Non-Interventional Study (NIS) Protocol

Document Number:	c35930967-01
BI Study Number:	*0205-0547*
BI Investigational Product(s):	Spiriva Respimat
Title:	Exacerbation Risk and Health Care Resource use among patients with asthma using ICS+Tiotropium versus ICS/LABA
Brief lay title:	Exacerbation Risk in Asthma
Protocol version identifier:	1.0
Date of last version of protocol:	5/12/2021
PASS:	No
EU PAS register number:	Study not registered
Active substance:	*Tiotropium 1.25 mcq.*
Medicinal product:	*N/A*
Product reference:	*N/A*
Procedure number:	*N/A*
Marketing authorisation holder(s):	*N/A*
Joint PASS:	*N/A*
Research question and objectives:	To conduct a comparative effective analysis of patients using Tiotropium in combination with Inhaled Corticosteroids (ICS) versus those that use LABA medication in combination with ICS.
Country(-ies) of study:	US

Author:	[redacted]
Marketing authorisation holder(s):	*N/A*
In case of PASS, add: MAH contact person:	***N/A***
In case of PASS, add:	*N/A*
In case of PASS, add:	***N/A***
Date:	5/12/2021

Page 1 of 23

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ADR , Adverse Drug Reaction
AE , Adverse Event
AESI , Adverse Event of Special interest
CA , Competent Authority
CCDS , Company Core Data Sheet
CI , Confidence Interval
CML , Local Clinical Monitor
CRA , Clinical Research Associate
CRF , Case Report Form
CTCAE , Common Terminology Criteria for Adverse Events
CTP , Clinical Trial Protocol
eCRF , Electronic Case Report Form
ENCePP , European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA , Food and Drug Administration
GCP , Good Clinical Practice
GEP , Good Epidemiological Practice
GPP , Good Pharmacoepidemiology Practice
GVP , Good Pharmacovigilance Practices
IB , Investigator's Brochure
IEC , Independent Ethics Committee
IRB , Institutional Review Board
MAH , Marketing Authorization Holder
MedDRA , Medical Dictionary for Regulatory Activities
NIS , Non-Interventional Study
PASS , Post-Authorization Safety Study
SAE , Serious Adverse Event Adapt and complete as appropriate

3. RESPONSIBLE PARTIES

Institution	Investigators
BI	[redacted]
[redacted]	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: *Spiriva Respimat*			
Name of active ingredient: *Tiotropium*			
Protocol date: *12 May 2021*	**Study number:** 0205-0547	**Version/Revision:** 1.0	**Version/Revision date:** 12 May 2021
Title of study:	Exacerbation Risk and Health Care Resource use among patients with asthma using ICS+Tiotropium versus ICS/LABA Date: 05/12 2021 Version Number:1 [redacted]		
Rationale and background:	Regardless of severity level, patients with uncontrolled asthma are prone to exacerbations, increased use of systemic corticosteroids, and rescue medications. Guidelines recommend increasing the dose of ICS product or use of ICS in combination with long-acting β2-agonists (LABA), and/or other add-on therapy such as with a long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonists (LTRA), biologics or oral corticosteroids. RCTs have found similar responses in terms of lung function and exacerbations between patients on ICS/Tiotropium and ICS/LABA. ICS/LABA is very commonly used in the real world since 2003, and Tiotropium was only available in the US since 2016, so it's important we generate real world evidence data complimenting the ICS/Tiotropium RCT data as an alternative to ICS/LABA. It is important to evaluate the role of a LAMA in combination with ICS using real world data to support further treatment recommendations.		
Research question and objectives:	To conduct a comparative analysis of patients using Tiotropium in combination with Inhaled Corticosteroids (ICS) versus those that use LABA medication in combination with ICS.		
Study design:	This is a non-interventional study based on existing data. Patients will be classified into two groups: 1. ICS+Tio and 2. ICS/LABA. We will record various baseline measures, including demographics such as gender, age, and region, comorbidity level defined using Charlson Comorbidity Index (CCI), other specific comorbidities not included in the CCI, inhaled medication use, ICS dose level, control level, and other listed measures. Using propensity score matching (PSM) technique, we will develop matched cohorts of patients between the ICS+Tio and ICS/LABA groups.		
Population:	1. ICS+Tio; and 2: ICS/LABA.		

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Name of finished medicinal product: *Spiriva Respimat*			
Name of active ingredient: *Tiotropium*			
Protocol date: *12 May 2021*	**Study number:** 0205-0547	**Version/Revision:** 1.0	**Version/Revision date:** 12 May 2021
Variables:	The exposure variables are ICS+Tio use vs. ICS/LABA use in combination with ICS. PSM ● Gender ● Age group ● Region ● ICS dose level ● Control level ● Rescue medication use ● Comorbidities included in the Charlson Comorbidity Index ● ICS history (yes/no) ● ICS history duration ● Season of index date ● Index year ● Baseline all-cause resource use (presence vs. absences of hospitalizations, or ER visits, or outpatient visits) ● Baseline other asthma medications (use vs. no use) ● Baseline overall medication history (polypharmacy defined as number of unique medications) ● Insurance type ● Hypertension ● Gastroesophageal reflux disease ● Allergic Rhinitis ● Obesity ● Sinusitis ● Obstructive sleep apnea ● Cardiovascular disease ● Diabetes ● Renal failure ● Arthritis ● Osteoporosis ● Depression ● Cancer (excluding basal cell carcinoma) ● Baseline pneumonia diagnosis ● Diagnosis of dyspnea during baseline identified using ICD 9 786.0x and ICD 10 R06.0x		

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Name of finished medicinal product: *Spiriva Respimat*			
Name of active ingredient: *Tiotropium*			
Protocol date: *12 May 2021*	**Study number:** 0205-0547	**Version/Revision:** 1.0	**Version/Revision date:** 12 May 2021
Variables:	● Diagnosis of alcohol dependence during baseline identified using ICD 9 303.xx, 305.0x and ICD 10 F10.xx ● Smoking dependence during baseline identified using ICD 9 305.1 and ICD 10 F17.xx Regression In addition to the key independent variable of interest (ICS+TIO vs ICS/LABA group), we will include time varying medication exposure as a covariate in the regression.		
Data sources:	We will utilize medical and pharmacy claim records from [redacted] medical and pharmacy claims data. This database is comprised of adjudicated claims for more than 150 million commercially insured and Medicare lives in the US.		
Study size:	There are 25,291 patients with a prescription claim for tiotropium (1.25mcg, October 2015-May 2020) identified for analysis and 1,125,657 patients with ICS/LABA prescription claims (July 2014-May 2020). After excluding patients with COPD there are 17,882 patients in the Tio group and 921,804 patients in the ICS/LABA group. Further inclusion-exclusion criteria as well as restricting the Tio group to those with concurrent ICS monotherapy, will be applied to arrive at the final sample.		

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Data analysis	Sample attrition at each step of the inclusion-exclusion criteria will be provided. We will develop the breakdown of the distribution of demographic, comorbidity, and baseline measures prior to and after the PSM (unmatched and matched cohorts). Significance of differences will be tested at $P<0.05$ for the matched cohort. Additionally, we will consider the use of standardized mean differences as noted above, in which SMD <0.1 indicates balance. The primary endpoint measure is time to first severe exacerbation and severe exacerbation will be defined as a hospitalization or an ER visit with a primary diagnosis of asthma. We will calculate the time in days to first exacerbation. We will conduct Cox proportional hazards modeling to estimate the risk of exacerbation and provide corresponding KM curves for the primary endpoint. Exposure to each of the study comparators (ICS+Tio and ICS/LABA) will be recorded using time-varying covariates for all primary and secondary endpoints. ICS+Tio vs. ICS/LABA will be the key independent variable and medication exposure will be a covariate included in the regression. Secondary endpoints will include time (in days) to first moderate-or-severe exacerbation defined as use of systemic corticosteroid or a hospitalization or ER visit with a primary diagnosis of asthma. Cox PH and KM curves will be conducted for this secondary end point as well. We will also calculate and compare the rate of exacerbation, proportion of patients with exacerbations after 6 months and one year among the sub-population of patients having at least 6 months and a one year of follow-up, respectively. We will report rates in patient-years to account for variable follow-up time. We will also compare the mean monthly (to account for variable follow-up time) per patient HCRU (all-cause and asthma related hospitalizations, ER visits, and outpatient visits) during the follow-up period, between the two groups. Proportions of patients with and without rescue medication use will be compared between the two groups as well.

5 . AMENDMENTS AND UPDATES

None

6. MILESTONES

Study design and core group alignment	Week 1-2
Data receipt, extraction, cleaning and evaluation for protocol development	Week 2
Study protocol draft	Week 4
Study protocol final	Week 6
IET/NPCC approval	Week 8/9
Descriptive statistics draft	Week 11-12
Multivariate analysis draft	Week 12-14
Final results (Excel)	Week 16-17
Study narrative report	Week 17-18

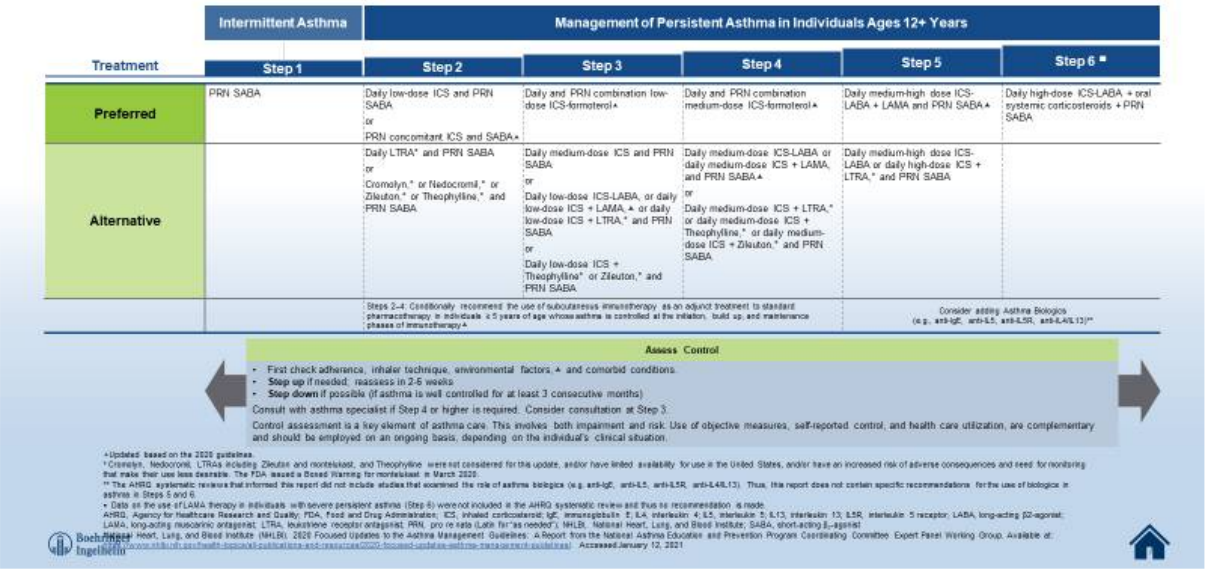
7. RATIONALE AND BACKGROUND

Asthma is associated with a significant burden on the healthcare system. More than half the population of asthma patients remains uncontrolled despite therapy, and uncontrolled asthma is associated with greater economic and health care burden (Braido et al. 2013; Peters et al. 2007). Stepwise treatment approach depending on control and severity levels has been the corner stone of asthma therapy. Regardless of severity level, patients with uncontrolled asthma are prone to exacerbations, increased use of systemic corticosteroids, rescue medications, deteriorating lung function (Chung et al. 2014), reduced quality of life, and increased health care resource use. In such cases, guidelines recommend increasing the dose of ICS product or use of ICS in combination with long-acting β2-agonists (LABA), and/or other add-on therapy such as with a long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonists (LTRA), biologics or oral corticosteroids. Treatment strategies that rely on step treatment may not always be sufficient in controlling asthma.

Given the unmet needs, other therapeutic options should be considered in this population. In investigating Tiotropium (Handihaler and Respimat) for the treatment of asthma, 6 clinical trials (found similar responses in lung function and exacerbations when comparing ICS/Tiotropium to ICS/LABA. In a randomized controlled trial of moderate asthma patients, Kerstjens et al 2015 reported a lower rate of exacerbations among patients with ICS/Tiotropium when compared to ICS/Salmeterol (ICS/LABA) however formal comparisons could not be made since the ICS/salmeterol group was included to provide a standard add-on active comparator and was not part of the inferential analysis. Kerstjens et al study concluded that “Once-daily tiotropium as add-on treatment to medium-dose inhaled corticosteroids provided significant improvements in lung function and asthma control that were similar to those recorded for twice-daily salmeterol. In summary, RCTs have found

similar responses in terms of lung function and exacerbations between patients on ICS/Tiotropium and ICS/LABA.

NHLBI recommendations: Stepwise approach for management of asthma in patients ≥12 years



In 2020 NHLBI updated the Asthma guidelines recommending low dose ICS+LAMA as an alternative in Steps 3 and 4 noting that" the majority of LAMA studies use a comparative efficacy design and thus, their clinical impact is not well understood in real-world settings." The NHLBI response highlighted the need for RWE to close this data gap. This proposed real world evidence (RWE) study will fill a data gap of assessing exacerbation differences with ICS/Tiotropium. ICS/LABA is very commonly used in the real world since 2003, and Tiotropium was only available in the US since 2016, so it's important we generate real world evidence data complimenting the ICS/Tiotropium RCT data as an alternative to ICS/LABA using real world data to support further treatment recommendations.

8. RESEARCH QUESTION AND OBJECTIVES

To conduct a comparative analysis of patients using Tiotropium in combination with Inhaled Corticosteroids (ICS) versus those that use LABA medication in combination with ICS.

9. RESEARCH METHODS

9.1 STUDY DESIGN

1. Patients with least two asthma diagnosis (ICD 9 CM: 493.xx or ICD 10: J45-J45.999) will be included.
2. Patients will be required to be concurrently on ICS+Tiotropium (specifically Tiotropium Respimat® 1.25 mcg) or ICS/LABA.
3. Patients with least two diagnosis of COPD at any time during the study period will be excluded.
4. Patients less than 12 years of age will be excluded.
5. Patients will be required to have enrollment for at least 6 months prior to ICS+Tio or ICS/LABA use.
6. Patients on biologics within 6 months prior to ICS+Tio or ICS/LABA use will be excluded.
7. Patients with prior Tio or ICS/LABA use during the 6-month baseline period will be excluded.
8. Patients with urinary bladder obstruction, urinary retention, and glaucoma will be excluded.
9. After the PSM process, unmatched patients will be excluded.

Patients will be classified into two groups based on the exposure on the index date: 1. ICS+Tio; and 2: ICS/LABA. The date of concurrent medication initiation will be defined as the index date based on the date of the first prescription claim defining their add-on medication. We will record various baseline measures, including demographics such as gender, age, and region, comorbidity level defined using Charlson Comorbidity Index (CCI), other specific comorbidities not included in the CCI (Table 1), inhaled medication use, and control level as defined in Table 1. Additionally, we will classify patients based on their daily ICS dose levels as ‘low dose ICS’, ‘medium dose ICS’, and ‘high dose ICS’. The dose levels will be assigned per GINA 2020 criteria (Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2020). Medications that are available with only two dose level indications will be tagged as ‘low’ for the lower of the two dose levels, and ‘high’ for the highest dose level.

Table 1: Baseline Parameters and Variable Definitions

Variable Name and Type	Description and Definition	Covariate Adjustment Method
Demographics	Age (5-year increments), Gender,	PSM
Region	Region (Northeast, Midwest, South, West)	PSM
CCI	Charlson Comorbidity Index score	PSM
Inhaled medication use	Identified using unique claims during the baseline period	PSM
Control Status: Not Well Controlled or Well Control	"Not Well Controlled" if patient has any one of the following events • Prescription for OCS • Asthma-related ER • Asthma-related hospitalizations "Well controlled" if patient has none of the above events (Ref: Stempel JACI 2005)	PSM
ICS history	Defined by use of ICS monotherapy prior to index date	PSM
ICS history duration	Days on ICS monotherapy prior to index date	PSM
ICS dose level	Daily dose of ICS classified as low dose ICS, medium dose ICS, and high dose ICS	PSM
Season	Season of cohort entry (Summer, Spring, Fall, Winter)	PSM
Index year	Year of the index date	PSM
All-cause resource use	All-cause hospitalizations, ER visits, outpatient visits	PSM
Other asthma medications	Leukotriene modifiers	PSM
Medication history	Polypharmacy calculated based on number of unique medications	PSM
Insurance type	Identified using payer type data field	PSM
Hypertension	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Allergic rhinitis	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Sinusitis	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Obstructive sleep apnea	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Gastro-esophageal reflux disease	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Obesity	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Cardiovascular disease	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Diabetes	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM

Table 1: Baseline Parameters and Variable Definitions (cont)

Variable Name and Type	Description and Definition	Covariate Adjustment Method
Renal failure	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Arthritis	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Depression	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Osteoporosis	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Cancer (excluding basal cell carcinoma)	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Pneumonia	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Acute bronchitis	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Dyspnea	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Alcohol dependence	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM
Smoking dependence	Identified using appropriate ICD codes. Coded as binary (yes/no) variables	PSM

Using propensity score matching (PSM) technique, we will develop matched cohorts of patients between the ICS+Tio and ICS/LABA groups. We will conduct 1:2 matching using nearest neighbor matching approach. Upon completion of matching, we will assess whether the cohorts are balanced by examining the statistically significant differences at $p<0.05$. We will also assess balance by calculating standardized mean differences (SMD). An SMD <0.1 will be considered balanced. Follow-up time will be calculated between index date and 'Censor date' which will be defined as the date of either one of the following events: 1. Date of first exacerbation, 2. Date of medication switch, 3. Discontinuation of medication (defined as date of prescription claim plus days' supply, plus 50% additional days), 4. Enrollment end date, or 5. Last date available in the dataset/End of study period. In this "new user", study design, primary analysis will be an "as-treated" analysis. In order to attribute events and outcomes to patients during the time that they are exposed to treatment (based on days-supply of prescription claims + a buffer window) as well as account for differences in inter-group adherence levels, we will use a time-varying covariate approach to classify drug exposure time for each comparator drug during follow up. This approach has been chosen to minimize bias based on potentially large differences in medication adherence rates, by only attributing outcomes to the time in which patients have medication in their possession based on days' supply as described below. For each individual study drug, we will identify and define medication exposure and non-exposure windows during the follow-up time for each medication using the date of prescription filled plus the days' supply listed on the prescription claim plus 50% additional days (to account for residual doses in canister, poor real-world adherence and latency of drug effects). For example, exposure start and stop dates

for a patient with a prescription claim with 30 days supply on January 1st will be January 1st and February 15th respectively (30 days' supply +15 days). We will run sensitivity analyses on the exposure window using 0% and 100% additional days. These time varying exposure covariates will be included in the Cox PH regression.

If statistical differences are found after PSM, then the study team will make a determination to either include them as covariates in the regression analysis (Cox PH), or develop interaction terms to match on, or discontinue the study. In the event of study discontinuation, partial results (all analysis leading up to and including PSM) will be provided in a final report.

9.2 SETTING

Please see section 9.1.

9.2.1 Study sites

Please see section 9.1 and 9.4

9.2.2 Study population

Please see section 9.1.

9.2.3 Study visits

Not applicable

9.2.4 Study discontinuation

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site, investigator, or research collaborator, disturbing the appropriate conduct of the study

The investigator/the study site/research collaborator will be reimbursed for reasonable expenses incurred in case of study/site termination (except in case of the third reason).

9.3 VARIABLES

9.3.1 Exposures

The exposure variables are Tio use vs. LABA use in combination with ICS. The operational definitions are provided in the sections above. After PSM, the cohort group will be the key predictor for the Cox PH regression to assess the primary outcome.

9.3.2 Endpoints

9.3.2.1 Primary endpoints

The primary endpoint measure is time to first severe exacerbation. Severe exacerbations will be defined as:

- A hospitalization with a primary diagnosis of asthma or
- An ER visit with a primary diagnosis of asthma

9.3.2.2 Secondary endpoints

Secondary endpoints will include:

- Time to first moderate-or-severe exacerbation
  - Any systemic corticosteroid use or
  - A hospitalization with a primary diagnosis of asthma or
    An ER visit with a primary diagnosis of asthma
- Proportion of patients with exacerbation
- Rate of exacerbation at 6 months and one year
- Proportions of patients with Health care resource utilization (HCRU). HCRU is defined as hospitalizations, emergency room (ER) visits, and outpatient visits during follow-up, all-cause and asthma related.
- Mean monthly HCRU (including frequency of hospitalizations, ER visits, OP visits)
- Proportion of patients with use of rescue medications (defined as patients with one or more SABA claims during the follow-up period)

9.3.3 Covariates

The covariates included in the PSM will be

- Gender
- Age group
- Region
- ICS dose level
- Control level
- Rescue medication use
- Comorbidities included in the Charlson Comorbidity Index
- ICS history (yes/no)
- ICS history duration
- Season of index date
- Index year
- Baseline all-cause resource use (presence vs. absences of hospitalizations, or ER visits, or outpatient visits)
- Baseline other asthma medications (use vs. no use)

- Baseline overall medication history (polypharmacy defined as number of unique medications)
- Insurance type
- Hypertension
- Gastroesophageal reflux disease
- Allergic Rhinitis
- Obesity
- Sinusitis
- Obstructive sleep apnea
- Cardiovascular disease
- Diabetes
- Renal failure
- Arthritis
- Osteoporosis
- Depression
- Cancer (excluding basal cell carcinoma)
- Baseline pneumonia diagnosis
- Baseline acute bronchitis diagnosis
- Diagnosis of dyspnea during baseline identified using ICD 9 786.0x and ICD 10 R06.0x
- Diagnosis of alcohol dependence during baseline identified using ICD 9 303.xx, 305.0x and ICD 10 F10.xx
- Smoking dependence during baseline identified using ICD 9 305.1 and ICD 10 F17.xx

In addition to the key independent variable of interest (ICS+TIO vs ICS/LABA group), we will include time varying medication exposure as a covariate in the regression.

9.4 DATA SOURCES

We will utilize medical and pharmacy claim records from [redacted] medical and pharmacy claims data. This database is comprised of adjudicated claims for more than 150 million commercially insured and Medicare lives in the US. Data between 2014 and 2020 will be extracted, with the first patient follow-up period for tiotropium 1.25 mcg dose patients starting in October of 2015. This longitudinal database allows documentation and analysis of the patient journey from diagnosis to intervention and follow-up. The database includes patients in the majority of three-digit zip codes and in every metropolitan statistical area of the US. It also covers data from 90% of US hospitals, 80% of all US doctors, and represents 85% of the Fortune 100 companies, with current HIPAA (Health Insurance Portability and Accountability Act) regulations. The database is constructed from a variety of geographic regions and employer groups and maintains a level of diversity while representing the overall trend in commercial health plan coverage. The underrepresentation of the population aged 65 years and older may affect external validity in the case of Medicare, Medicare Advantage or Medicaid patients.

9.5 STUDY SIZE

There are 25,291 patients with a prescription claim for tiotropium (1.25mcg, October 2015-May 2020) identified for analysis and 1,125,657 patients with ICS/LABA prescription claims (July 2014-May 2020). After excluding patients with COPD there are 17,882 patients in the Tio group and 921,804 patients in the ICS/LABA group. Further inclusion-exclusion criteria as well as restricting the Tio group to those with concurrent ICS monotherapy, will be applied to arrive at the final sample.

9.6 DATA MANAGEMENT

The data management plan is summarized below. Full details of the data management plan are documented in a separate NIS-Data Management and Review Plan (NIS-DMRP).

All established security and confidentiality procedures will be observed by BI and/or [redacted] personnel who are assigned appropriate access to the data. Enrolment data, medical claims, and prescription claims will be accessed from the administrative claims dataset. The analyses will be performed on limited data sets that are void of member protected health information and all results were shared in aggregate form only.

9.7 DATA ANALYSIS

9.7.1 Main analysis

Sample attrition at each step of the inclusion-exclusion criteria will be provided. We will develop the breakdown of the distribution of demographic, comorbidity, and baseline measures prior to and after the PSM (unmatched and matched cohorts). Significance of differences will be tested at $P<0.05$ for the matched cohort. Additionally, we will consider the use of standardized mean differences as noted above, in which SMD <0.1 indicates balance of baseline covariates. The primary endpoint measure is time to first severe exacerbation and severe exacerbation will be defined as a hospitalization or an ER visit with a primary diagnosis of asthma. We will calculate the time in days to first exacerbation. Also, as part of the primary end point analysis, we will develop KM curves based on initial exposure and conduct time varying Cox proportional hazards modeling accounting for changes in exposure status over the follow up time to estimate the risk of exacerbation between ICS+Tio vs. ICS/LABA. Secondary endpoints will include a number of measures. We will calculate the time in days to first moderate-or-severe exacerbation defined as use of systemic corticosteroid or a hospitalization or ER visit with a primary diagnosis of asthma. KM curves based on initial exposure and time varying Cox PH models will be conducted for this secondary end point as well. We will also calculate and compare the rate of exacerbation, proportion of patients with exacerbations after 6 months and one year among the sub-population of patients having at least 6 months and a year of follow-up, respectively. We will report rates in patient-years to account for variable follow-up time. We will also compare the mean monthly (to account for variable follow-up time) per patient HCRU (all-cause and asthma related hospitalizations, ER visits, and outpatient visits) during the follow-up period, between the two groups. Proportions of patients with and without rescue medication use will be compared between the two groups as well.

[redacted]

9.7.3 Safety Analysis

No Adverse Events are anticipated to be identified in this study.

9.8 QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below. Greater details are documented in the NIS-DMRP.

All programming will be quality controlled by two-step code checking by [redacted]. All results generated will be reviewed internally by two co-investigators separately prior to finalization.

9.9 LIMITATIONS OF THE RESEARCH METHODS

As with all studies utilizing claims data, there are certain limitations. The presence of a claim for a filled prescription or prescription absent claim does not indicate that the medication was consumed or that it was taken as prescribed. Medications filled over-the-counter or provided as samples by the physician will not be observed in the claims data. Patients with commercial health insurance may be different from those with non-commercial or without (commercial) health insurance, and hence study results may not be generalizable to the overall population. Population aged 65 years and older might be underrepresented, which may affect external validity in the case of Medicare, Medicare Advantage or Medicaid patients. Socioeconomic data is not available and can affect asthma outcomes. Since unmatched patients will be excluded, the results may not be generalizable to all patients. Some study measures and outcomes will include missing data and hence reduce the sample size. Patient misclassification, missing data, objective and reliable measurement of patient outcomes, and lack of detailed information regarding subjects' clinical history or clinical status during the study timeframe may undermine the accuracy of our study results.

9.10 OTHER ASPECTS

None

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Study records

NA

9.10.2.1 Source documents

NA

9.10.2.2 Direct access to source data and documents

NA

9.10.3 Completion of study

NA

9.10.4 Protocol deviations

NA

9.10.5 Compensation available to the patient in the event of study related injury

NA

10.PROTECTION OF HUMAN SUBJECTS

Ethical approval is not required for this study.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

NA

10.2 STATEMENT OF CONFIDENTIALITY

NA

11.MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

12.PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

13.REFERENCES

13.1 PUBLISHED REFERENCES

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13.2 UNPUBLISHED REFERENCES

NA

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Not applicable

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

None

ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

Signatures will be provided electronically via approval workflow in the DMS for submission documents.