatient treatment in the history of the disease. In addition, the 2012 guideline also recommended such a treatment in case a FEV_1<50% could be observed. Based on this, the following percentages will be reported:

        - Percentage of patients not treated in line with the 2018 guideline
            - Only one or no confirmed outpatient diagnosis and no inpatient diagnosis of a COPD exacerbation (ICD-10 J44.1) before date of prescription of a triple therapy.
        - Percentage of patients not treated in line with the 2012 guideline
            - Only one or no confirmed outpatient diagnosis and no inpatient diagnosis of a COPD exacerbation (ICD-10 J44.1) and only one or no outpatient diagnosis and no inpatient exacerbation diagnoses as documented in the DMP dataset and no documented FEV_1 value <50%.

Second Secondary

Description of exacerbation frequency

For all samples (COPD-12, COPD-24, COPD 36, COPD DMP-12, COPD DMP-24, COPD DMP-36, COPD-FULL DATA), exacerbation frequency in the pre-defined follow-up periods (12 months, 24 months, 36 months, patient-individual follow-up times) will be described. Because of the higher diagnosis validity, in the main analysis only severe exacerbations leading to an inpatient hospitalization (COPD exacerbation documented as main diagnosis: ICD-10 J44.1) will be considered. Moreover, in a separate analysis proxies will be used to estimate non-severe exacerbations. Therefore prescriptions of SCS/OCS either separately or in combination with antibiotics, will be considered as proxy for the treatment of a non-severe exacerbation (without an inpatient hospitalization). Exacerbation frequency (once for severe and once for non-severe exacerbations) will be reported as percentage of patients having experienced at least 1 exacerbation, exactly 1 exacerbation, exactly 2 exacerbations, exactly 3 exacerbations, and >3 exacerbations, and as mean number of exacerbations per observed patient-year. [redacted]

Third Secondary

Description of health care resource use and direct treatment cost

Health care resource use (HCRU) and direct cost will be reported as described in Table 3, based on the perspective of a German sickness fund and based on prices of the respective years as reported in the claims data base. HCRU and cost will be reported for the following samples in separate analyses: COPD-12, COPD-24, and COPD-36.

Generally, HCRU/cost will be reported per observed patient year. HCRU and cost will be compared between the following patient groups:

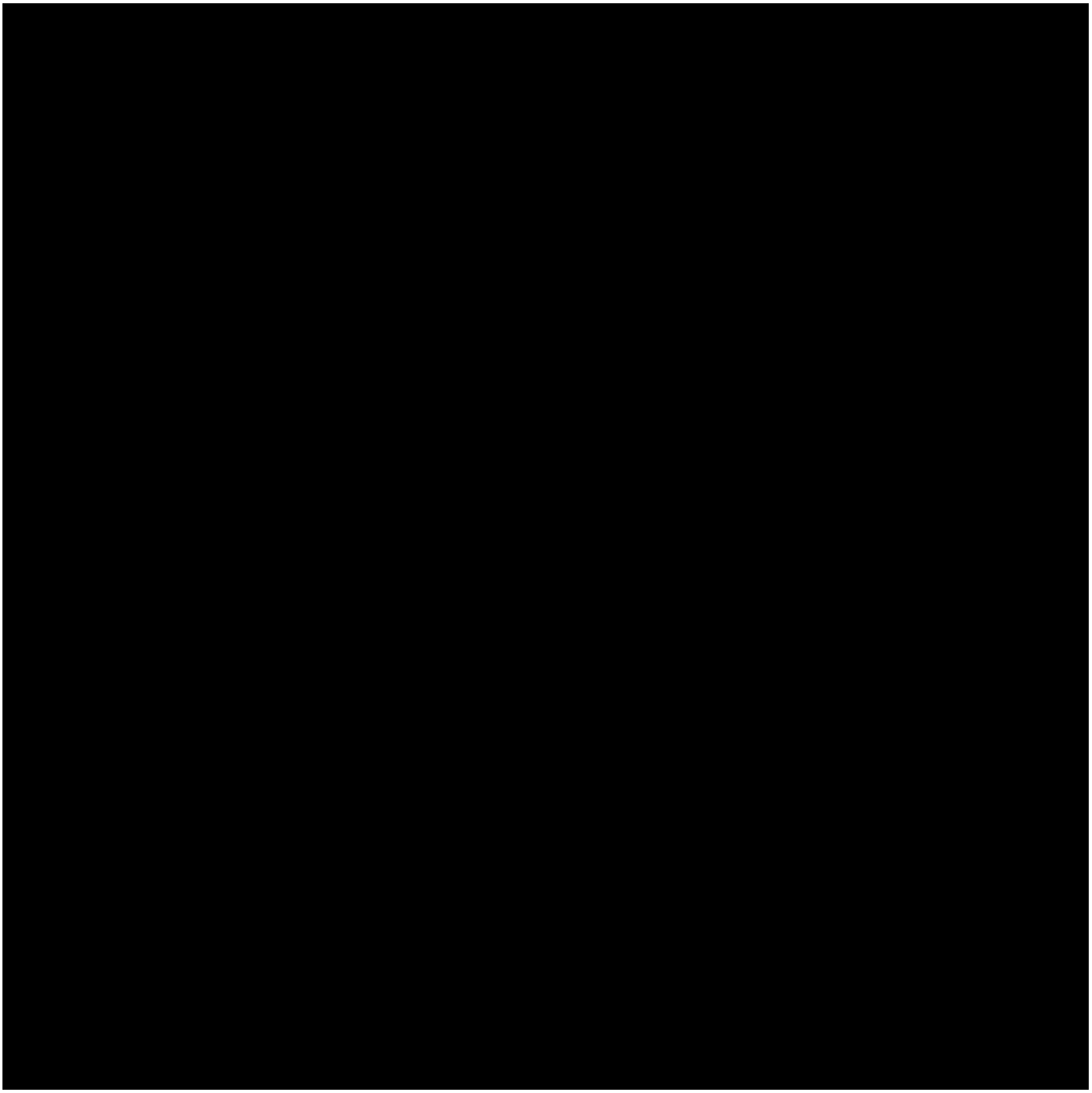
- Patients participating in a DMP versus those who did not participate
- Patients having received early (first 3 months after index date) a triple combination therapy (LABA+LAMA+ICS) versus those who did not.

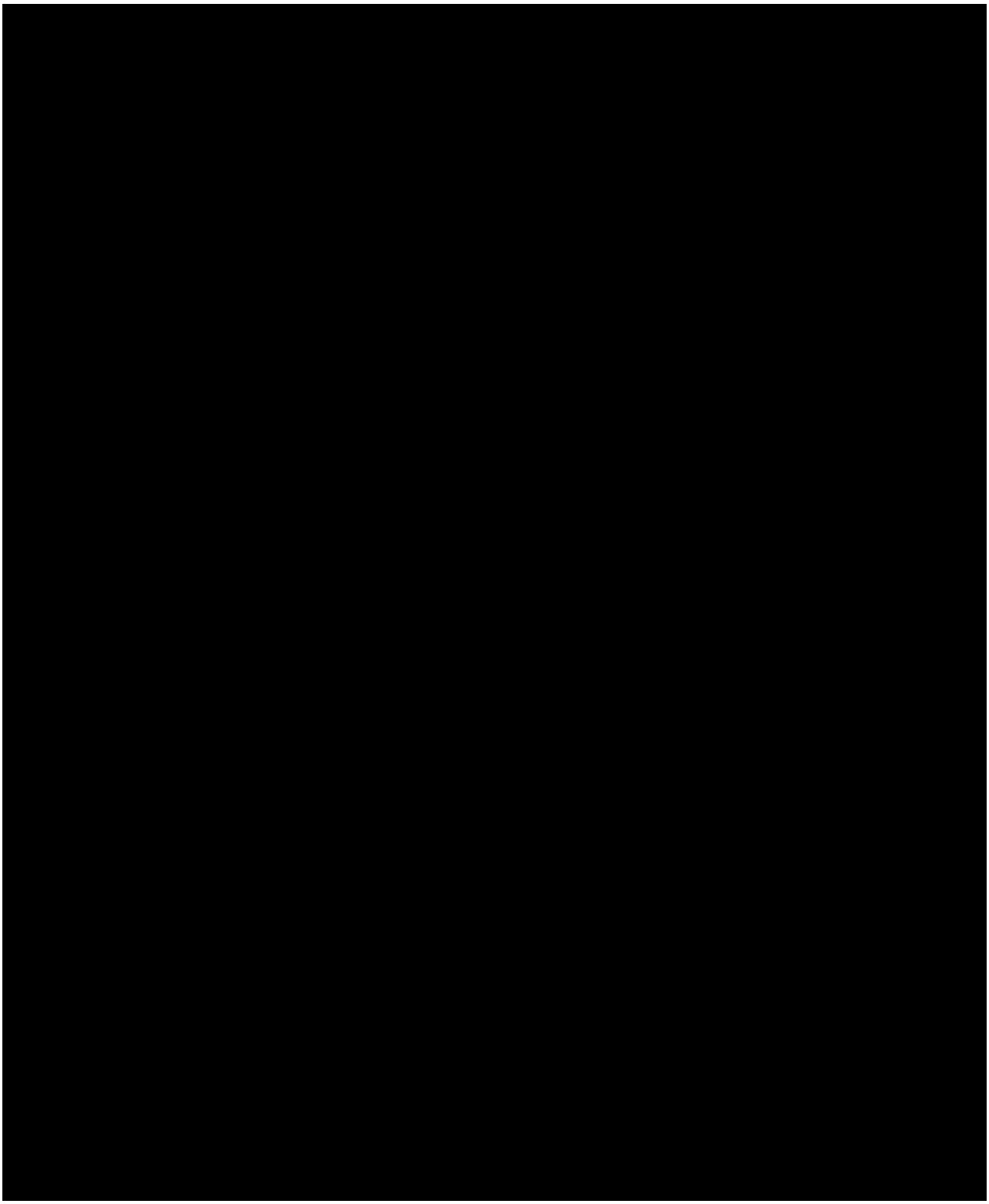
In a separate analysis based on COPD-36 sample, cost during the first year after incident COPD diagnosis will be compared with costs in the second and third year after incident diagnosis.

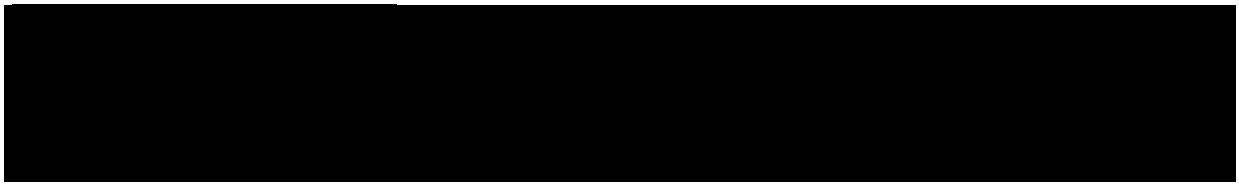
Table 3 HCRU and direct healthcare cost definition

Item	HCRU	Cost
COPD medication	• Nb. of prescriptions for medications as reported in Suppl. Table 2, per agent type • Nb. of prescribed DDDs for medications as reported in Suppl. Table 2, per agent type	• Drug cost (based on list prices) for medications as reported in Suppl. Table 2.
Other medications	• Nb. of non COPD-medications, defined as at least 2 prescriptions of an agent (on third level of ATC groups) • Antibiotics for systemic use (ATC J02AA) and antibiotics in combination with corticosteroids (ATC D07C)	• Drug cost of prescribed non-COPD medications
Outpatient treatment	• Nb. of GP visits • Nb. of pneumologist visits • Nb. of other outpatient specialist visits	• Cost of outpatient visits as defined in the HCRU column, based on the proxy of "treatment points"
Hospitalizations	• Nb. of hospitalizations with a COPD-exacerbation (J44.1) including mean duration of stay in days • Nb. of hospitalizations with any COPD diagnosis as main diagnosis (J44.-) including mean duration of stay • Other non-COPD hospitalizations including mean duration of stay in days • Time to first all-cause hospitalization	• Cost for hospitalizations as defined in the HCRU column
Long-Term Oxygen Therapy (LTOT)[17]	• Number of patients who received LTOT • Mean/median time from incident COPD diagnosis until start of LTOT for those patients	• Cost for LTOT

[17] J96.1, Z99.0, Z99.1, Z99.8, Z99.9, Z46.8, Z46.9 (ICD-10-GM-2018); 8-712.1, 8-713.0, 8-716 (OPS 2016)







9.3.3 Covariates

[redacted]

9.4 DATA SOURCES

An analysis based on anonymous claims data provided by two cooperating German sickness funds (planned: [redacted] + one additional sickness fund) covering the years 2013 - 2017 will be conducted. German claims data are a valid and often used source for health-economic analyses [5, 6, 7, 8, 9, 10, 11]. Validity of recording and coding can be evaluated as high in these databases. This is especially the case for any inpatient and prescription data because these data are directly relevant for reimbursement of hospitals/pharmacies by sickness funds. One of the main strengths of a claims data analysis are the use of an unselected large patient sample. This allows us to define cohorts, which are adequately powered to address the issues we are exploring.

For the claims data analysis, [redacted] will involve its university-affiliated partner, the [redacted] will close a contract with the cooperating sickness fund. This includes a detailed and mutually agreed list of a data extraction manual defining inclusion/exclusion criteria as well as all variables and formats to be used. Moreover, it outlines which data protection measures need to be implemented by [redacted] The sickness funds will participate in the Steering Board of the study as well as being a co-author of all future publications of study results.

For a subsample of patients, disease management program (DMP) data might be available. These provide disease specifics such as FEV_1 values, specifics of prescribed therapy, and exacerbation frequency and severity. Respective subsamples with availability of DMP data have been defined.

9.5 STUDY SIZE

Based on an initial feasibility assessment/previous study done by [redacted] based on the [redacted] dataset only, **N>40,000** incident COPD patients meeting above inclusion/excl criteria can be expected. Among them, about 26,000 (~65%) received at least one prescription of a long-acting bronchodilator in the 12 months follow-up period. Percentage of incident patients with at least one DMP documentation (providing more detailed information for additional analysis) is about 30%.

9.6 DATA MANAGEMENT

[redacted] will be responsible for data management, including quality checking of the data. Especially, the confidentiality of records that could identify patients within the database must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). Confidentiality is ensured by pseudonymizing of the dataset. A data protection plan will be in place ensuring that no data will be transferred to third parties and that access to data will be granted only to the core project team. Please note that no data but only aggregated study results will be transferred to the steering board of this study. The data protection plan is based on applicable German law; it is available on request

(in German language). Initial data processing will be undertaken using Microsoft SQL Server 2014 later statistical analyses will be done using SPSS version 20, MS-Excel version 2016, and STATA version 14.1.

9.7 DATA ANALYSIS

9.7.1 Main analysis

Generally, for all analyses specific samples will be used; these have been defined further above. Mainly, descriptive statistics will be applied in this study. Descriptive analysis of the data will be performed using summary statistics for continuous and categorical data. Continuous data will be described by the number of non-missing values, median, mean, range, standard deviation and 95% confidence intervals (CIs). Frequency tables will be generated for categorical data. Selected continuous variables will be categorized in a clinically meaningful way.

For rates/frequencies related to time periods, that might vary between the patients (e.g. shorter follow-up period due to death), respective numbers will be reported per patient-year (PY).

Furthermore, time-to-event analyses (Kaplan-Meier curves) will be conducted whenever applicable and appropriate. Especially, for the [redacted] KM curves will be evaluated.

Comparisons for categorical variables will be conducted using either Chi-square tests or Fisher's exact test (when the values in any of the cells of a contingency table are below 5). For continuous variables, statistical comparisons will be conducted using t-test or a suitable non-parametric test (for variables with skewed distribution). [redacted]

The main analyses planned are summarized in Table 5.

Table 4 Overview of main planned analyses

Endpoint/study objective	Time period	Main reporting/analyses	
PRIMARY: Description of drug treatment of incident COPD patients	Different follow-up periods since index date	Descriptive statistics (categorical variables: frequencies/percentages; continuous variables: mean, SD, median, ranges and 95% CIs)	Comparisons for categorical variables: either Chi-square tests or Fisher's exact test; Comparison for continuous variables: t-test or a suitable non-parametric test Analysis of time to escalation therapy (therapy including ICS) using KM methodology

Table 4 (cont'd) Overview of main planned analyses

FIRST SECONDARY: Comparison of drug treatment with 2012/18 guidelines	12-month follow-up since index date	Reporting of frequency tables regarding proportion of patients treated in line with guidelines, using different criteria as outlined above	*Comparisons of patients treated in line/not in line with guidelines* Comparisons for categorical variables: either Chi-square tests or Fisher's exact test; Comparison for continuous variables: t-test or a suitable non-parametric test Multivariable logistic regression to assess independent factors associated with treatment according to guidelines
SECOND SECONDARY: Description of exacerbation frequency	Different follow-up periods since index date	*Exacerbations as measured by inpatient encounters associated with respective ICD-10 code and, in additional analysis, based on DMP samples only, based on inpatient ICD-10 codes plus DMP documentation:* Number patients with at least one, at least two, >2 exacerbations per PY Time to first exacerbation since index date	*Comparison of patients with/without an exacerbation in different follow-up periods* Comparisons for categorical variables: either Chi-square tests or Fisher's exact test; Comparison for continuous variables: t-test or a suitable non-parametric test Analysis of time to exacerbation using KM methodology
THIRD SECONDARY: Description of HCRU and direct cost	Different follow-up periods based on index date	*HCRU/Cost:* Descriptive statistics for continuous variables whereas the numbers will be reported on the basis of PY	Comparisons for categorical variables: either Chi-square tests or Fisher's exact test; Comparison for continuous variables: t-test or a suitable non-parametric test

Table 4 (cont'd) Overview of main planned analyses

9.8 QUALITY CONTROL

The study data management will adhere to pre-defined process guidelines which mainly consist of the following elements:

- Internal staff engaged in this study will be trained; training will be documented.
- A data validation based on a 100% computer-assisted checking of variables/values (MIN, MAX, MEAN, MEDIAN, cross-checking of variables etc.) will be done after data delivery.

Study design and study conduct will be in line with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices such as *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines, Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar rules.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The main limitation of this claims data analysis is the limited availability of clinical information (clinical parameters, prescribed dosages, reasons for prescribing specific agents etc.). Information available in claims data is limited to parameters, which are generally relevant for reimbursement purposes. Clinical parameters will be only available for patients who participate in a DMP, whereas the validity and frequency of these documentations as well as the time of first documentation for incident COPD patients need to be checked. For a substantial part of the patients, these data might not be valid/available.

In addition to that, the available claims dataset will be a regional dataset, which probably covers only the regions of [redacted].

[redacted]

9.10 OTHER ASPECTS

Not applicable

9.11 SUBJECTS

In this claims data analysis, patient selection takes place according to pre-defined inclusion criteria as outlined above. The overall sample of COPD-incident patients will be divided into subgroups, according to minimum follow-up periods and availability of DMP data. The assumptions/criteria for the assignment of each patient to the respective subgroups was described above.

9.11.1 Cases

Not applicable

9.11.2 Controls

Not applicable

9.12 BIAS

By nature of the dataset, there does not exist any study site/patient selection bias. As [redacted] insures selection of persons from [redacted] only, a regional bias might exist due to the fact that only two specific regions of Germany will be covered. Further only patients continuously insured over the study period within the [redacted] will be included in the analysis, as this restriction is necessary for not considering patients multiple times. Thus, a potential selection bias is possible and the extent of the resulting effects will be estimated by describing the patients who were not continuously insures. Moreover, patients insured by the cooperating sickness funds may not be representative of the German COPD patients in terms of patient demographics. However, it is planned to involve another sickness fund in this study and thus, to cover another region of Germany. Furthermore, due to uniform treatment rules treatment of patients will not significantly differ from other regions.

10. PROTECTION OF HUMAN SUBJECTS

In this study, anonymous data only will be analyzed. Patient/physician names will remain anonymous at any time. All data will be collected and processed with adequate precautions to ensure confidentially and compliance with applicable data privacy protection laws and regulations.

10.1 PRINCIPLES OF GOOD RESEARCH PRACTICE

The guidelines of Good Clinical Practice developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP guidelines) will be followed whenever applicable for this cross-sectional patients' survey.

10.2 PATIENT INFORMATION AND CONSENT

Generally, no informed consent (IC) is needed for this claims data analysis.

10.3 INDEPENDENT ETHICS COMMITTEE (IEC)

The study protocol will be approved by a Scientific Committee, consisting of external experts, the cooperating sickness funds, BI, and [redacted]. Due to the anonymous nature of the data, no ethical approval is needed.

10.4 CONFIDENTIALITY

BI as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded / anonymous form only. The entire documentation made available to BI does not contain any data, which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.
All records identifying the subject will be kept confidential and will not be made publicly available. Study findings stored on a computer will be stored in accordance with local data protection laws.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable based on secondary use of data without any potential that any employee of BI or agent working on behalf of BI will access individually identifiable patient data.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

As part of the policy of German sickness funds, the results of this study need to be published. The members of the Steering Board will be authors of those publications. The publication strategy includes one full-text manuscript published in a peer-reviewed journal and (optional) one conference abstract/poster presented at a medical congress. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP2 Guidelines [12], STROBE [13]).

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ENEPP

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Real-world treatment of newly diagnosed COPD patients: A retrospective German claims data analysis

Study reference number: xxxxxx

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[23]	☒	☐	☐	6
1.1.2 End of data collection[24]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.3
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7

[23] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[24] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				9.2
	4.2.1 Study time period?	☒	☐	☐	
	4.2.2 Age and sex?	☒	☐	☐	
	4.2.3 Country of origin?	☒	☐	☐	
	4.2.4 Disease/indication?	☒	☐	☐	
	4.2.5 Duration of follow-up?	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4	Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

This retrospective study is an anonymous data analysis, which is based on prescription data only with regard to drug exposure. So specific exposure measurement will not be done.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.11
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.11
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.7

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				9.4
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.3 Covariates?	☒	☐	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				9.3
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	
9.3 Is a coding system described for:				9.3
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	
9.3.3 Covariates?	☒	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☐	☒	☐	
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.6

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				9.11/ 9.9
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date:

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

Supplemental Table 1: Variables available for DMP patients

DMP-key	*Type*	*Meaning (German)*	*Meaning (English)*
BETA2.LANG.BEDARF	*Boolean*[1]	*Bedarf einer kurzfristigen langwirksamen Beta-2-Sympathomimetikatherapie*	*Need for a short therapy with long-acting beta-2-sympathomimetics*
BETA2.LANG.DAUER	*Boolean*[1]	*Bedarf einer dauerhaften langwirksamen Beta-2-Sympathomimetikatherapie*	*Need for a long-lived therapy with long-acting beta-2-sympathomimetics*
BETA2_LANG.KEINE	*Boolean*[1]	*Keine Langwirksame Beta-2-Sympathomimetikatherapie indiziert*	*No therapy with long-acting beta-2-sympathomimetics indicated*
BETA2_LANG.KI	*Boolean*[1]	*Langwirksame Beta-2-Sympathomimetikatherapie kontraindiziert*	*Long-acting beta-2-sympathomimetics contraindicated*
ANTI_LANG.BEDARF	*Boolean*[1]	*Bedarf einer kurzfristigen langwirksamen Anticholinergikatherapie*	*Need for a short therapy with long-acting anticholinergics*
ANTI_LANG.DAUER	*Boolean*[1]	*Bedarf einer dauerhaften langwirksamen Anticholinergikatherapie*	*Need for a long-lived therapy with long-acting anticholinergics*
ANTI_LANG.KEINE	*Boolean*[1]	*Keine langwirksame Anticholinergikatherapie indiziert*	*No anticholinergics indicated*
ANTI_LANG.KI	*Boolean*[1]	*Langwirksame Anticholinergikatherapie kontraindiziert*	*Anticholinergics contraindicated*
COP.STATIONAER	*Integer*[2]	*Stationäre notfallmäßige Behandlungen wegen COPD seit der letzten Dokumentation (Anzahl)*	*Emergency inpatient hospitalizations due to COPD since last documentation*
COP_EINWEISUNG.JA	*Integer*[2]	*COPD-bezogene Über- bzw. Einweisung veranlasst (Anzahl)*	*COPD-related referral / admission arranged (number of)*
COP_EINWEISUNG.NEIN	*Integer*[2]	*COPD-bezogene Über- bzw. Einweisung nicht veranlasst (Anzahl)*	*No COPD-related referral / admission arranged (number of)*
COP_EXA	*Integer*[2]	*Häufigkeit der COPD Exazerbation*	*Number of COPD-related hospitalizations*
COP_SCHULUNG.NICHT_EMPF	*Boolean*[1]	*Schulung nicht empfohlen*	*COPD-related training not recommended*
COP_SCHULUNG.NM	*Boolean*[1]	*Schulung nicht möglich (Fehlende Schulungskapazität, Krankenhausaufenthalt, private Gründe, …)*	*COPD-related training not possible*
COP_SCHULUNG.NW	*Boolean*[1]	*Schulung nicht wahrgenommen*	*COPD-related training not participated*
COP_SCHULUNG.OK	*Boolean*[1]	*Empfohlene Schulung(en) wahrgenommen*	*Participated in recommended COPD-related training*

[1]*Boolean variables represent one of two possible values (e.g. "1" or "0", "yes" or "no"),*
[2]*Integer variables are variables that must take an integer value (0, 1, 2, …)*

Supplemental Table 2: COPD medications available in the German market

Medication class	Agents	ATC-Codes
SABA	Salbutamol	R03AC02
	Terbutaline	R03AC03
	Fenoterol	R03AC04; R03CC04
	Reproterol	R03CC14; R03AC15
LABA	Salmeterol	R03AC12
	Formoterol	R03AC13
	Indacaterol	R03AC18
	Olodaterol	R03AC19
	Bambuterol	R03CC12
	Clenbuterol	R03CC13
LABA-combi	Clenbuterol, combinations	R03CC63
SABA-combi	Fenoterol and sodium cromoglycate	R03AK03
	Salbutamol and sodium	R03AK04
	Reproterol and sodium	R03AK05
ICS+LABA	Salmeterol and fluticasone	R03AK06; R03AK61
	Formoterol and budesonide	R03AK07; R03AK28;
	Formoterol and beclometasone	R03AK08; R03AK27;
	Vilanterol and fluticasone furoate	R03AK10
	Formoterol and fluticasone	R03AK11
SABA+SAMA	Fenoterol and ipratropium bromide	R03AL01
	Salbutamol and ipratropium	R03AL02
LABA+LAMA	Vilanterol and umeclidinium	R03AL03
	Indacaterol and glycopyrronium	R03AL04
	Formoterol and aclidinium bromide	R03AL05
	Olodaterol and tiotropium bromide	R03AL06
ICS	Beclometasone	R03BA01; R01AD01
	Budesonide	R03BA02; R01AD05
	Fluticasone	R03BA05; R01AD08
SAMA	Ipratropium bromide	R03BB01; R01AX03
LAMA	Tiotropium bromide	R03BB04
	Aclidinium bromide	R03BB05
	Glycopyrronium bromide	R03BB06
	Umeclidinium	R03BB07
LAMA+LABA+ICS	Glycopyrronium and Formoterol	R03AL09

Medication class	Agents	ATC-Codes
Methylxanthine	Theophylline	R03DA04
	Aminophylline	R03DA05
PDE-4	Roflumilast	R03DX07
Systemic/oral corticosteroids	Prednisolone	R01AD02
	Methylprednisolone	D07AA01; D10AA02;

[1]for exacerbations

Supplemental Table 3: Calculation of the Charlson Comorbidity Index (CCI)

No	Comorbidity	Charlson Score	ICD-10 Code
1	Coronary artery disease	1	I20.-, I21.-, I22.-, I23.-, I24.-, I25.-
2	Congestive heart failure	1	I11.-, I50.-
3	Peripheral vascular disease	1	I73.-, I74.-, I77.-
4	Cerebrovascular disease	1	G45.-, G46.-, I6.-
5	Dementia	1	F00.-, F01.-, F02.-, F03.-, G30.-
6	Chronic pulmonary disease	1	J4.-, J6.- w/o J67.-, J68.-, J69.-
7	Connective tissue disorder	1	M05.-, M06.-, M07.-, M08.-, M3.-
8	Peptic ulcer disease	1	K25.-, K26.-, K27.-, K28.-
9	Mild liver disease	1	B18.-, K70.-, K73.-, K75.-
10	Diabetes mellitus without complications	1	E109.-, E119.-, E129.-, E139.-, E149.-
11	Hemiplegia	2	G81.-, G82.-
12	Moderate or severe renal disease	2	N17.-, N18.-, N19.-
13	Diabetes mellitus with end-organ damage	2	E10.-, E11.-, E12.-, E13.-, E14.- w/o [No 10]
14	Tumor without metastases, leukemia, lymphoma, multiple myeloma	2	C% w/o [No 16]
15	Moderate or severe liver disease	3	K72.-, K74.-, I85.-
16	Metastatic solid tumor	6	C77.-, C78.-, C79.-, C80.-
17	AIDS	6	B20.-, B21.-, B22.-, B23.-, B24.-
18	Age factor (was excluded from index)	For each decade ≥50 years of age, 1 point was added to the score	