Protocol for non-interventional studies based on existing data

Document Number:	c26865718-02
BI Study Number:	0205-0542
BI Investigational Product(s):	Spiriva® HandiHaler® & Respimat® (Tiotropium)
Title:	Non-interventional study to compare effectiveness of LAMA to fixed dose combination of inhaled corticosteroid and long-acting beta agonists (ICS/LABA) in patients with chronic obstructive pulmonary disease (COPD) based on existing data
Protocol version identifier:	Version 1
Date of last version of protocol:	8 Apr 2020
PASS:	No
EU PAS register number:	32329
Active substance:	Tiotropium Bromide Monohydrate
Medicinal product:	Spiriva® HandiHaler®,Respimat®
Product reference:	Ba 679 BR
Procedure number:	
Joint PASS:	No
Research question and objectives:	A study to compare the occurrence of several outcomes after initiation of ICS/LABA therapy with their occurrence after initiation of LAMA therapy in COPD will be conducted. More specifically, the objective is to compare: - Comparison of pneumonia incidence in COPD patients using LAMA and ICS/LABA - Comparison of exacerbations frequency and rate in COPD patients using LAMA and ICS/LABA - Comparison of time to start triple combination therapy (time from initial 'LAMA mono' or ICS+LABA' to 'LAMA+LABA+ICS' combination) in COPD patients using LAMA and ICS/LABA - Comparison of health care utilization: Medical cost / No. of prescriptions, visits and hospitalizations

	- Ly Expected adverse events after long term use of ICS : recurrence of TB (tuberculosis), incidence of NTM(Non-tuberculosis Mycobacteria) lung disease - Comparison of all-cause mortality differences in COPD patients using LAMA and ICS/LABA - Comparison of lung cancer incidence in COPD patients using LAMA and ICS/LABA
Country of study:	South Korea
Author:	[redacted]
Marketing authorisation holder(s):	[redacted]
MAH contact person:	[redacted] Phone: [redacted]
In case of PASS, add: **<EU-QPPV:>**	NA
In case of PASS, add: <**Signature of EU-QPPV:>**	NA
Date:	3 Jun 2020

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Confidence Interval
[redacted]	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
IEC	Independent Ethics Committee
IRB	Institutional Review Board
FDC	Fixed dose combination
MD	Medical doctor
HR	Hazard Ratio
SPC	Summary of Product Characteristics
TMM	Team Member Medicine
TMW	Trial Medical Writer
TBD	To Be Decided
[redacted]	[redacted]
ER	Emergency Room

3. RESPONSIBLE PARTIES

Principal investigator:

[redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva® HandiHaler®,Respimat® (Tiotropium Bromide Monohydrate)			
Name of active ingredient: Tiotropium Bromide Monohydrate			
Protocol date: 3 Jun 2020	**Study number**: 0205-0542	**Version/Revision:** 1	**Version/Revision date:**
Title of study:	Non-interventional study to compare effectiveness of LAMA to fixed dose combination of inhaled corticosteroid and long-acting beta agonists (ICS/LABA) in patients with chronic obstructive pulmonary disease (COPD*)* based on exiting data		
Rationale and background:	According to the GOLD guidelines, ICS use should be limited in scope to a small portion of COPD patients[3]. However, ICS is largely overprescribed in clinical practice, regardless of COPD severity and exacerbation risk[4-10]. Even though Regular maintenance ICS therapy is associated with an increased risk of pneumonia, physicians do not change their current practice easily[1,3,11]. Therefore, we need a supportive data to niche on the proper role of ICS in treating COPD patients Tiotropium has been the No. 1 COPD maintenance therapy over the past 12 years in Korea and it is time to a timely review its clinical benefit in the real world setting through cumulated data. Spiolto Respimat® (it is called as Vaheleva® Respimat® in Korea) data has not been cumulated enough to be compared with ICS/LABA because its launch date in Korea was April 1st 2016.		
Research question and objectives:	A study to compare the occurrence of several outcomes after initiation of ICS/LABA therapy with their occurrence after initiation of LAMA therapy in COPD will be conducted. More specifically, the objective is to compare: - Comparison of pneumonia incidence in COPD patients using LAMA and ICS/LABA (pneumonia relative hospitalization and death will be seen as sub-analysis) - Comparison of exacerbations frequency and rate in COPD patients using LAMA and ICS/LABA - Comparison of time to start triple combination therapy (time from initial 'LAMA mono' or ICS+LABA' to		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva® HandiHaler®,Respimat® (Tiotropium Bromide Monohydrate)			
Name of active ingredient: Tiotropium Bromide Monohydrate			
Protocol date: 3 Jun 2020	**Study number**: 0205-0542	**Version/Revision:** 1	**Version/Revision date:**
	'LAMA+LABA+ICS' combination) in COPD patients using LAMA and ICS/LABA - Comparison of health care utilization: Medical cost / No. of prescriptions, visits and hospitalizations - Expected adverse events after long term use of ICS : recurrence of TB and incidence of NTM lung disease - Comparison of all-cause mortality differences in COPD patients using LAMA and ICS/LABA Ccomparison of lung cancer incidence in COPD patients using LAMA and ICS/LABA		
Study design:	Non-interventional, Single-country study based on existing data from medical records of COPD patients treated with LAMA or fixed dose combination of ICS/LABA		
Population:	• Inclusion criteria − Diagnosed with COPD [**based on ICD-10 code (J43.x-44.x except J430), as the primary or within the forth secondary diagnosis and initiated LAMA or ICS/LABA more than twice a year from Jan 1, 2005 to Apr 30 2016].** − Age>55 years old as of 2005 when enroll started • Exclusion criteria − Prescription history with any long acting and short bronchodilator for maintenance therapy (the patient should be inhaler naïve) from 2002 to 2005 − Prescription history with Leukotriene receptor antagonist(LTRA) or ICS − Prescription history of LABA/LAMA FDC Patients with lung cancer, IPF, ILD or lung transplantation at the time of COPD diagnosis		
Variables:	Detailed definitions of variables that will be derived for statistical analyses and summaries will be included in the Statistical Analysis Plan (SAP).		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva® HandiHaler®,Respimat® (Tiotropium Bromide Monohydrate)			
Name of active ingredient: Tiotropium Bromide Monohydrate			
Protocol date: 3 Jun 2020	**Study number**: 0205-0542	**Version/Revision:** 1	**Version/Revision date:**
Data sources:	Korea National Health Insurance claim data & mortality data from the Bureau of Statistics from Jan 2005 to Apr 2016.		
Study size:	At least 10,000 total. At least 5,000 for each arm.		
Data analysis:	All analyses will be performed with SAS and R . All variables will be summarized descriptively through displays of mean(± standard deviations), median, and ranges for continuous variables, and frequency distributions of categorical variables. To address the imbalance of potential confounders between LAMA ICS/LABA groups, we matched treatment groups using propensity scores estimated as by multiple logistic regression analysis based on as age, sex, socioeconomics status, Charlson Comorbidity Index, and asthma, and history of COPD exacerbation. Cox proportional hazards regression analyses will be used to estimate hazard ratios (HRs) HRs and 95% confidence intervals (95% CIs) for all outcomes. For (possibly) repeating events (such as exacerbation event) additionally a Poisson regression model will be fitted for the number of events (taking into account the matching). Detailed methodology for summary and statistical analyses of data in this study will be documented in an SAP.		
Milestones:	Start of data collection in 2020 April 15 End of data collection in 2020 Dec 31 Start of data analysis in 2021 Jan 1 End of data analysis in 2021 Dec 31 Final report of study results expected in 2022 Aug		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	8 Apr 2020	Milestones	Update	Specific dates have been added for the study timeline
2	3 Jun 2020	Milestones	Update	Dates have been added for the study timeline

6. MILESTONES

Milestone	Planned Date
Registration in the EU PAS register	15 Nov 2019
Start of data collection	15 Apr 2020
End of data collection	31 Dec 2020
Final report of study results	30 Aug 2022

7. RATIONALE AND BACKGROUND

According to the GOLD guidelines, ICS use should be limited to a small portion of COPD patients[3]. However, ICS are largely overprescribed in clinical practice, regardless of COPD severity and exacerbation risk[4-10]. Even though maintenance ICS therapy is associated with an increased risk of pneumonia, physicians do not change their current practice easily[1,3,11]. Therefore, we need a supportive data on the proper role of ICS in treating COPD patients.

Tiotropium has been the No. 1 COPD maintenance therapy over the past 12 years in South Korea and a timely review its clinical benefit in the real world setting through cumulated data.

Spiolto Respimat® has not been accumulated enough data to be compared with ICS/LABA because its launch date in Korea was April 1st 2016.

8. RESEARCH QUESTION AND OBJECTIVES

In COPD patients, long-term use of ICS is reported to be linked to an increase in the rate of serious pneumonia[1]. A study to compare the occurrence of several outcomes after initiation of ICS +LABA therapy with the occurrence after initiation of LAMA therapy in COPD will be conducted. More specifically, the objective is to compare:
- Comparison of pneumonia incidence in COPD patients using LAMA and ICS/LABA
- Comparison of exacerbations frequency and rate in COPD patients using LAMA and ICS/LABA
- Comparison of time to start triple combination therapy (time from initial 'LAMA mono' or ICS+LABA' to 'LAMA+LABA+ICS' combination) in COPD patients using LAMA and ICS/LABA
- Comparison of health care utilization: Medical cost / No. of prescriptions, visits and hospitalizations
- Expected events after long-term use of ICS: osteoporosis, bone fracture, diabetes mellitus, cataracts and recurrence of tuberculosis, Non-tuberculosis Mycobacteria lung disease
- Comparison of all-cause mortality differences in COPD patients using LAMA and ICS/LABA
- Comparison of lung cancer incidence in COPD patients using LAMA and ICS/LABA

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional, single-country study based on existing data from medical records of patients in Korea National Health Insurance claim data & mortality data from the Bureau of Statistics from Jan 2005 to Apr 2016. This is a retrospective review study of nationwide cohort, which analyses the claims data of the entire Korean population.

In total, at least 10,000 eligible patients are planned to be enrolled to this study.

9.2 SETTING

The study will be conducted in a general practice setting, Korea National Health Insurance claim data & mortality data from the Bureau of Statistics, which includes computerized medical records of more than half million patients in South Korea. The maximal observation period will be from Jan 2005 to Apr 2016.

- Inclusion criteria
  - Diagnosed with COPD [**based on ICD-10 code(J43.x-44.x except J430), as the primary or within the fourth secondary diagnosis and initiated LAMA or ICS/LABA more than twice a year from Jan 1, 2005 to Apr 30 2016].**
  - Age >55 years old as of 2005 when enroll started

- Exclusion criteria
  - Prescription history with any long acting bronchodilator for maintenance therapy (the patient should be inhaler naïve) from 2002 to 2005.
  - Prescription history with ipratropium bromide
  - Prescription history with Leukotriene receptor antagonist(LTRA) or ICS
  - Prescription history of LABA/LAMA FDC
  - Patients with lung cancer, IPF, ILD or lung transplantation at the time of COPD diagnosis

9.3 VARIABLES

Detailed definitions of variables that will be derived for statistical analyses and summaries will be included in the Statistical Analysis Plan (SAP). Variables and their description are shown on (see Appendix Table 1).

9.3.1 Exposures

The exposure measures are based on the prescription of LAMA or fixed dose combination of ICS/LABA. Using the medication possession ratio (MPR), to describe adherence, the case of overall

mean MPR ≥80% defined as good adherence. Therefore, usually one inhaler is used per month, this study includes patients who have been prescribed total more than 10 inhalers per 12 months (1 year).

9.3.2 Outcomes

9.3.2.1 Primary outcomes

Primary endpoint
– Recorded pneumonia based on 1)ICD-10 code (J12.x-J18.x, J69.0, J84.9, B96.0, J85.1) AND 2) CPT code of chest x-ray(71045-71048) or chest CT(71250,71260,71270,G0297) AND 3) prescription of antibiotics for pneumonia in Korean Guideline) incidence rate per year
– Frequency rate of COPD exacerbation per year
Moderate exacerbation: recorded as when COPD patients visited outpatient clinics with an ICD-10 code of COPD and systemic steroid medication and/or antibiotics were prescribed (within the first year after initial prescription of inhalers)
Severe exacerbation: when COPD patients visited the emergency room or were admitted to hospital with an ICD-10 code of COPD*(due to COPD worsening)* and were prescribed systemic steroid medication and/or antibiotics (within the first year after initial prescription of inhalers)
–Time to start triple combination therapy ICS/LABA/LAMA)
Time to add LAMA in patients with using ICS/LABA or, time to add ICS/LABA in patients with using LAMA before.

9.3.2.2 Secondary outcomes

Secondary endpoint
– Health care utilization : Medical cost / number of annual visits, prescriptions and hospitalizations (hospitalization mainly due to severe exacerbation of COPD) over one year.
– All-cause mortality
– Recorded incidence of lung cancer (based on ICD-10 code C34.XX)

[redacted]

9.3.3 Covariates

Age, sex and history of COPD exacerbation, income status(quartile) or medical health insurance are all matching factors and will thus inherently be accounted for.

9.4 DATA SOURCES

Korea National Health Insurance claim data & mortality data from the Bureau of Statistics from Jan 2005 to Apr 2016 will be used for this study. It includes computerized medical records of more than half million patients practices in South Korea.

9.5 STUDY SIZE

In 2008~2013 NHI database, approximately 200,000 patients per year with COPD were diagnosed using COPD diagnostic code and a prescription for COPD medications (LAMA, LABA, ICS + LABA, SAMA, SABA, SAMA + SABA, PDE-4, systemic beta agonist, theophylline). In COPD patients, the use of LAMA and ICS/LABA was 26 to 37%, respectively. We expect the study to include a minimum of 5,000 patients per arm, a conservative estimate.

9.6 DATA MANAGEMENT

We will collect the data from the medical insurance claims from the Korean National Health Insurance (NHI) claims database, which will be provided for research purposes by the Korean NHIC with strict confidentiality guidelines All analyses were performed with SAS and R .

Data for this study will be obtained via the following sources:

·Eligibility DB
- Sociodemo-graphics variables : sex, age, residential area, insurance type (the employee insured, the self-employed insured, dependants, medical aid), monthly contributions, occupation
- Vital statistics : dates of birth and death, cause of death (ICD-10 codes)

·Health care utilization DB
- Diagnosis : International Classification of Disease-10 codes (main disease code, sub disease code)
- Utilization and cost : date of visit, types of medical institutions (clinics/hospitals/tertiary hospitals/public health centres), types of visit (inpatient/outpatient/emergency/intensive care), length of stay, medical cost (insurer/patient), et al.
- Health care procedures and medications : Operation and procedure codes, medication history (generic name code, dose, duration of prescription), material codes, et al.

Data is extracted from the NHIS and stored on a secured, shared server for statistical analyses. The original data will be stored in its own, read-only directory to protect the integrity of the extracted data. After obtaining an approval from the NHIS, data analysts can access the data and conduct analysis in a secured computer. NHIS's policy strictly forbids exportation of the original data, however, results obtained from statistical analyses can be exported after an internal review.

9.7 DATA ANALYSIS

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The study population consists of COPD patients that have received LAMA and ICS/LABA treatment. The study consists of three stages: a) identification and extraction of LAMA-exposed and ICS/LABA-

exposed cohort, b) matching between LAMA-exposed and ICS/LABA-exposed and c) descriptive analysis of cohorts and analysis of outcomes.

Detailed methodology for summary and statistical analyses of data generated in this study will be documented in an SAP. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

For the purpose of this study, analyses will be conducted using SAS statistical software and R. To address the imbalance of potential confounders between LAMA *ICS/LABA* groups, we matched treatment groups using propensity scores estimated as by multiple logistic regression analysis *based on* as age, sex, socioeconomics status, *Charlson Comorbidity Index*, and asthma, history of COPD exacerbation. Demographics and clinical characteristics will be tabulated. Frequencies and percentages will be presented for categorical variables. For continuous variables, means, standard deviations, and ranges, or medians and inter-quartile ranges, will be reported as appropriate. We used a standardised difference to compare baseline characteristics between COPD patients who were treated with LAMA and those treated with ICS/LABA. The matched Cox proportional hazards regression analyses will be used to estimate hazard ratios (HRs) HRs and 95% confidence intervals (95% CIs) for all outcomes. For (possibly) repeating events (such as *exacerbation event) additionall*y a Poisson regression model will be fitted for the number of events (taking into account the matching). The cox and Poisson models will be adjusted for unbalanced PS-variables at baseline. Mortality was estimated by the Kaplan-Meier method, and results were compared between groups using the log-rank test.

9.7.1 Analysis Dataset : Patients selection

The matching between LAMA[Spriva® HandiHaler® Respimat® (Tiotropium Bromide Monohydrate)] and ICS/LABA are performed by sex, age category (5 year spans above 55 years), years since diagnosis of COPD, as available in the database, and propensity score.

9.7.1.1 Propensity score methodology

The propensity score will model the likelihood among COPD patients of receiving LAMA and ICS/LABA. The model for the propensity score will to the extent possible include the following elements:

1) Age and sex
2) Socioeconomic status (e.g. income, educational level, single living
3) History of COPD exacerbation
4) Charlson Comorbidity Index
5) History of asthma

A logistic regression analysis will be performed on the identified COPD patients where treatment with LAMA and ICS/LABA groups is the dependent, dichotomous variable and the independent variables are listed above (age, sex and history of COPD exacerbation et al.). Based on this analysis, the propensity score is calculated for each patient. For subgroup analyses, PS matching and evaluation of its success, as presented below, will be re-done as covariate balance is not automatically maintained in sub-cohorts.

Smoking may be an important confounder in COPD but smoking status is usually not available in the databases at all. If smoking status is confirmed to be available, the data will be analysed with and without smoking status included in the model and the magnitude of the confounding effect assessed (sensitivity analysis).

PS matching will be done in a 1:1 ratio using the nearest-neighbor algorithm, using calipers of width equal to 0.2 of the standard deviation of the logit of the PS (matches of the main exposure sub-cohort and the comparator sub-cohort are formed if the caliper width is not exceeded for the logit of PS). For LAMA-exposed patient to ICS/LABA-exposed patients will be selected within the same matching interval of the propensity score. The distribution of propensity scores will be examined between LAMA-exposed and eligible ICS/LABA-exposed. In the matching procedure, matched comparator sub-cohort patients (ICS/LABA) will be removed from the pool of eligible patients among the comparator sub-cohort so that a matched patient is no longer available for consideration as a potential match for another exposed patient.

Evaluation of the success of the matching procedure will be based on a standardized difference (detailed below) of a covariate that is less than 0.1 between treatment groups. A standardized difference of a covariate of less than 0.1 between treatment groups in this study indicates a negligible difference in the mean or prevalence of the covariate. If larger standardized differences than 0.1 for some covariates exist after matching, they will be used in post-matching adjustments (i.e. PS-variables with standardized difference >0.1 will be adjusted for in the analyses). Further adjustments can also be made as appropriate in additional models. Based on differences identified through exploratory analysis of baseline variables, we matched individual patients from each cohort (1:1) to ensure comparison of similar patients.

9.7.2 Main analysis

For the primary effectiveness outcomes incidence rates (events per 1,000patients-years) with corresponding 95% confidence intervals (CI) will be calculated. This will be evaluated by a matched Cox proportional hazards regression model for counting processes, which allow the follow-up time to be divided into several periods and therefore control for baseline and time-dependent covariates, using the full observational period of available data, i.e. up to 11 years of follow up. The Cox proportional hazards regression will take into account the fact that individual matching (1:1) will be performed by considering the exposed patient and his/her matched controls as one stratum and including this as a stratum in the Cox proportional hazards model. Additional variables will be included in the model if available. The cumulative incidence plots will be accompanied by number of patients at risk at different time points during follow-up. For (possibly) repeating events (such as exacerbation event) additionally a Poisson regression model will be fitted for the number of events (taking into account the matching). Time in the study will be included as an offset variable in the model. The cox and Poisson models will be adjusted for unbalanced PS-variables at baseline.

The outcome will be analyzed separately for each:

1) Primary outcome
   - Comparison of pneumonia incidence in COPD patients using LAMA and ICS/LABA
   - Comparison of exacerbations frequency and rate in COPD patients using LAMA and ICS/LABA : moderate or severe exacerbation

- Comparison of time to start triple combination therapy (time from initial 'LAMA mono' or ICS+LABA' to 'LAMA+LABA+ICS' combination) in COPD patients using LAMA and ICS/LABA

2) Secondary outcome
   - Comparison of all-cause mortality differences in COPD patients using LAMA and ICS/LABA
   - Comparison of lung cancer incidence in COPD patients using LAMA and ICS/LABA

- Comparison of health care utilization: Medical cost / No. of prescriptions, visits and hospitalizations (hospitalization mainly due to severe exacerbation of COPD)

Health care utilization

Health care utilization outcomes will be analyzed separately in each treatment group. Analyses will be conducted for 1)total health care expenditure 2)COPD-related utilization and cost for all of the medical resource utilization and costs during the follow-up period. For outpatient services, analyses were confined to visits with the ICD-10 code of COPD (J43.x–J44.x, except J430) with the prescription of COPD-related medication. For inpatient services, analyses were confined to admission with ICD-10 code of COPD or COPD-related disease (pneumonia: J12.x–J17.x, pulmonary thromboembolism: I26, I26.0, and I26.9; dyspnea: R06.0; or acute respiratory distress syndrome: J80) with the prescription of COPD-related medication. Medical costs per person per year will be reported overall and separately based on type of service: inpatient healthcare visits, outpatient healthcare visits, and pharmacy dispensations. This involves calculating the average cost among members who are alive in the beginning of a month.

9.8 QUALITY CONTROL

The study will be conducted as specified in this protocol. The principal investigator, the co-investigators and the sponsors of the study must approve all revisions to the protocol. All changes must be documented as protocol amendments.

All analyses will be performed in a manner consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and applicable sections of the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

9.9 LIMITATIONS OF THE RESEARCH METHODS

9.9.1 Data sources and variables

As this study will incorporate data sources from the availability, coverage, and validity of information will vary.

9.9.2 Identifying patients with COPD

The beginning of COPD symptoms cannot be determined from the utilized data sources, whereas date of diagnosis usually can be determined. Therefore, COPD patients were determined using COPD diagnostic code and a prescription for COPD medications

9.9.3 Drug exposure

Secondary data sources do not include information on actual drug use patterns and, therefore, the drug exposure in this study may be misclassified. Further, the data sources might not include complete information on drug prescriptions. Prescription data is one further potential source for exposure misclassification as the dispensation date cannot be determined.

9.9.4 Bias and confounding

Confounding by indication cannot be completely excluded from this study although several approaches will be used to minimize confounding. Further, there will be residual confounding related to, for example, incomplete recording of diagnoses and lack of variables in the data sources to be utilized.

9.9.5 Analyses

This will be a non-interventional, population-based, and observational study. Therefore, the results will indicate correlation between drug use and selected outcomes.

9.10 OTHER ASPECTS

No

9.11 PATIENTS

9.11.1 Cases

9.11.2 Controls

Cases and Controls were previously described.

9.12 BIAS

This study will include users of LAMA and ICS/LABA. Immortal time bias will be minimal, as the follow-up will begin at the initiation of drug use. Adherence to drug use will be unknown.

Comparing the outcomes between users of LAMA and ICS/LABA will decrease confounding by indication, as the comparison group will have a similar indication to drug use than the patients in the LAMA-exposed cohorts.

The compared sub-cohorts will be matched on the basis of PS. The PS will be computed on the basis of a wide range of covariates related to sociodemographic characteristics, history of exacerbation, other comorbidities, and prior/concomitant use of other drugs. The PS matching will decrease the systematic differences between the sub-cohorts and, thus, decrease confounding.

10. PROTECTION OF PATIENTS

This study is based on existing data collected in general practices and does not require patient informed consent. All data used for this study are anonymized.

Approval of the study protocol will be obtained from IRB/IEC in South Korea before coding, extraction, and processing of Korea National Health Insurance claim data & mortality data from the Bureau of Statistics data. Ethics approval for this study will be obtained from the name of the IEC/IRB

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable. Data is anonymized and extracted, analyzed, and reported in aggregate.
There is no potential that any employee of BI or agent working on behalf of BI will access individual patient data in which the patient may be identified during data compilation, data reporting or data analysis.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

We plan to publish the study in a peer-reviewed medical journal. Authorship and publication will follow the corresponding BI SOP and guidelines of good scientific practise.

13. REFERENCES

13.1 PUBLISHED REFERENCES

1. Crim C, Calverley PM et al. Pneumonia risk in COPD patients receiving inhaled corticosteroid alone or in combination: TORCH study results. Eur Respir J 2009; 34 :641–647.
2. Nieto A et al. Adverse effects of inhaled corticosteroids in funded and nonfunded studies. Arch Intern Med. 2007;167:2047–53.
3. Vogelmeier CF et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. 2017;53:128–49.
4. Barrecheguren M et al. Treatment patterns in COPD patients newly diagnosed in primary care. A population-based study. Respir Med. 2016;111:47–53.
5. Reddel HK et al. Assessment and management of asthma and chronic obstructive pulmonary disease in Australian general practice. Aust Fam Physician. 2017;46:413–9.
6. Price D et al. Management of COPD in the UK primary care setting: an analysis of real-life prescribing patterns. Int J Chron Obstruct Pulmon Dis. 2014;9:889–904.
7. Izquierdo JL et al. Misdiagnosis of patients receiving inhaled therapies in primary care. Int J Chron Obstruct Pulmon Dis. 2010;5:241–9.
8. Burgel PR et al. Real-life use of inhaled corticosteroids in COPD patients versus the GOLD proposals: a paradigm shift in GOLD 2011 Eur Respir J. 2014;43:1201–3.
9. Roche N et al. Real-life use of fluticasone propionate/salmeterol in patients with chronic obstructive pulmonary disease: a French observational study. BMC Pulm Med. 2014;14:56.
10. Calle Rubio M et al. Clinical audit of COPD in outpatient respiratory clinics in Spain:the EPOCONSUL study. Int J Chron Obstruct Pulmon Dis. 2017;12:417–26.
11. Nieto A et al. Adverse effects of inhaled corticosteroids in funded and nonfunded studies. Arch Intern Med. 2007;167:2047–53.

13.2 UNPUBLISHED REFERENCES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:
Comparing the Incidence between Tiotropium and ICS/LABA in Real world Use in South Korea
Acronym title : CITRUS study

EU PAS Register® number: EUPAS32329
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☒	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
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:	☒	☐	☐	7,8
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)	☒	☐	☐	7,8
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)	☒	☐	☐	9.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	7
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

[1] 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.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.2
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.2
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)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2
	4.2.2 Age and sex	☒	☐	☐	9.2
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	9.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2
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)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.7
5.3	Is exposure categorised according to time windows?	☐	☐	☒	

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.2
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1

Comments:

The claimed data does not indicate the smoking status of the patients and only includes patients who have used inhalers for 80% in the past year. Therefore study's exposure categories are non-applicable.

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?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.7.1, 9.7.3
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	9.3.2

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.12
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7.3

Comments:

As per section 9.12, this study compares that outcome between users of LAMA and ICS/LABA. As both groups have similar indication to drug confounding by indication effect is minimal.

Section 8: Effect measure 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:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.7
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.7
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.3-9.6

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5, 9.7
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.3.3
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.3

Comments:

There is no missing data as we are using national health claim data source and this is universal health plan covering all Korean population

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?	☐	☒	☐	

Comments:

Our study will only go through internal BI review process and external CRO.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
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 uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2, 9.5

Comments:

There is very little possible chance of information bias as there is only one national health insurance scheme.

Section 13: Ethical/data protection 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?	☐	☐	☒	

Comments:

Our data set are extracted from the National Health Insurance Service and will be stored securely on its own in a shared server. The original data will be stored on its own, read-only directory to protect the integrity of the extracted data.

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: 07/April/2020

Signature: [redacted]

ANNEX 3. ADDITIONAL INFORMATION

Appendix Table 1. List of variables in the NHIS database

DB (number of variables)	Variable name	Details
The eligibility of the insured DB	STND_Y	Standard year for the eligibility of the insured
	PERSON_ID	Personal identification number is replaced by serial number
	SEX	Sex
	AGE_GROUP	Age group at time of diagnosed
	DTH_YM	Year and month of death
	DTH_CODE1	Level 1 (detailed) cause of death
	DTH_CODE2	Level 2 cause of death
	SIDO	Province of residence
	SGG	District of residence
	CTRB_PT_TYPE_CD	Percentile group of income level
The medical treatment DB (called Table 20) [electronic bill of medical treatment]	PERSON_ID	Personal identification number is replaced by serial number
	KEY_SEQ	Key sequence number of claim
	YKIHO_ID	Medical care institution identification number
	RECU_FR_DT	The first day of receiving treatment
	FORM_CD	Form of claimed bill
	DSBJT_CD	Medical subject code
	MAIN_SICK	Main disease code
	SUB_SICK	Sub disease code
	IN_PAT_CORS_TYPE	Route through hospitalization
	OFFC_INJ_TYPE	Type of injuries incurred while on duty

DB (number of variables)	Variable name	Details
	RECN	Days of receiving medical care
	VSCN	Days of visit hospitals or inpatient
	FST_IN_PAT_DT	First date of inpatient
	DMD_TRAMT	Amount of medical expenses based on claims
	DMD_SBRDN_AMT	Expenses paid by beneficiary based on claims
	DMD_JBRDN_AMT	Expenses paid by insurer based on claims
	DMD_CT_TOT_AMT	Total amount for CT based on claims
	DMD_MRI_TOT_AMT	Total amount for MRI based on claims
	EDEC_ADD_RT	Extra rate applied based on claims reviewed
	EDEC_TRAMT	Amount of medical expenses based on claims reviewed
	EDEC_SBRDN_AMT	Amount of expenses paid by beneficiary based on claims reviewed
	EDEC_JBRDN_AMT	Amount of expenses paid by insurer based on claims reviewed
	EDEC_CT_TOT_AMT	Total amount for CT based on claims reviewed
	EDEC_MRI_TOT_AMT	Total amount for MRI based on claims reviewed
	DMD_DRG_NO	DRG number of claim
	MPRSC_ISSUE_ADMIN_ID	Institution identification number which issued prescriptions
	MPRSC_GRANT_NO	Prescription identification number (newly added since 2011 database)
	TOT_PRES_DD_CNT	Total days of prescription
	KEY_SEQ	Key sequence number of claim

DB (number of variables)	Variable name	Details
The medical treatment DB (called Table 30) [details of medical treatment bill]	SEQ_NO	Sequence number
	RECU_FR_DT	Date of the first treatment
	CLAUSE_CD	Code for clause
	ITEM_CD	Code for item
	DIV_TYPE_CD	Code for the type of treatment
	DIV_CD	Code for treatment
	I_II_TYPE	Code for an application of additional rate (Type I or II))
	UN_COST	Amount of unit cost
	AMT	Amount of cost paid
	DD_MQTY_EXEC_FREQ	Amount of daily dose or frequency of medication
	MDCN_EXEC_FREQ	Total days of medication or frequency of medication
	DD_MQTY_FREQ	Amount of single dose
The medical treatment DB (called Table 40) [details of disease]	KEY_SEQ	Key sequence number of claim
	SEQ_NO	Sequence number
	RECU_FR_DT	Date of the first treatment
	DSBJT_CD	Code for medical examination
	SICK_SYM	Code for disease
The medical treatment DB (called Table 60) [details of prescription]	KEY_SEQ	Key sequence number of claim
	SEQ_NO	Sequence number
	RECU_FR_DT	Date of the first treatment
	DIV_TYPE_CD	Code for the type of treatment
	DIV_CD	Code for treatment

DB (number of variables)	Variable name	Details
	GNL_NM_CD	Code for generic medication name
	DD_MQTY_FREQ	Amount of single dose
	DD_EXEC_FREQ	Amount of daily dose
	MDCN_EXEC_FREQ	Total days of medication or frequency of medication
	UN_COST	Amount of unit cost
	AMT	Amount of cost