TITLE PAGE

Division: Pharma Research and Development
Information Type: Epidemiology PASS Protocol

Title:	Cohort study to estimate incidence of pneumonia in users of Trelegy 100 or multiple inhaler triple therapy among patients with chronic obstructive pulmonary disease using health insurance claims data provided by Medical Data Vision Co., Ltd. in Japan

Compound Number:	GSK2834425
Development Phase	IV (Post-marketing Surveillance)
Effective Date:	30-Aug-2021

Subject: Chronic obstructive pulmonary disease (COPD), Trelegy 100 Ellipta, Multiple inhaler triple therapy (MITT)

Author(s): PPD

Indication Studied: COPD

Title	Cohort study to estimate incidence of pneumonia in users of Trelegy 100 or multiple inhaler triple therapy among patients with chronic obstructive pulmonary disease using health insurance claims data provided by Medical Data Vision Co., Ltd. in Japan
Protocol version identifier	Version 1.0
Date of last version of protocol	30-Aug-2021
EU PAS (ENCEPP) register number	TBD
Active substance	Fluticasone furoate/Umeclidinium/Vilanterol
Medicinal product	Fluticasone furoate/Umeclidinium/Vilanterol
Product reference	Not applicable
Procedure number	Not applicable
Marketing authorisation holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK (GlaxoSmithKline K.K. Akasaka Intercity AIR, 1-8-1 Akasaka, Minato-ku, Tokyo 107-0052 Japan)
Joint PASS	No

Research question and objectives	Primary objectives Compare the occurrence of hospitalization due to community-acquired pneumonia (CAP) among patients with COPD who were incident users of Trelegy 100 or MITT. Hazard ratio (HR) will be calculated to investigate if the risk of CAP in Trelegy 100 group is not higher than a certain level (HR>3) compared to MITT group. Secondary objectives a) Estimate the incidence rate of hospitalization due to CAP among COPD patients who were treated with Trelegy 100 or MITT. Overall, or incident triple use patients will be analysed in Trelegy group and MITT group, respectively. b) Describe characteristics of COPD patients who were treated with Trelegy 100 or MITT. Overall, or incident triple use patients will be analysed in Trelegy group and MITT group, respectively. c) Calculate crude and adjusted HRs for hospitalization due to CAP within Trelegy 100 or MITT group for each covariate, with one of the covariate subgroups serving as the reference group. Each model would be adjusted for all the other stated covariates. Overall, or incident triple use patients will be analysed in Trelegy 100 group and MITT group, respectively. In the model, following subgroups will be considered; gender, age, calendar year of Index date, month of Index date, COPD treatments in look-back period, hospitalization due to COPD exacerbation in look-back period, hospitalization due to CAP in look-back period, comorbidities of pre-defined disease such as asthma, myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, peptic ulcer, peripheral vascular disease, connective tissue disease, diabetes, anxiety, depression, body mass index (BMI), smoking history, and execution of lung function test within Trelegy 100 or MITT group. d) Describe change over time in the expansion of triple therapy, use of an ICS-containing medications, and proportion of asthma comorbidity among COPD patients. Over-time refers to 360 days prior to date of launch of Trelegy 100, and 0-359 days, 360-719 days, 720- 1079 days after the launch. Target population for this objective includes COPD patients regardless of treatment. *Overall users refer to those have prescriptions of Trelegy 100 or MITT between May 22, 2019 (launch date of Trelegy 100) and May 5, 2022. The index date will be the first prescription date on or after May 22, 2019. Incident users are subpopulation of overall users who do not have any triple therapies for 360 days before the index date.
Country(-ies) of study	Japan

Author(s)	PPD

PASS information
MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK (GlaxoSmithKline K.K. Akasaka Intercity AIR, 1-8-1 Akasaka, Minato-ku, Tokyo 107-0052 Japan)
MAH contact person	PPD PPD, Therapeutic Group PPD Development Global Regulatory Pharma Research & Development GlaxoSmithKline Research & Development Limited

TABLE OF CONTENTS

PAGE

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CAP	Community-acquired pneumonia
COPD	Chronic obstructive pulmonary disease
CRO	Contract research organization
CT	Computerized tomography
DPC	Diagnosis Procedure Combination
FEV_1	Forced expiratory volume in 1 second
FF	Fluticasone furoate
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GPSP	Good Post-marketing Study Practice
GSK	GlaxoSmithKline
HAP	Hospital-acquired pneumonia
HOT	Home oxygen therapy
HR	Hazard ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
ICS	Inhaled corticosteroid
IHD	Individual Human Data
IRB	Institutional review board
JRS	Japanese Respiratory Society
LABA	Long-acting $beta_2$-agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
MAH	Marketing authorisation holder
MDV	Medical Data Vision Co., Ltd.
MHLW	Ministry of Health, Labour and Welfare
MITT	Multiple inhaler triple therapy
MRC	Medical Research Council
OCS	Oral corticosteroid
PMDA	Pharmaceuticals and Medical Devices Agency
PRC	Protocol Review Committee
QC	Quality control
QOL	Quality of life
SITT	Single inhaler triple therapy
SOP	Standard operating procedure
TBD	To be determined
UMEC	umeclidinium bromide
VI	vilanterol trifenatate

Definition of terms

Term	Definition
Terms related to study design	
Study design	Study methods of choice in light of research questions. e.g., cohort design and nested case-control design
Terms for target population	
Exclusion criteria	Criteria to exclude from the target population
Inclusion criteria	Criteria for inclusion in the target population
Study population	Scope of the study group is defined by inclusion and exclusion criteria by combining information on the attributes of the study population (age, gender, presence of disease, use of drugs, etc.), location (medical institutions, etc.), time (date and time information, etc.).
Terms for duration	
At risk	Condition in which the outcome of interest can occur
Exposure period	Period starting at the index date and ending at 30 days (grace period) after the end date of the final prescription
Follow-up period	Duration of follow-up to confirm the presence or absence of an outcome in each case
Gap	Period between the prescription periods
Grace period	Period in which we consider prescription to be continuing
Index date	Key date for design: Date of start of treatment
Look-back period	Period for each covariate to be measured
Observational period	Period within which each case can be observed within the data source used
Prescription period	Period from the date of prescription until the end of treatment estimated from the package insert
Study period (data period)	Period of data extracted from the database
Terminology for analysis	
Base case analysis	Analysis to determine the results corresponding to the objective of the study
Exploratory analysis	Analysis to determine the results corresponding to the exploratory objectives
Data review	Data review performed to confirm the certainty of the code used in the definition
Sensitivity analysis	Analysis performed to confirm the robustness of the analysis results
Other	
Validation study	In the secondary use of data, the validity of the information contained in the data should be investigated in agreement with other reliable sources. Algorithms that extract specific cases, especially for injury and disease name codes, from the data are often investigated.

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
Trelegy 100 Ellipta	Respimat hand inhaler

2. RESPONSIBLE PARTIES

Sponsor

The marketing authorisation holder (MAH) will serve as the sponsor of this study. It is the responsibility of the MAH to ensure proper monitoring of the study and compliance with all applicable regulatory guidelines and laws.

Role/Title: PPD , Therapeutic Group, PPD , Development Global Regulatory, Pharma Research & Development,

Name: PPD

Address: GlaxoSmithKline Research & Development Limited.

SPONSOR SIGNATORY:

[Name] Primary Author/Study Accountable Person	**Date**
[Name] Therapy Area Leader/+1 Manager	**Date**
[Name] Head, Safety Evaluation and Risk Management	**Date**

3. ABSTRACT

Title

Cohort study to estimate incidence of pneumonia in users of Trelegy 100 or multiple inhaler triple therapy (MITT) among patients with chronic obstructive pulmonary disease using health insurance claims data provided by Medical Data Vision Co., Ltd. (MDV) in Japan.

Rationale and background

The Japanese Respiratory Society (JRS) Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (COPD), 5th Edition (2018 Revision)[1)] states that inhaled corticosteroid (ICS)-based drugs are used concomitantly with long-acting bronchodilators in asthma-complicated COPD. In general, the risk of developing pneumonia increases with treatments including ICS, so the use of this drug should be carefully determined according to the individual patient's condition.

Trelegy 100 is convenient because ICS, a long-acting muscarinic antagonist (LAMA) and a long-acting $beta_2$-agonist (LABA) can be administered simultaneously with one inhalation, and the number of patients prescribed with "triple therapy" may increase compared to the past when only Multiple inhaler triple therapy was available. It is important to investigate the risks of developing pneumonia when administering drugs in clinical practice and to ensure proper use. On consultation with the Pharmaceuticals and Medical Devices Agency (PMDA), we decided to conduct a database-study for community-acquired pneumonia (CAP) requiring hospitalization.

Research question and objectives

Primary objectives

Compare the occurrence of hospitalization due to community-acquired pneumonia (CAP) among patients with COPD who were incident users of Trelegy 100 or MITT. Hazard ratio (HR) will be calculated to investigate if the risk of CAP in Trelegy 100 group is not higher than a certain level (HR>3) compared to MITT group.

Secondary objectives

a) Estimate the incidence rate of hospitalization due to CAP among COPD patients who were treated with Trelegy 100 or MITT. Overall, or incident triple use patients will be analysed in Trelegy 100 group and MITT group, respectively.

b) Describe characteristics of COPD patients who were treated with Trelegy 100 or MITT. Overall, or incident triple use patients will be analysed in Trelegy group and MITT group, respectively.

c) Calculate crude and adjusted HRs for hospitalization due to CAP within Trelegy 100 or MITT group for each covariate, with one of the covariate subgroups serving as the reference group. Each model would be adjusted for all the other stated covariates. Overall, or incident triple use patients will be analysed in Trelegy 100 group and MITT group, respectively.
In the model, following subgroups will be considered;
gender, age, calendar year of Index date, month of Index date, COPD treatments in look-back period, hospitalization due to COPD exacerbation in look-back period, hospitalization due to CAP in look-back period, comorbidities of pre-defined disease such as asthma, myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, peptic ulcer, peripheral vascular disease, connective tissue disease, diabetes, anxiety, depression, body mass index (BMI), smoking history, and execution of lung function test within Trelegy 100 or MITT group.

b) Describe change over time in the expansion of triple therapy, use of an ICS-containing medications, and proportion of asthma comorbidity among COPD patients. Over-time refers to 360 days prior to date of launch of Trelegy 100, and 0-359 days, 360-719 days, 720- 1079 days

after the launch. Target population for this objective includes COPD patients regardless of treatment.

*Overall users refer to those have prescriptions of Trelegy 100 or MITT between May 22, 2019 (launch date of Trelegy 100) and May 5, 2022. The index date will be the first prescription date on or after May 22, 2019.
Incident users are subpopulation of overall users who do not have any triple therapies for 360 days before the index date.

Study design

This is a retrospective cohort study using health insurance claims (outpatient and inpatient) data provided by Medical Data Vision Co., Ltd. (MDV) (Tokyo, Japan).
HRs for hospitalization due to CAP among incident users of Trelegy 100 compared to MITT is estimated by identifying and following patients without the pneumonia event at the index date (at risk).
In this study, data will be collected retrospectively with the 1,080-day identification period to have as much patient data as possible within the time frame to submit study results for the reexamination application for Trelegy 100. We plan to conduct data review in 2022 as described at the bottom of ABSTRACT, and we need time to agree on the protocol with PMDA after the endorsement by Protocol Review Committee (PRC), and thus we prepared this protocol in 2020.

Population

Primary objective

Incident users of Trelegy 100 or MITT

Secondary objective-a) to c):

Overall users or incident users of Trelegy 100 or MITT.
Overall users refer to those have prescriptions of Trelegy 100 or MITT between May 22, 2019 (launch date of Trelegy 100) and May 5, 2022. The index date will be the first prescription date on or after May 22, 2019.
Incident users are subpopulation of overall users who do not have any triple therapies for 360 days before the index date.

Secondary objective-d):
COPD patients (regardless of treatment)

Variables

Exposures

There are two types of triple therapy: single inhaler triple therapy (SITT) (Trelegy 100 only) and MITT as described below. Exposures of this study are Trelegy 100 (SITT) and MITT.

1. Single inhaler triple therapy (SITT):
   a. Trelegy 100 (Fluticasone furoate (FF)/Umeclidinium bromide (UMEC)/ Vilanterol trifenatate (VI) delivered in an Ellipta inhaler)
   b. SITTs other than Trelegy 100 (for secondary objective-d) only)
2. Multiple inhaler triple therapy (MITT):
   a. LAMA combined with fixed dose ICS/LABA (two devices), or
   b. Fixed dose LAMA/LABA with ICS (two devices), or
   c. ICS, LABA, and LAMA (three devices)
   d. Any other combinations of the 3 components (ICS, LAMA and LABA)

Outcomes

Hospitalization due to CAP which occurs 1 day or more after the index date. Admission date will be treated as the first day of hospitalization due to CAP.
Hospitalization due to CAP during follow-up period (defined in 8.1 Study Design) will be identified using Diagnosis Procedure Combination (DPC) data. The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes, DPC

disease classification codes, prescription data and diagnostic imaging data will be used as follows.

Definition 1

1) Any of the ICD-10 codes of J10.0, J11.0 or J12-J18
2) The above ICD-10 codes in DPC disease segment #21 (disease which triggered the hospitalization)
3) Prescription of antibiotics (Anatomical Therapeutic Chemical (ATC) code: J01) on the day of admission or the next day of hospitalization
4) Diagnostic imaging (X-ray or computerized tomography (CT) scan) conducted between 2 days before and 7 days after the hospitalization

Definition 2 (for supplemental analysis only)

1) Any of the ICD-10 codes of J10.0, J11.0 or J12-J18
2) The above ICD-10 codes in DPC disease segment #21 (disease which triggered the hospitalization)
3) Prescription of antibiotic injection (ATC code): J01, dosage form code:4(injection) on the day of admission or the next day of hospitalization
4) Diagnostic imaging (X-ray or computerized tomography (CT) scan) conducted between 2 days before and 7 days after the hospitalization

If all of the above 1), 2) ,3) and 4) are recorded on the same hospitalization, it is defined as "hospitalization due to CAP". Medical/medical care-related pneumonia will be included if it meets the outcome definition. Although the JRS guideline recommends the use of injectable antibiotics, we considered that there might be a few patients who received oral antibiotics for the treatment of CAP. Therefore, in definition 1, we use oral antibiotics as well as injectable antibiotics to include those patients who were hospitalized due to CAP and received oral antibiotics. We also use definition 2 focusing on injectable antibiotics to include only patients who were treated according to the guideline.

Data sources

Data will be derived from MDV database.

Study size

From the sales forecast, the number of patients with the following treatment between May 22, 2019 and May 5, 2022 in MDV database is provided below:

- Trelegy 100 group: 6450 patients
- MITT group: 4370 patients

Considering inclusion and exclusion criteria (refer to "Sec 8.2.1 Inclusion criteria" and "Sec 8.2.2 Exclusion criteria"), the number of patients in this study is assumed to be from 30% to 50%.

- Trelegy 100 treatment: 1935 to 3225 patients
- MITT treatment: 1311 to 2185 patients

In primary analysis, HR for hospitalization due to CAP among incident Trelegy 100 users compared to incident MITT users within the 360-day follow-up period will be estimated along with 95% confidence intervals using Cox proportional hazard model (follow-up period will be up to 360 days in the base-case analysis). Probability of observing HR > 3 is displayed for different scenarios in "Sec 8.5 Study Size".
In secondary analysis, incidence rates for hospitalization due to CAP in Trelegy 100 and MITT groups within the 360-day follow-up period will be calculated along with 95% exact poisson confidence intervals using chi-square distribution (follow-up period will be up to 360 days in the base-case analysis). The expected 95% confidence intervals for incidence rate of hospitalization due to CAP for different scenarios are described in "Sec 8.5 Study Size".

Data analysis

Primary analysis

- ✓ HRs for hospitalization due to CAP among incident Trelegy 100 users compared to incident MITT users

Secondary analysis

- ✓ Incidence rates of "hospitalization due to CAP" in Trelegy 100 or MITT groups

- ✓ Characteristics of patients in Trelegy 100 or MITT groups
  Age, gender, medical history/comorbidities, history of COPD treatments/exacerbation/pneumonia

  For secondary objectives, both Trelegy 100 and MITT groups will be analysed in overall or incident users.
  *Overall users refer to those have prescriptions of Trelegy 100 or MITT between May 22, 2019 (launch date of Trelegy 100) and May 5, 2022. The index date will be the first prescription date on or after May 22, 2019.
  Incident users are subpopulation of overall users who do not have any triple therapies for 360 days before the index date.

- ✓ Crude and adjusted HRs for "hospitalization due to CAP" by gender, age, calendar year of Index date, month of Index date, COPD treatments in look-back period, hospitalization due to COPD exacerbation in look-back period, hospitalization due to CAP in look-back period, comorbidities of pre-defined disease such as asthma, myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, peptic ulcer, peripheral vascular disease, connective tissue disease, diabetes, anxiety, depression, BMI, smoking history, and execution of lung function test within Trelegy 100 or MITT group in overall or incident users.
- ✓ Proportion of triple therapy among COPD patients before the launch date of Trelegy 100 (May 22, 2019) and annually after the launch date (360 days prior to date of launch of Trelegy 100, and 0-359 days, 360-719 days, 720- 1079 days after the launch). Proportion of any ICS-containing therapies and comorbid asthma will be calculated as well. Target population for this objective includes COPD patients regardless of treatment.

Milestones

Milestone	**Planned date**
Start of data collection	May 22, 2019
End of data collection	Apr 30, 2023
Registration in the EU PAS register	To be determined (TBD)
Data extraction for data review	Sep 17, 2022
Data review	Dec 17, 2022
Data extraction for final report	Sep 17, 2023
Statistical analysis complete (End of Study)	Dec 17, 2023
Final report of study results	May 17, 2024

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
<1>	<Date>	<Text>	<Text>	<Text>
<2>	<Date>	<Text>	<Text>	<Text>
<n>	<Date>	<Text>	<Text>	<Text>

5. MILESTONES

Milestone	Planned date
Start of data collection	May 22, 2019
End of data collection	Apr 30, 2023
Registration in the EU PAS register	To be determined (TBD)
Data extraction for data review	Sep 17, 2022
Data review	Dec 17, 2022
Data extraction for final report	Sep 17, 2023
Statistical analysis complete (End of Study)	Dec 17, 2023
Final report of study results	May 17, 2024

6. RATIONAL AND BACKGROUND

6.1. Background

Trelegy 100 is a 3-component combination inhaler (Fluticasone furoate (FF)/Umeclidinium bromide(UMEC)/ Vilanterol trifenatate(VI)) of FF, inhaled corticosteroid (ICS); UMEC, a long-acting muscarinic antagonist (LAMA); and VI, a long-acting beta$_2$-agonist (LABA); for the treatment of Chronic obstructive pulmonary disease (COPD).

COPD is a progressive disease characterized by increased airflow obstruction caused by both peripheral airflow lesions and emphysematous lesions in complex manner with various degrees of contribution and causes progressive aggravation of respiratory symptoms such as dyspnea on exertion, chronic cough, and increased sputum. COPD is also known to significantly reduce patients' quality of life (QOL). Aggravation of COPD is generally considered to be an acute exacerbation of symptoms beyond the range of daily fluctuations that requires changes in treatment in a stable phase. Aggravation of COPD reduces QOL and respiratory function of patients with COPD and worsens their vital prognosis.

COPD pharmacotherapy is helpful in improving symptoms and QOL, increasing (and maintaining) exercise tolerance and physical activity, and preventing exacerbations. The Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2017 Revision)[2)] , developed by Global Initiative for Chronic Obstructive Lung Disease (GOLD)[3)], recommended LAMA+LABA or LAMA+LABA+ICS as a preferred treatment for patients with severe symptoms of COPD and at-risk of exacerbation. The Japanese Respiratory Society (JRS) Guidelines for the Diagnosis and Treatment of COPD, 4th Edition (2013-Amendment)[4)] indicated that the mainstay of drug treatment was bronchodilators, and it was recommended that the use of ICS combination drugs be considered when exacerbations of COPD are repeated. Based on these findings, it was considered that ICS plus LAMA+LABA triple therapy should be used in patients with "recurrent exacerbations even with LAMA+LABA " or "patients with severe symptoms even when treated with ICS+LABA." Because the treatment of COPD is long-lasting and many patients get older and take more than one drug for other comorbidities, increasing adherence, such as adherence and treatment continuation rates, is critical for achieving good treatment outcomes. Trelegy 100, a 3-component inhalant, was also developed with the hope of improving patient convenience and contributing to improved adherence. The superiority of Trelegy 100 over UMEC/VI and FF/VI was verified in CTT116855(IMPACT) study, which is a phase 3 joint study, and there were no new safety concerns[5)].

Therefore, an application was submitted for marketing approval in Japan for the indication of remission of symptoms of COPD (chronic bronchitis/emphysema) (when concomitant use of ICS, inhaled LAMA, and inhaled LABA is required), and approval was obtained in March 2019.

The JRS Guidelines for the Diagnosis and Treatment of COPD, 5th Edition (2018 Revision)[1)] states that ICS-based drugs are used concomitantly with long-acting bronchodilators in asthma-complicated COPD. In general, the risk of developing pneumonia increases with treatments including ICS, so the use of this drug should be carefully determined according to the individual patient's condition.

Trelegy 100 is convenient because ICS, LAMA and LABA can be administered simultaneously with one inhalation, and the number of patients prescribed with “triple therapy” may increase compared to the past when only Multiple inhaler triple therapy (MITT) was available. It is important to investigate the risks of developing pneumonia when administering drugs in clinical practice and to ensure proper use. On consultation with the Pharmaceuticals and Medical Devices Agency (PMDA), we decided to conduct a database-study for CAP requiring hospitalization.

6.2. Rationale

This study must be conducted as an approval condition under Japan regulation.

7. RESEARCH QUESTION AND OBJECTIVE(S)

Primary objectives

Compare the occurrence of hospitalization due to community-acquired pneumonia (CAP) among patients with COPD who were incident users of Trelegy 100 or MITT. Hazard ratio (HR) will be calculated to investigate if the risk of CAP in Trelegy 100 group is not higher than a certain level (HR>3) compared to MITT group.

Secondary objectives

a) Estimate the incidence rate of hospitalization due to CAP among COPD patients who were treated with Trelegy 100 or MITT. Overall, or incident triple use patients will be analysed in Trelegy 100 group and MITT group, respectively.

b) Describe characteristics of COPD patients who were treated with Trelegy 100 or MITT. Overall, or incident triple use patients will be analysed in Trelegy 100 group and MITT group, respectively.

c) Calculate crude and adjusted HRs for hospitalization due to CAP within Trelegy 100 or MITT group for each covariate, with one of the covariate subgroups serving as the reference group. Each model would be adjusted for all the other stated covariates. Overall, or incident triple use patients will be analysed in Trelegy 100 group and MITT group, respectively.
In the model, following subgroups will be considered;
gender, age, calendar year of Index date, month of Index date, COPD treatments in look-back period, hospitalization due to COPD exacerbation in look-back period, hospitalization due to CAP in look-back period, comorbidities of pre-defined disease such as asthma, myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, peptic ulcer, peripheral vascular disease, connective tissue disease, diabetes, anxiety, depression, body mass index (BMI), smoking history, and execution of lung function test within Trelegy 100 or MITT group.

d) Describe change over time in the expansion of triple therapy, use of an ICS-containing medications, and proportion of asthma comorbidity among COPD patients. Over-time refers to 360 days prior to date of launch of Trelegy 100, and 0-359 days, 360-719 days, 720- 1079 days after the launch. Target population for this objective includes COPD patients regardless of treatment.
*Overall users refer to those have prescriptions of Trelegy 100 or MITT between May 22, 2019 (launch date of Trelegy 100) and May 5, 2022. The index date will be the first prescription date on or after May 22, 2019.

Incident users are subpopulation of overall users who do not have any triple therapies for 360 days before the index date.

Trelegy 100 is convenient because ICS, LAMA and LABA can be administered simultaneously with one inhalation, and the number of patients prescribed with “triple therapy” may increase compared to the past when only MITT was available. By considering this situation, it makes sense to examine risks for pneumonia in patients treated with Trelegy 100 in real world.

Based on the definition of the follow-up period described in “Sec 8.1 Study Design”, there will be large variation in the observational period among patients. Thus the incidence rate is appropriate for measuring occurrence of pneumonia, and HR is appropriate for comparing the pneumonia occurrence between Trelegy 100 or MITT group.

8. RESEARCH METHODS

Patients will be identified between May 22, 2019 and May 5, 2022 (1080 days).
For patient identification, visit records are required in two periods; (1) within 360 days (look-back period) prior to the date of onset of treatment (index date), and (2) within 180 days prior to the look-back period. Follow-up period will be maximum 360 days after the index date, therefore the end of study period will be Apr 30, 2023. Sensitivity analysis will be performed on patients who will have a 1,440-day follow up.

8.1. Study Design

This is a retrospective cohort study using health insurance claims (outpatient and inpatient) data provided by MDV (Tokyo, Japan).
This is a comparative study to investigate the risk of hospitalization due to CAP among COPD patients who were incident users of Trelegy 100 or MITT. HR of hospitalization due to CAP between two groups is estimated by identifying and following patients without the pneumonia event at the index date (at risk). Follow-up period will be up to 360 days in the base-case analysis.

The scheme of the study is shown below.

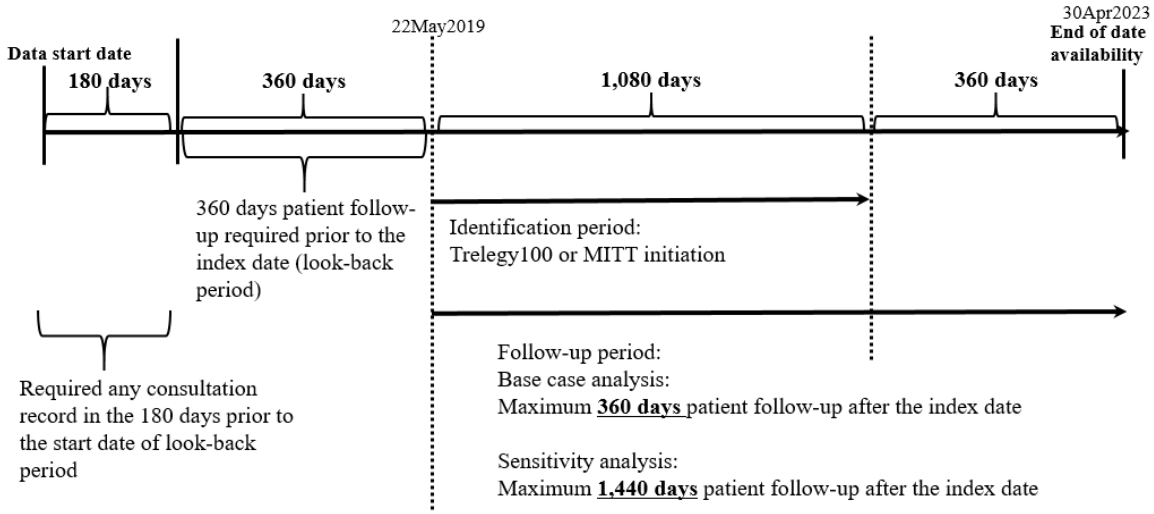

Figure1 Study design

Identification of the study population will be conducted using health insurance claims data (outpatient and inpatient) and Diagnosis Procedure Combination (DPC) data. Patients surveyed are aged 40 years or older at the start date of prescription (index date) for Trelegy 100 or MITT during the 1,080-day identification period (from May 22, 2019 to May 5, 2022).
In this protocol, one month is defined as 30 days based on the manner of Post-marketing Surveillance in Japan.

In this study, data will be collected retrospectively with the 1,080-day identification period to have as much patient data as possible within the time frame to submit study results for the reexamination application for Trelegy 100. We plan to conduct data review in 2022 as described at the bottom of ABSTRACT, and we need time to agree on the protocol with PMDA after the endorsement by Protocol Review Committee (PRC), and thus we prepared this protocol in 2020.

Patients with records of International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD -10) codes for COPD (J42, J43 or J44), one record at the index date and additional 2 records (outpatient visit or hospital admission) in the 360 days look-back period [index date, index date -360 days]. This criterion is to exclude patients with infrequent visits and to secure collection of patient characteristics data in the look-back period.
At least one record (outpatient visit or hospital admission) with any ICD-10 codes in the 180 days

prior to the start date of look-back period [index date – 360 days, index date – 540 days]. This criterion is to secure patient records throughout the look-back period.

Follow-up period will be from the index date (including the index date) to the earliest date of the followings: 1) admission date of hospitalization due to CAP or 2) date of death or 3) end date of exposure period with Trelegy 100 or MITT by discontinuation (defined in 8.3.1.1. continuation of exposure), or 4) 360 days after the index date.
In base case analysis, the 360-day follow-up period will be applied, while the 1,440-day follow-up period will be used in sensitivity analysis.

The reason for the 360-day follow-up period is based on the article by Suissa et al. which demonstrated that the effect of ICS on pneumonia occurrence among COPD patients peaked in the first year of use[6].
A patient will be censored at the first event of "hospitalization due to CAP" because identification of "time at risk for pneumonia" is feasible for the first event but difficult for the second or subsequent events. For example, if hospitalization due to CAP continued longer than the recovery from CAP by another comorbidities, it is not clear when the patient recovered from CAP during the hospitalization. Namely, "the end date of the current pneumonia" and thus "time at risk for the next pneumonia" cannot be identified.

8.2. Study Population and Setting

COPD patients who meet the inclusion and exclusion criteria.

8.2.1. Inclusion criteria

To be included in the study population, patients must meet all of the following criteria:

- Aged 40 years or older on the index date
  As 96% of the patients with COPD were aged 40 years or older in the Ministry of Health, Labour and Welfare (MHLW)'s Patient Survey (2017)[7], the target of this study was set at patients aged 40 years or older.
- Patients with records of ICD-10 codes for COPD (J42, J43 or J44), one record at the index date and additional 2 records (outpatient visit or hospital admission) in the 360 days look-back period [index date, index date -360 days]. This criterion is to exclude patients with infrequent visits who may not be COPD patients, and to secure, collection of patient characteristics data in the look-back period.
- At least one record (outpatient visit or hospital admission) with any ICD-10 codes in the 180 days prior to the start date of look-back period [index date – 360 days, index date – 540 days]. This criterion is to secure patient records throughout the look-back period.
- Two study populations will be set up in Trelegy 100 and MITT users, respectively; COPD patients who started Trelegy 100 or MITT between May 22, 2019 and May 5, 2022 (overall users), and subpopulations of the overall users without any triple therapies in the 360-day look-back period (incident users). Pneumonia occurrence in overall users as well as incident users will be calculated to have good generalizability of study results, since incident users will be a part of overall users. The first use of Trelegy 100 or MITT in the identification period will be included as overall cases. The index date for MITT overall users will be the first prescription date after the launch date of Trelegy 100 (May 22, 2019). In the identification of incident users, "any triple therapies in the look-back period" refer to triple therapies with only COPD indication, mixture of COPD and asthma indications, and only asthma indication.

8.2.2. Exclusion criteria

Patients who meet any of the following criteria are excluded from the study population:

- Patients without any record of COPD diagnosis from May 22, 2019 to May 5, 2022.Patients hospitalized within 30 days before the index date by "hospitalization due to CAP" by the same definition as the Outcome definitions (Sec 8.3.2). This criterion is to exclude cases of readmission of "hospitalization due to CAP" and nosocomial infection.

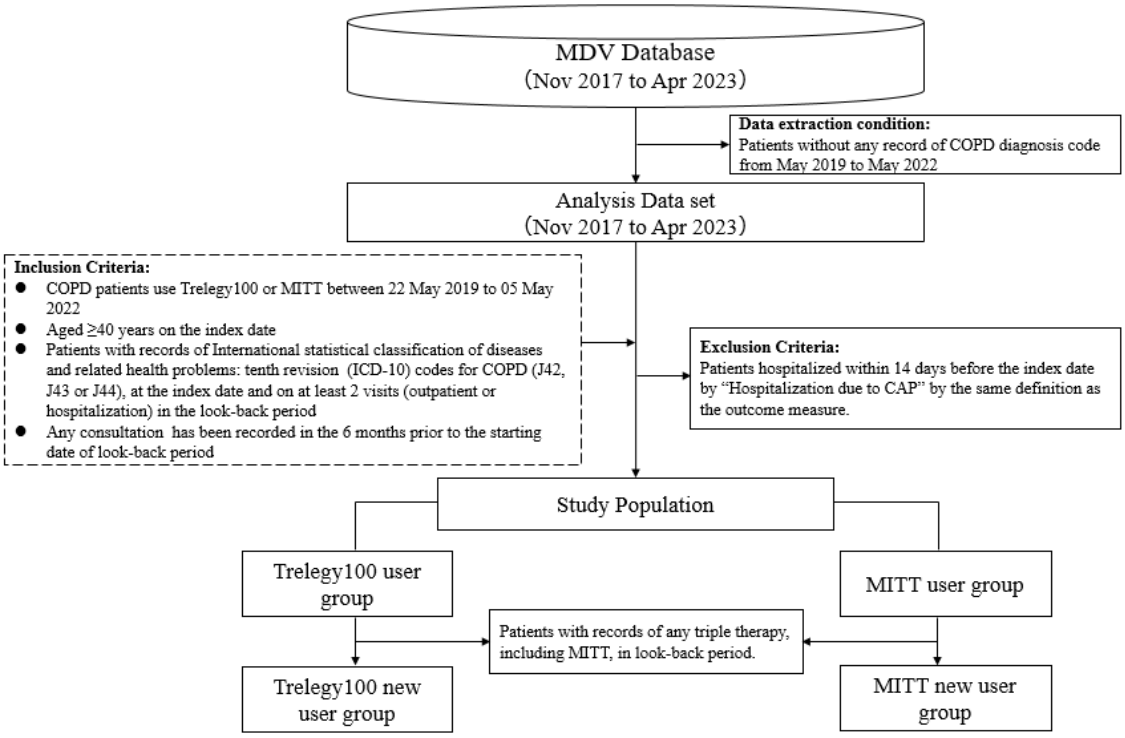

Figure2 Schematic diagram: Cohort selection of primary endpoint

8.3. Variables

8.3.1. Exposure definitions

There are two types of triple therapy: single inhaler triple therapy (SITT) (Trelegy 100, other than Trelegy 100) and MITT as described below. Exposures of this study are Trelegy 100 and MITT.

1. Single inhaler triple therapy (SITT):
   a. Trelegy 100 (FF/UMEC/VI delivered in an Ellipta inhaler)
   b. SITTs other than Trelegy 100 (for secondary objective-d) only)
2. Multiple inhaler triple therapy (MITT):
   a. LAMA combined with fixed dose ICS/LABA (two devices), or
   b. LAMA/LABA with ICS (two devices), or
   c. Fixed dose ICS, LABA, and LAMA (three devices)
   d. Any other combinations of the 3 components (ICS, LAMA and LABA)

The date of the first prescription of Trelegy 100 or MITT between May 22, 2019 and May 5, 2022 will be identified as the index date.

Only SITT users of Trelegy 100 Ellipta with COPD indication will be eligible in this study.

MITT user will be defined as overlapping prescriptions of LAMA, ICS, and LABA, in either two or three devices. Inhaled respiratory medicines have different indications e.g. COPD only, asthma only, or both COPD and asthma. Among medicines composing MITT, at least one medicine must have an indication of COPD at the timing of prescription by considering that the indication of a medicine may

change during the study period. The initial inhaler triple therapy initiation during the identification period that will be used to mark the index date will be defined as the date when the 3rd component is added to the treatment regimen (or 2nd/3rd component if a dual therapy [e.g. ICS/LABA or LAMA/LABA] is added to a monotherapy).
After identifying MITT use by the above rules, continuation of the MITT use will be determined by the rules for exposure continuation described in Sec 8.3.1.1.
All patients who have at least one day of overlap of all 3 components will be classified as MITT users as a base case analysis. The definition of MITT exposure including only one day of overlap of ICS, LABA and LAMA on the index date may overestimate the MITT exposure, and thus another option to include patients who have at least 14 days (index date plus 13 days) of overlap of all 3 components will be given as a sensitivity analysis.
Trelegy 100 or MITT prescriptions in the database will be defined using Anatomical Therapeutic Chemical (ATC) codes (atccode) and Health claim code (receiptcode).

8.3.1.1. Continuation of exposure

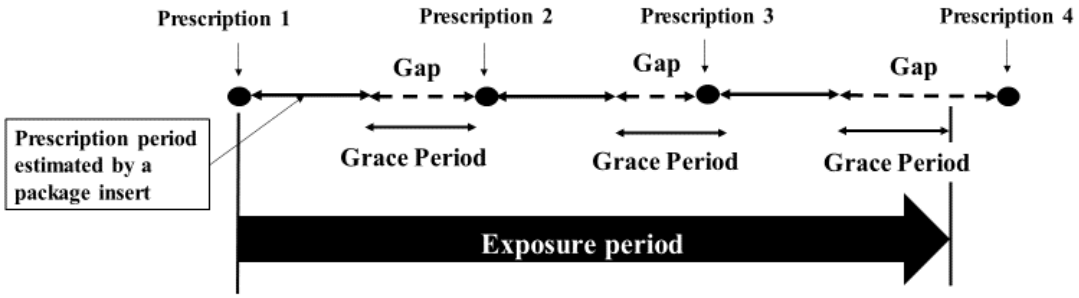

Figure3 Exposure period

1) Gap (variable): Actual period between 2 consecutive prescriptions
2) Grace period (constant): The threshold used to determine if an interruption in therapy causes a patient to be considered non-persistent

Continuation of exposure will be defined by using “prescription period”, “gap” and “grace period” (see Figure3).
Prescription period: Treatment period estimated by dosage in package insert (as described in a separate “statistical analysis plan”)
Gap: Actual period between 2 consecutive prescription periods
Grace period: The threshold used to determine discontinuation of treatment
In this study, we set the “grace period” at 30 days.
If a gap between 2 consecutive prescription periods is 30 days or less, the treatment is considered continuation.
If a gap between 2 consecutive prescription periods is 31 days or more, the treatment is considered discontinuation.

Japan’s medical fee system recommends careful consideration for long-term prescription more than 30 days. Restrictions on prescription period for 14 days right after the launch was not applied to Trelegy 100. Based on these situations, we regarded 30 days as a standard prescription period for both Trelegy 100 and MITT. By considering 30-day prescription, potential delay in physician visits and missing medicine, the grace period was set to 30 days.

Exposure period in follow-up period will be defined as the period starting at the index date and ending at 30 days (grace period) after the end date of the final prescription period* of Trelegy 100 or MITT during 360 days after the index date. If the final prescription period starts before the end date of the previous prescription period, the overlapped days of the 2 prescription periods will be added to the grace period (30 days) in calculating the end date of the final prescription period.

*Final prescription period of Trelegy 100 or MITT will be defined as follows:

1) Subsequent prescription period of Trelegy 100 or MITT started 31 days or more (longer than grace period) after the end date of the last prescription period. In MITT group, the end date of the last prescription period is the end date of overlapping prescription period.
2) MITT includes a variety of combination of ICS/LAMA/LABA, and only the change in components of MITT is not considered discontinuation.

Continuation of exposure to Trelegy 100 or MITT in the look-back period will be defined by using "prescription period", "gap" and "grace period" in the same manner as that in the follow-up period. This approach is applied forwards (and not backwards) in the look-back period and before the look-back period to identify any triple therapy during the look-back period.

8.3.2. Outcome definitions

1. Algorithm of outcome definitions

- Hospitalization due to CAP which occurs 1 day or more after the index date. Admission date will be treated as the first day of hospitalization due to CAP.
  Hospitalization due to CAP during follow-up period (defined in 8.1 Study Design) will be identified using DPC data. ICD-10 codes, DPC disease segments, prescription data and diagnostic imaging data will be used as follows.

  Definition 1
  1) Any of the ICD-10 codes of J10.0, J11.0 or J12-J18
  2) The above ICD-10 codes in DPC disease segment #21 (disease which triggered the hospitalization)
  3) Prescription of antibiotics (ATC code: J01) on the day of admission or the next day of hospitalization
  4) Diagnostic imaging (X-ray or computerized tomography (CT) scan) conducted between 2 days before and 7 days after the hospitalization

  Definition 2 (for supplemental analysis only)
  1) Any of the ICD-10 codes of J10.0, J11.0 or J12-J18
  2) The above ICD-10 codes in DPC disease segment #21 (disease which triggered the hospitalization)
  3) Prescription of antibiotics (ATC code): J01, dosage form code:4(injection) on the day of admission or the next day of hospitalization
  4) Diagnostic imaging (X-ray or computerized tomography (CT) scan) conducted between 2 days before and 7 days after the hospitalization

  If all of the above 1), 2) ,3) and 4) are recorded on the same hospitalization, it is defined as "hospitalization due to CAP". Medical/medical care-related pneumonia will be included if it meets the outcome definition. Although the JRS guideline recommends the use of injectable antibiotics, we considered that there might be a few patients who received oral antibiotics for the treatment of CAP. Therefore, in definition 1, we use oral antibiotics as well as injectable antibiotics to include those patients who were hospitalized due to CAP and received oral antibiotics. We also use definition 2 focusing on injectable antibiotics to include only patients who were treated according to the guideline.

2. Reasons for setting "hospitalization due to CAP" as the outcome

We set "hospitalization due to CAP" as the outcome measure by the following reasons.

1) High accuracy: We can identify "hospitalization due to CAP" in the MDV database with high accuracy, while outpatients due to pneumonia and hospital-acquired pneumonia (HAP) are difficult to identify accurately in MDV database.
2) Appropriateness: To evaluate the occurrence of more severe condition of pneumonia, "hospitalization due to CAP" can meet the study objective.

3. Rationales for algorism of outcome definition

Rationales for the algorithm of outcome definitions are as follows.

1) We can identify "hospitalization due to CAP" in MDV database with high accuracy by referring to DPC disease segments. DPC disease segment #1 (disease with the greatest resource utilization), #11 (main disease) and #21 (disease which triggered the hospitalization) are mandatory fields and always specified in every DPC claims. Ando et al. reported high positive predictive value in identifying cases with acute myocardial infarction in DPC claims data by using information of DPC disease segment #1, #11 and #21[8].
2) For the purpose of identifying "hospitalization due to CAP" in this study, we can focus on information of DPC disease segment #21 among the 3 codes, since disease names other than pneumonia can be recorded in the segment #1 if its resource use is greater than that for pneumonia, and time point of pneumonia diagnosis is unknown if pneumonia is recorded in the segment #11.
3) This study will not include HAP as the outcome because DPC disease segments #51-#54 (disease occurred during hospitalization) are not mandatory fields and HAP is not completely recorded in DPC claims.
4) Pneumonia recorded on medical receipt data (and not DPC data) will not be included as the outcome in this study because there is no code available for the time of pneumonia onset (presence of pneumonia on admission, or pneumonia onset after admission) to differentiate between CAP and HAP.
5) We set up the algorithm of outcome definitions by referring to the JRS Guidelines for the Management of CAP in Adults (JRS 2017)[9]. The guideline recommends the use of antibiotics right after the diagnosis, and we included the use of antibiotics on the day or the next day of hospitalization in the algorism. The guideline also recommends to perform chest X-ray or CT scan for confirming diagnosis, and record of diagnositic imaging (X-ray or CT scan) around the admission date was included in the algorithm.

4. Validation of algorism of outcome definitions

Since this study does not aim to generate evidence for taking safety assurance measures (e.g. amendment of package insert), no validation study for study outcomes is required by the PMDA (agreed with the PMDA on Sep 20, 2019).

5. Evaluation of outcomes in this study

A patient will be censored at the first event of "hospitalization due to CAP," because identification of "time at risk for pneumonia" is feasible for the first event but difficult for the second or subsequent events. For example, if hospitalization due to CAP continued longer than the recovery from CAP by another comorbidities, it is not clear when the patient recovered from CAP during the hospitalization. Namely, "the end date of the current pneumonia" and thus "time at risk for the next pneumonia" cannot be identified.

6. Consideration of COVID-19 pandemic

Index dates for starting triple therapy will be between May 22, 2019 and May 5, 2022 including the period of the COVID-19 pandemic. Effects of the COVID-19 pandemic on the results will be described according to the GSK internal guidance for retrospective database studies.
"Hospitalization due to CAP" will be classified into with or without disease code for COVID-19 in the same hospitalization record.

- DPC disease segment #21 (disease which triggered the hospitalization): ICD-10 codes for pneumonia for all cases
- DPC disease segments other than #21 (primary disease, comorbidities at admission, etc.): with or without disease code for COVID-19

Detailed methods for identifying pneumonia cases in COVID-19 infected patients will be defined later in the analysis plan when a medical recording method for the case is generalized.

If COVID-19 infection is the disease with the greatest resource utilization (i.e. applicable to DPC

disease segment #1), diagnosis in the same hospitalisation are recorded on medical receipt data (not DPC claim data). Therefore we cannot identify “Hospitalization due to CAP” in DPC claim data if patients have COVID-19 infection and COVID-19 infection is the disease with the greatest resource utilization throughout the hospitalisation.

Record of COVID-19 testing during “hospitalization due to CAP” will be collected. If the test result is positive, “confirmed disease code for COVID-19” will be recorded. Higher rate of testing could be indicative for robustness of the proportion of COVID-19 infection among “hospitalization due to CAP”.

8.3.3. Confounders and effect modifiers

8.3.3.1. Covariates

The following covariates data will be used to calculate the marginal HR for hospitalization due to CAP among incident Trelegy 100 users compared to incident MITT users (primary objective), to characterize target patients (secondary objective-b) and to calculate adjusted HRs for "hospitalization due to CAP" among subgroups within Trelegy 100 or MITT groups (secondary objective-c)).

- **Sex**
- **Age:** Age at index date
- **Calendar year of index date:** Because medical practice changes over time
- **Month of index date (and not the month of hospitalization due to CAP):** Because of seasonal differences in pneumonia occurrence
- **COPD treatments in look-back period**
  1) Immediate previous treatment as COPD maintenance therapy (LAMA, LABA, LAMA/LABA, ICS/LABA, ICS/LAMA/LABA or no COPD maintenance therapy): As potential confounding factors
     - Immediate previous therapy will be identified during 180 days before the index date (and not during the entire look-back period).
  2) Prescriptions of ICS as treatment of COPD or asthma: As a risk factor for pneumonia occurrence during the look-back period
     Confirm that ICD-10 code for COPD (J42, J43 or J44) or asthma (J45 or J46) is recorded in the receipt of the month which includes prescription of ICS.
  3) Prescriptions of oral corticosteroid (OCS) as treatment of COPD or asthma: As a risk factor for pneumonia occurrence during the look-back period
     Confirm that ICD-10 code for COPD (J42, J43 or J44) or asthma (J45 or J46) is recorded in the receipt of the month which includes prescription of OCS.
  4) Home oxygen therapy (HOT) for COPD: As an index for COPD severity
     Confirm that ICD-10 code for COPD (J42, J43 or J44) is recorded in the receipt of the month which includes the conduct of HOT.
     - Other therapies (including rescue therapy, xanthine, biologicals) for COPD or asthma will not be included as covariates.
- **History of COPD exacerbation**
  In MDV database, hospitalization due to COPD exacerbation (severe COPD exacerbation) will be identified correctly by using DPC data, while it is difficult to identify mild/moderate COPD exacerbation without hospitalization (i.e., without DPC data) because systemic corticosteroids/antibiotics are prescribed for various diseases and prescription data are not linked with disease data one by one.
  Hospitalizations due to COPD exacerbation in the look-back period.
  - Definition: Hospitalization due to COPD exacerbation in the look-back period will be identified using DPC data. The following ICD-10 codes, DPC disease classification codes and prescription data will be used.
    1) Any of the following ICD-10 codes as DPC disease segment #21 (disease which triggered the hospitalization)
       Pneumonia-related codes: J10.0, J11.0, J12-J18
       Acute lower respiratory tract infection-related codes: J20-J22
       COPD exacerbation-related codes: J44.1
       Chronic respiratory failure: J96.1
    2) Prescription of any systemic corticosteroid combined with any systemic antibiotics at the admission day or the next day. Date of prescription with systemic corticosteroid can be the same as or different from that of antibiotics prescription.

    If both of the above 1) and 2) are recorded on the same hospitalization, it is defined as "COPD exacerbation requiring hospitalization".
    Only the presence or absence of the event in the look-back period will be identified.
- **History of pneumonia**

Hospitalization due to CAP in the look-back period
- Definition: Same definition as the outcome measure (see "Sec 8.3.2 Outcome definitions")
- Only the presence or absence of the event n look-back period will be identified.

- **Medical history or comorbidities**

The following medical history or comorbidities in the look-back period
- Definition: ≥1 record (outpatient visit or hospital admission) with relevant ICD-10 codes for each comorbidities in the look-back period [Index date – 360 days]
  1) Asthma (ICD-10 codes: J45, J46)
  2) Myocardial infarction (ICD-10 codes: I21.x, I22.x, I25.2)
  3) Congestive heart failure (ICD-10 codes: I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0)
  4) Cerebrovascular disease (ICD-10 codes: G45.x, G46.x, H34.0, I60.x-I69.x)
  5) Dementia (ICD-10 codes: F00.x-F03.x, F05.1, G30.x, G31.1)
  6) Peptic ulcer (ICD-10 codes: K25.x-K28.x)
  7) Peripheral vascular disease (ICD-10 codes: I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9)
  8) Connective tissue disease (ICD-10 codes: M05–M08, M30–M36)
  9) Diabetes (ICD-10 codes: E10.0-E10.9, E11.0-E11.9, E12.0-E12.9, E13.0-E13.9, E14.0-E14.9)
  10) Anxiety (ICD-10 codes: F40-F42)
  11) Depression (ICD-10 codes: F32, F33)
- Data of medical history/comorbidity of asthma will be collected by the definition using both ICD-10 codes and prescription data, in addition to the definition using only ICD-10 codes.
  Definition: ≥1 records of visits (outpatient visit or hospital admission) with ICD-10 codes (J45, J46) and ≥1 records of prescriptions of at least one of ICS, ICS/LABA or leukotriene receptor antagonist (LTRA)[10)]

- **BMI**

BMI will be calculated by body weight and height. Data of body weight and height are available from hospitalization records (DPC data or medical receipt data). If a study participant is hospitalized by any reasons in the look-back period, BMI data can be available from the hospitalization record.

- **Smoking history**

Smoking history data are available from hospitalization records (DPC data or medical receipt data). If a study participant is hospitalized by any reasons in the look-back period, smoking history data can be available from the hospitalization record.

- **Lung function test**

Presence or absence of lung function test in the look-back period. Lung function test results are not available but Yes/No of conducting lung function test are recorded in MDV database.

The following covariates have been considered in previous studies[11)12)13)14)15)16)] which had evaluated the association between ICS treatment and pneumonia occurrence among COPD patients. These covariates are baseline characteristics of study population and a certain length of time close to the period with exposure (Trelegy 100 or MITT) will be needed to collect data. Therefore we will collect these covariate data in the 360 days before the index date (look-back period).

- COPD treatments in the look-back period
  1) Immediate previous treatment as COPD maintenance therapy (LAMA, LABA, LAMA/LABA, ICS/LABA, ICS/LAMA/LABA or no COPD maintenance therapy) [12)13)14)15)]
  2) Prescriptions of ICS as treatment of COPD or asthma: As a risk factor for pneumonia occurrence
  3) Prescriptions of OCS as treatment of COPD or asthma: As a risk factor for pneumonia occurrence[11)13)14)15)]

- History of COPD exacerbation[11)12)13)14)15)16)]
- History of pneumonia[15)16)]
- Medical history or comorbidities
  1) Asthma[16)]
  2) Myocardial infarction[14)16)]
  3) Congestive heart failure[14)16)]
  4) Cerebrovascular disease[14)16)]
  5) Dementia[14)16)]
  6) Peptic ulcer[14)16)]
  7) Peripheral vascular disease[14)16)]
  8) Connective tissue disease[14)16)]
  9) Diabetes[14)16)]
  10) Anxiety[16)]
  11) Depression[16)]
- BMI[16)17)]
- Smoking history[16)]

8.3.3.2. Other variables

The variable below will be included only in the table confirming patient characteristics.

- **Length of follow-up period:** To confirm the difference between Trelegy 100 and MITT groups.

8.4. Data Sources

The proposed study will be conducted using the Japanese MDV hospital claims database. MDV is a Japanese company specializing in integrated medical systems that manages a large administrative database constructed from hospitals (mainly tertiary) in Japan. The MDV data cover around 25% of acute care hospitals in Japan (439 hospitals) and include both inpatient and outpatient services. For the cumulative period between April 2008 and February 2021, the database has over 35.7 million patients, making it one of the largest Japanese healthcare datasets.

This study will use all available data between November 2017 and Apr 2023 in the MDV hospital claims database to assess the proposed study objectives. The data is updated monthly, thereby minimizing the time lag for data access and analyses. The database contains disease diagnoses, claims for medical procedures and pharmacy prescriptions (from inpatient and outpatient services in the hospitals covered), and laboratory test results available for approximately 10% of patients. As this study will only use de-identified data, approval from an institutional review board (IRB) will not be necessary for the conduct of this study.

8.5. Study Size

From the sales forecast, the number of patients which are “overall” with the following treatment between May 22, 2019 and May 5, 2022 in MDV database is provided below:

- Trelegy 100 treatment: 6450 patients
- MITT treatment: 4370 patients

Considering inclusion and exclusion criteria (refer to “Sec 8.2.1 Inclusion criteria” and “Sec 8.2.2 Exclusion criteria”), the number of patients which are “incident users” is assumed to be from 30% to 50%.

- Trelegy 100 treatment: 1935 to 3225 patients
- MITT treatment: 1311 to 2185 patients

As a result of the phase 3 multinational study (CTT116855) in patients with COPD, the incidence rate of serious pneumonia in Japanese patients with FF/UMEC/VI treatment was 122.8 (/1000 patient-years). Therefore, we assume that incident rate of hospitalization due to CAP for each group within the 360-day follow-up period in this study is 80, 100, 120 or 140 (/1000 patient-years) (follow-up period will be up to 360 days in the base-case analysis).

8.5.1. Study Size for HR in primary analysis

In primary analysis, HR for hospitalization due to CAP among incident Trelegy 100 users compared to incident MITT users within the 360-day follow-up period will be estimated along with 95% confidence intervals using Cox proportional hazard model (follow-up period will be up to 360 days in the base-case analysis).

For a relative risk in HR between incident Trelegy 100 users and incident MITT users in real-world data, according to the report [18], it's stated that "relationships with relative risks varying between 0·5 and 2 are the ones most commonly reported in analyses of real-world data, and are those most susceptible to unaccounted for confounding that can only be addressed with an randomised controlled trials.". Also, some key data (ex. lung function test results, respiratory symptoms evaluated by questionnaires and so on) are not available in MDV database, and the difference in the patient characteristics between Trelegy 100 users and MITT users in Japan is not known. Considering these situations, it's reasonable that we won't consider an HR =< 3 to be a signal.

Given the following combination of sample size, probability of observing HR > 3 is displayed as below. we considered the following patients, as sample size is being projected based on market forecast.

Table 1 Sensitivity based on different hospitalization due to CAP rates, HRs and patients

Incident Trelegy Users	Incident MITT Users	Expected annual hospitalization due to CAP rate (%)	True HR#	Probability of observing HR > 3 (%)
3225	2185	8	2	0.0
			2.5	6.0
			3	50.0
			3.5	88.1
			4	98.2
3225	2185	10	2	0.0
			2.5	4.1
			3	50.0
			3.5	90.7
			4	> 99.0
3225	2185	12	2	0.0
			2.5	2.9
			3	50.0
			3.5	92.6
			4	> 99.0
3225	2185	14	2	0.0
			2.5	2.0
			3	50.0
			3.5	94.1
			4	> 99.0
1935	1311	8	2	0.2
			2.5	11.4
			3	50.0
			3.5	82.0
			4	94.9
1935	1311	10	2	0.1
			2.5	8.9
			3	50.0
			3.5	84.7

			4	96.6
1935	1311	12	2	0.0
			2.5	7.0
			3	50.0
			3.5	86.9
			4	97.7
1935	1311	14	2	0.0
			2.5	5.6
			3	50.0
			3.5	88.7
			4	98.5

Note: Probability of observing HR > 3 using asymptotically normal distribution

8.5.2. Study Size for incidence rates in secondary analysis

In secondary analysis, incidence rates for hospitalization due to CAP in Trelegy 100 and MITT groups within the 360-day follow-up period will be calculated along with 95% exact poisson confidence intervals using chi-square distribution (follow-up period will be up to 360 days in the base-case analysis).

The incidence rates of hospitalization due to CAP per 1000 patient-years of follow-up is displayed for different scenarios for each group (Table 2, Table 3, Table4, Table5).

8.5.2.1. Incidence rates of hospitalization due to CAP for overall users

Table 2 Incidence rate of hospitalizations due to CAP (Trelegy 100 group)

Total Patient Years	Number of patients with hospitalizations due to CAP	Incidence rate (/1000 Patient Years)	
		Estimate	95% confidence interval
6450	516	80	[73.25, 87.21]
	645	100	[92.43, 108.02]
	774	120	[111.69, 128.76]
	903	140	[131.02, 149.44]

Note: Exact poisson confidence intervals using chi-square distribution

Table 3 Incidence rate of hospitalizations due to CAP (MITT group)

Total Patient Years	Number of patients with hospitalizations due to CAP	Incidence rate (/1000 Patient Years)	
		Estimate	95% confidence interval
4370	350	80	[71.92, 88.94]
	437	100	[90.84, 109.83]
	524	120	[109.86, 130.63]
	612	140	[129.17, 151.59]

Note: Exact poisson confidence intervals using chi-square distribution

8.5.2.2. Incidence rates of hospitalization due to CAP for incident users

Table 4 Incidence rate of hospitalizations due to CAP (Trelegy 100 group)

Total Patient Years	Number of patients with hospitalizations due to CAP	Incidence rate (/1000 Patient Years)	
		Estimate	95% confidence interval
3225[*1]	258	80	[70.54, 90.38]
	323	100	[89.53, 111.70]
	387	120	[108.34, 132.57]
	452	140	[127.53, 153.69]
1935[*2]	155	80	[67.99, 93.75]
	194	100	[86.65, 115.40]

	232	120	[104.96, 136.36]
	271	140	[123.87, 157.76]

* 1: 50% of the sales forecast
* 2: 30% of the sales forecast
Note: Exact poisson confidence intervals using chi-square distribution

Table 5 Incidence rate of hospitalizations due to CAP (MITT group)

Total Patient Years	Number of patients with hospitalizations due to CAP	Incidence rate (/1000 Patient Years)	
		Estimate	95% confidence interval
2185[*1]	175	80	[68.66, 92.88]
	219	100	[87.39, 114.42]
	262	120	[105.83, 135.34]
	306	140	[124.79, 156.65]
1311[*2]	105	80	[65.51, 96.96]
	131	100	[83.55, 118.57]
	157	120	[101.76, 140.02]
	184	140	[120.80, 162.16]

* 1: 50% of the sales forecast
* 2: 30% of the sales forecast
Note: Exact poisson confidence intervals using chi-square distribution

8.6. Data Management

This study is performed using health insurance claims (outpatient and inpatient) data provided by MDV (Tokyo, Japan). The data extraction conditions will be described in the statistical analysis plan.

8.6.1. Data handling conventions

Details of data handling will be described in the statistical analysis plan.

8.6.2. Resourcing needs

The analysis for this study will be outsourced to CMIC Co., Ltd. (contract research organization (CRO)). After being independently analysed by double programming within CRO, the results will be delivered to GSK. The GSK analyst then checks if the analyses are done correctly. This study is overseen by a senior PhD level Epidemiologist and department manager of post-marketing surveillance Dept. at GSK.

8.6.3. Timings of assessment during follow-up

For timings of assessment, refer to “Sec 5 MILESTONES”.

8.7. Data Analysis

An overview of the analytical methods is provided in this protocol. Details of the analysis methods are provided in the statistical analysis plan.
Data of this study are provided by MDV. GSK transfers the data received from MDV to CRO and statistical analysis is conducted by the person responsible for performing the statistical analysis of CRO.

8.7.1. General considerations

If there are more than 10% of missing data within covariates, we will discuss at the timing of the Data review (refer to “Sec 5 MILESTONES”) whether to supplement the missing data or exclude them from covariates. The result of the discussion will be approved by the senior manager. The confidence coefficient for the interval estimation is set at 95%. SAS version 9.1 (SAS Institute, Cary, North Carolina) or later is used as statistical analysis software.

8.7.2. Study population

The number of patients who meet or don’t meet eligibility criteria (refer to “Sec 8.2 Study

Population and Setting") is shown in flow chart.

8.7.3. Endpoints

Endpoint will be occurrence of pneumonia including those with COVID-19 code.
We will include patients with COVID-19 in the main analysis to increase generalizability of the results. Occurrence of pneumonia excluding those with COVID-19 code will be estimated separately as a supplemental analysis.

- Scientific knowledge has not been accumulated to explain how COVID-19 affects pneumonia occurrence.
- Inflated occurrence of pneumonia during COVID-19 pandemic period cannot be interpreted scientifically (including interaction between COVID-19 infection, ICS exposure and pneumonia events)

The above approach is applicable to primary endpoints (8.7.3.1) and secondary endpoint-a) (8.7.3.2.1).

8.7.3.1. Primary endpoints

8.7.3.1.1. HRs for hospitalization due to CAP among incident Trelegy 100 users compared to incident MITT users

To adjust covariates (refer to "8.3.3.1 Covariates"), propensity score[19)] which is defined as a probability of Trelegy 100 treatment selection conditional on observed covariates will be estimated for an individual using logistic regression. Multicollinearity will be considered when selecting covariates. By inverse probability of treatment weighted Cox models using the propensity score[20)], the marginal HR along with 95% confidence intervals will be estimated among incident Trelegy 100 users compared to incident MITT users. Variance estimation will be calculated using robust sandwich variance method[21)].

8.7.3.2. Secondary endpoints

8.7.3.2.1. Incidence rate of hospitalization due to CAP

Incidence rates and 95% confidence interval of outcomes (refer to "Sec 8.3.2 Outcome definitions") for overall or incident users in Trelegy 100 group or MITT group will be estimated by using Poisson regression model.. Incidence rates of outcomes sorted by diagnostic imaging conducted (X-ray only, CT scan only, or X-ray combined with CT scan) will be estimated as well. Also, The unadjusted and adjusted rates by covariates (refer to "8.3.3.1 Covariates") along with 95% confidence intervals will be calculated for each group for overall or incident users. Multicollinearity will be considered when selecting covariates.

8.7.3.2.2. Characteristics of users of Trelegy 100 or MITT among COPD patients

The distribution of patient information (refer to "Sec 8.3.3.1 Covariates" and "8.3.3.2 Other variables") is summarized for overall or incident users in Trelegy 100 group or MITT group. For the categorical data, the number and proportion of patients will be calculated. For the continuous data, descriptive statistics values will be calculated. Regarding the test for differences between groups of patient information, χ^2 test or analysis of variance (ANOVA) will be performed.

8.7.3.2.3. Characteristics of the Unweighted and Weighted incident Trelegy 100 users vs incident MITT users

To adjust covariates (refer to "8.3.3.1 Covariates"), propensity score will be estimated for an individual using logistic regression. Multicollinearity will be considered when selecting covariates. By inverse probability of treatment weighting using the propensity score, the descriptive statistics and standardized differences will be estimated. Patient characteristics will be evaluated during look-back period and will be compared between unweighted and weighted incident Trelegy 100 users and incident MITT users. Descriptive statistics will include mean and standard deviation (SD) values for the continuous variables, and relative proportions for the

categorical variables. Differences in patient characteristics between unweighted and weighted users will be assessed using standardized differences. A standardized difference of less than 10% is considered not statistically relevant[22)].

8.7.3.2.4. Graph of cumulative incidence of first occurence of hospitalization due to CAP Curves

The date of outcome onset will be defined as the event date, and the probability of the event in the Trelegy 100 group or MITT group will be illustrated using non-parametric cumulative incidence function for overall or incident users. Death will be considered as the competing event. In addition, cumulative incidence of hospitalization due to CAP is also plotted using inverse probability of treatment weighting in incident users only.

8.7.3.2.5. HRs for hospitalization due to CAP between subgroups within Trelegy 100 or MITT group

The univariate and multivariate HRs divided by patient information (refer to "8.3.3.1 Covariates") along with 95% confidence intervals will be calculated for each group for overall or incident users. Also, forest plots will be created. In addition, multicollinearity will be considered when selecting variables for multivariate analysis. HRs will be calculated using cause-specific hazard model in the competing event setting. Death will be considered as the competing event.

8.7.3.2.6. Change over time in the proportion of triple therapy among COPD patients

The status of COPD maintenance therapy for COPD patients will be counted for each year, and the proportion of COPD maintenance therapy based on the number of COPD patients will be calculated. In addition, the details of triple therapy will be calculated. The change over time in the proportion of any ICS-containing therapies and comorbid asthma among COPD patients will be calculated. Over-time refers to 360 days prior to date of launch of Trelegy 100, and 0-359 days, 360-719 days, 720- 1079 days after the launch. Target population for this objective includes COPD patients regardless of treatment.

8.7.3.2.7. Change over time in the proportion of COVID-19 among follow-up period

The number of patients with COVID-19 in each group among the follow-up period will be counted for each month, and the proportion of patients with COVID-19 based on the number of each group will be calculated. Also, the graph will be created. Over-time refers to calendar month after launch of Trelegy 100. Target population for this objective includes COPD patients regardless of treatment. In case there is a surge in COVID-19 cases in Japan during the study period, we will consult with PMDA to add a supplemental analysis by time period to see the impact of COVID-19 pandemic on the results.

8.7.3.3. Sensitivity analysis

The primary endpoints and explanatory analysis will be performed by the following conditions. When one of the 3 conditions are applied, other 2 conditions will not be applied but original conditions will be kept.

- One of inclusion criteria is changed from "patients with ICD-10 codes for COPD (J42, J43 or J44)" to "patients with ICD-10 codes for COPD (J42, J43 or J44) and with prescription of any inhaled medicine with the indication of COPD", at the index date and on at least 2 visits (outpatient visit or hospital admission) in the look-back period
- Overlap of 3 components for MITT group is changed from at least 1 day to at least 14 days (including the index date)
- Follow-up period is changed from maximum 360 days to maximum 1,440 days (after the index date)

8.7.3.4. Data review

The following data review will be conducted to confirm the certainty of the code used in the definition.

i. To check the number of patients by each group
ii. To check the patient information by each group
iii. To confirm multicollinearity between covariates
iv. To check for outliers
v. To check the number of patients with hospitalization due to CAP by each group
vi. To confirm the definition of hospitalization due to CAP

Statistical test will not be performed. The definition of endpoints will not be changed except for a way of identifying COVID-19 infection whose coding can be updated over time. Some codes in the code list will be updated to the latest ones.

8.8. Quality Control and Quality Assurance

The analysis for this study will be outsourced to CRO. Standard operating procedure (SOP) for analysis will be created between GSK and CRO. Based on the SOP, double programming will be performed independently within CRO and quality control (QC) records will be created. The results and QC documents will be sent to GSK as soon as QC is complete. GSK analyst will confirm that the results are correct and record them.

8.9. Limitations of Research Methods

This study uses MDV database which consists of hospital data, and thus only patient data in the hospitals included in MDV database are available. If a patient is treated in hospitals outside of MDV database, treatment records are not available. In MDV database, data can be extracted from health insurance claims and DPCs, but some key data (including smoking history, BMI) are not recorded completely. Based on these characteristics of MDV database, there are some limitations listed below:

- Outcome:
  - It is possible that some pneumonia events requiring hospitalization are recorded outside of DPCs, resulting in underestimation of the outcome measure. If pneumonia requiring hospitalization is treated in hospitals outside of MDV database, such data are not available and outcome measure is underestimated.
  - If data in DPC disease segment #21 (disease which triggered the hospitalization) are incorrect, occurrence of CAP will be overestimated or underestimated.
  - Pneumonia identified by only ICD-10 codes may be overestimated. Addition of prescription of antibiotics and imaging diagnosis to the outcome definition can increase the accuracy, but still there may be some overestimation.
- Risk factors for pneumonia:
  - Old age, lower % predicted forced expiratory volume in 1 second (FEV1), history of COPD exacerbations, worse Medical Research Council (MRC) dyspnea score and lower BMI were treatment-independent risk factors for pneumonia[7]. In MDC database, data of lung function and respiratory symptoms are not available, and BMI data are only partially available.
- Exposure:
  - The reason (e.g., transfer, death) is unknown when Trelegy 100 or MITT prescription records are no longer available after the index date if a patient is treated in hospitals outside of the database. In MDV database, there are no records of the reasons for change in prescription. Dosage information is not available for inhaled drugs, and the estimated daily dose and prescription period could be different from the actual ones.
  - In MDV database, treatment adherence data are not available, and the estimated exposure period could be different from the actual one.
- Study population:
  - At least one record before the look-back period is required to secure patients records throughout the look-back period, but still there could be some missing data during the look-back period, for example, lack of treatment records in hospitals outside of MDV database.
- Others:
  - Some key data are not available including:
    - Medical history or comorbidities in the look-back period treated at hospitals outside of the

database
- Pneumonia treatment in the look-back period at hospitals outside of the database.

The results from this study should be carefully interpreted and generalized, however if the above limitations affect both Trelegy 100 and MITT groups to a similar extent, negative impact on the internal validity of the study could be minimum.

8.9.1. Study closure/uninterpretability of results
This study will be conducted in accordance with "Sec 5 MILESTONES". If this study is terminated prematurely, GSK will determine the study closure in consultation with PMDA.

8.10. Other Aspects
Not Applicable

9. PROTECTION OF HUMAN SUBJECTS
9.1. Ethical Approval and Subject Consent
No direct subject contact or primary collection of individual human data (IHD) will occur in this study. This study will use existing, fully de-identified data and the subject(s) cannot be identified, directly or through identifiers. Prior to the start of analysis, GSK will ask the ethics committee to review the study protocol.

9.2. Subject Confidentiality
No direct subject contact or collection of personally identifiable information will occur in compliance with all applicable laws regarding subject privacy. Study results will be in tabular form and aggregate analyses that omit subject identification. Any publications and reports will not include subject identifiers.

10. LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA
This study will comply with all applicable laws regarding subject privacy. No direct subject contact or primary collection of IHD will occur. This study will be conducted under Good Post-marketing Study Practice (GPSP), therefore informed consent, ethics committee or IRB approval are not mandatory required. Any publications and reports will not include subject identifiers.
The authors confirm that study data is IHD not owned by GSK, but that the proposed use of the IHD aligns with the 'purpose of use' outlined in the source contract and/or the terms and conditions of use of the data source and will it comply with any specified prohibitions of use.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS
There is no potential to collect serious and non-serious adverse events (AEs), pregnancy exposures, or incidents related to any GSK product during the conduct of this research, as the minimum criteria needed to report AEs, pregnancy exposures, and incidents are not present in the data source. Further, as the research utilises existing data sources of anonymised patient data, the minimum criteria needed to report serious and non-serious AEs, pregnancy exposures, and other incidents related to a GSK product are not present in the data and thus there is no potential for reporting of AEs, pregnancy exposures and other incidents in this study.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS
We plan to publish the results of our study by the methods of presenting conferences and papers.
The study results will be submitted for publication in a suitable peer-reviewed journal and presented at relevant conferences or meetings where possible.

13. REFERENCES

1) The Japanese Respiratory Society Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (COPD), 5th Edition (2018 Revision)
2) The Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2017 Revision)
3) The Japanese Respiratory Society Guidelines for the Diagnosis and Treatment of COPD (Chronic Obstructive Pulmonary Disease), 4th Edition (2013-Amendment)
4) The Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org. (Accessed November 2020)
5) Lipson DA et al., New England Journal of Medicine. 2018;378: 1671-80
6) Thorax 2013;68: 1029-1036
7) Patient survey 2017 by the Ministry of Health, Labour and Welfare. Available from: https://www.e-stat.go.jp/dbview?sid=0003300681 (Accessed Feb 21, 2020)
8) Ando T et al., BMC Health Serv Res 2018;18: 895
9) The Japanese Respiratory Society Guidelines for the Management of Community-acquired pneumonia in Adults (JRS 2017)
10) Japanese guidelines for prevention and management of adult asthma, 2018
11) Am J Respir Crit Care Med 2007; 176: 162-166
12) K.H. Cho et al., Respiratory Medicine 2017;130: 75-84
13) Wilairat et al., Chronic Respiratory Disease 2018; 16: 1-11
14) Yang et al., International Journal of COPD 2017;12: 2477-2485
15) Suissa S et al., CHEST 2015; 148(5): 1177- 1183
16) Hana M et al., Respiratory Medicine 2012; 106: 1124-1133
17) Crim C et al., Eur Respir J 2009;34: 641-647
18) Hertzel C et al., Lancet 2019;393: 210-211
19) Ralph B Statist. Med. 1998;17: 2265-2281
20) Mohammad Ali et al., BMJ 2016;352: i189
21) Di et al., Biometrics. 2020; 1-17
22) Austin et al., Pharmacoepidemiol Drug Saf. 2008;17(12):1202-1217

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

The following documents are the stand-alone documents for this study. The versions of these documents will be managed individually.

- Statistical analysis plan
- Table, figure and listing shells
- Code list

ANNEX 2. PVP ELEMENTS AND REQUIREMENTS TABLE

Not Applicable

ANNEX 3: RETENTION OF RECORDS

Implement appropriately according to GPSP Operating Procedures.