Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document Number:	**c28659325-01**
BI Study Number:	0205-0543
BI Investigational Product(s):	Tiotropium Bromide 1.25 mcq.
Title:	*The effectiveness of Tiotropium Add-on therapy using a Real-world cohort of patients with Asthma*
Protocol version identifier:	*V. 1.0*
Date of last version of protocol:	*Not applicable*
PASS:	*"No"*
EU PAS register number:	*"Study not registered"*
Active substance:	*Tiotropium bromide 1.25 mcq.*
Medicinal product:	*N/A*
Product reference:	*N/A*
Procedure number:	*N/A*
Joint PASS:	*"No"*
Research question and objectives:	To evaluate the effectiveness of add on therapy with Tiotropium Respimat® compared to increasing the dose of ICS in patients with a diagnosis of Asthma and on ICS/LABA therapy.
Country(-ies) of study:	*U.S.A.*
Author:	
Marketing authorisation holder(s):	*N/A*
MAH contact person:	*N/A*
In case of PASS, add:	***N/A***

<EU-QPPV:>	
In case of PASS, add: <**Signature of EU-QPPV:>**	*N/A*
Date:	02/18/2019

Page 1 of 28

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

CCI	Charlson Comorbidity Index
COPD	Chronic obstructive pulmonary disease
CTMF	Clinical Trial Master File
ACAAI	American College of Allergy, Asthma and Immunology
ACT	Asthma control test
ATS	American Thoracic Society
BI	Boehringer Ingelheim
EMR	Electronic Medical Records
EMA	European Medicines Agency
ERS	European Respiratory Society
FDA	Food and Drug Administration
GPV	Global Pharmacovigilance
HCRU	Health Care Resource Utilization
HIPPA	Health Insurance Portability and Accountability Act
ICD	International Classification of Diseases
ICS	Inhaled Corticosteroid
LABA	Long-acting beta-agonist
LTRA	Leukotriene Receptor Antagonists
PSM	Propensity Score Matching

3. RESPONSIBLE PARTIES

Company	Personnel
Clinical advisors	
BI	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva Respimat 1.25 mcq			
Name of active ingredient: Tiotropium Bromide® 1.25 mcg			
Protocol date: 18 Feb 2019	**Study number:** 0205-0543	**Version/Revision:** 1	**Version/Revision date:** NA
Title of study:	*The effectiveness of Tiotropium Add-on therapy using a Real-world cohort of patients with Asthma*		
Rationale and background:	While asthma imposes a substantial burden on the healthcare system, the cost of uncontrolled asthma is more than double that for controlled asthma patients. Asthma therapy involves a stepwise approach depending on control and severity levels. To better guide treatment decision making, it is imperative to understand the impact of different treatment choices on health outcomes in a real-world setting for patients taking ICS/LABA combinations.		
Research question and objectives:	To evaluate the effectiveness of add on therapy with Tiotropium Respimat® compared to increasing the dose of ICS in patients with a diagnosis of Asthma and on ICS/LABA therapy.		
Study design:	Retrospective cohort data analysis of patients with asthma prescribed with ICS/LABA therapy. Patients will be followed after the date of first ICS/LABA prescription and those prescribed Tiotropium Respimat® will be classified under the 'Tio' group while the rest will be under the 'NonTio' group. Outcomes will be compared between these two groups.		
Population:	Asthmatics 6 years and above and on ICS/LABA at baseline		
Variables:	Baseline measures will include patient demographics, medications, control status, comorbidities, resource use, eosinophil levels (if available), ACT score (if available).		
Data sources:	IMS Pharmetrics (IMS or Database I); EMRClaims+ (Database II)		
Study size:	>6,300 (expected)		
Data analysis:	Propensity Score Matching will be conducted using baseline characteristics in order to ensure as much similarity between the two groups. Time to first exacerbation (primary outcome) will be compared between the two groups descriptively, as well as using Cox PH modelling techniques. Secondary outcomes will include rate of exacerbation, proportion of patients with exacerbation, health care resource use and cost during follow-up,		
Milestones:	Study protocol; Draft Results; Final Results		

5. AMENDMENTS AND UPDATES

None

7. RATIONALE AND BACKGROUND

While asthma imposes a substantial burden on the healthcare system, the cost of uncontrolled asthma is more than double that for controlled asthma patients (ACAAI). The European National Health and Wellness Survey (P19-00715) and the Real-world Evaluation of Asthma Control and Treatment (US) (R16-0701) survey both found that 55% of asthma patients were uncontrolled, even among those who are treated. Asthma therapy involves a stepwise approach depending on control and severity levels. Uncontrolled asthma, which may present regardless of severity level, results in exacerbations, use of systemic corticosteroids, and declined lung function (P14-03600). When asthma is not controlled, guidelines recommend increased ICS dose, and use of ICS in combination with long-acting β2-agonists (LABA), and/or other add-on therapy, including leukotriene receptor antagonists (LTRA), antibody biologics or oral corticosteroids. The ERS/ATS guidelines (P14-03600) define severe asthma as that which remains uncontrolled despite use of high dose ICS as well as controller medications or systemic corticosteroids. Uncontrolled asthma is associated with an increased risk of exacerbation, which results in impaired lung function, reduced patient quality of life and increased health care resource use. To better guide treatment decision making, it is imperative to understand the impact of different treatment choices on health outcomes in a real-world setting for patients taking ICS/LABA combinations.

The intended audience will be health systems, payers and prescribers. The results of the study will be used to provide evidence of the effectiveness of tiotropium as add-on therapy in reducing exacerbations, reducing the increased dosing of current medications and health care resource utilization for their asthma patients.

In September 2015, the FDA approved Spiriva Respimat for Inhalation Spray for the long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older (6 years and above approved in Feb 2017).

8. RESEARCH QUESTION AND OBJECTIVES

To evaluate the effectiveness of add on therapy with Tiotropium Respimat® compared to increasing the dose of ICS in patients with a diagnosis of Asthma and on ICS/LABA therapy.

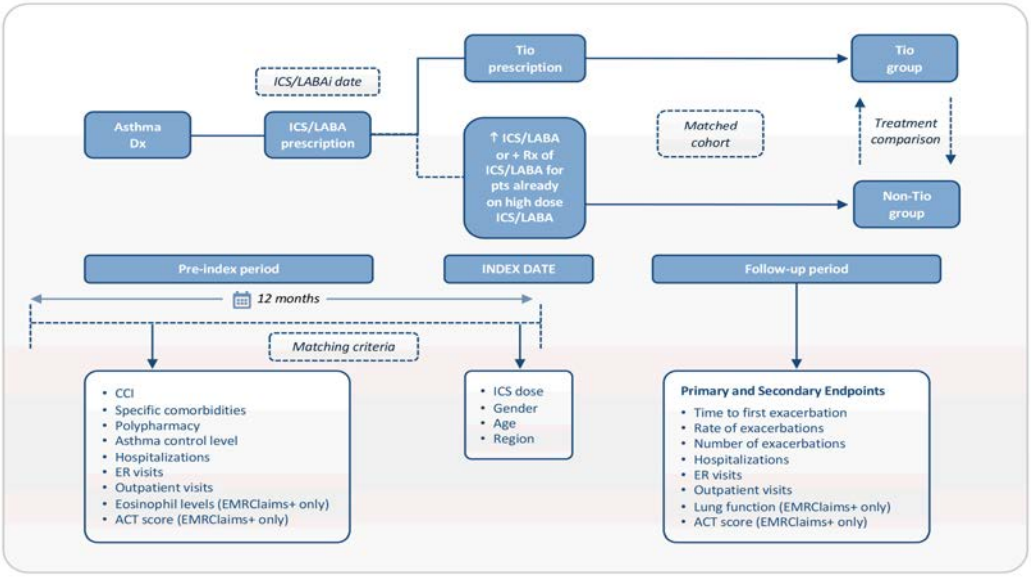
9. RESEARCH METHODS

9.1 STUDY DESIGN

Data extraction from both databases (I and II, see section 9.4) will be conducted by . All patients will be required to have a prescription for ICS/LABA therapy [e.g. Advair (Diskus and HFA), Airduo, Breo, Dulera, or Symbicort]. The date of the first prescription of ICS/LABA within the study period (Jan 1st 2016 to Nov 30th 2018) will be defined as ICS/LABA-initiation (ICS/LABAi) date. This baseline cohort will then be followed to identify two cohorts (two arms of the study). One cohort that receives a prescription for Tiotropium Respimat® 1.25 mcg (on top of baseline ICS/LABA) will be classified as the 'Tio' group, and the second cohort that receives a "step-up" from baseline low-dose ICS/LABA to medium/high dose ICS/LABA or from baseline medium dose ICS/LABA to high dose ICS/LABA or an additional prescription/refill of high-dose-ICS/LABA following the first prescription of baseline high dose ICS/LABA within the study period, will be classified as the 'NonTio' group. The date of the first prescription for Tiotropium Respimat® 1.25 mcg in the 'Tio' group will be defined as the index date for the 'Tio' group. Similarly the date of the first prescription for a "step-up" from baseline low-dose ICS/LABA to medium/high dose ICS/LABA or from baseline medium dose ICS/LABA to high dose ICS/LABA or an additional prescription/refill of high-dose-ICS/LABA following the first prescription of baseline high dose ICS/LABA (evidenced by at least 90-days of prescription utilization) within the study period will be defined as the index date for the 'NonTio' group.

Patients will be required to have a minimum follow-up period of 30 days after the index date for the analyses of the primary endpoint with no limit on the maximum period (this 30-day minimum follow-up period requirement will be waived in a sensitivity analysis). Subject to sample size requirements, patients will be required to have available records for at least 12 months prior to the index date to ensure no prior use of Tiotropium Respimat® and to establish baseline patient characteristics. This 12-month period prior to the index date will be defined as the pre-index period.

Figure 9.1.1 Study Design



9.2 SETTING

See section 9.11 below.

9.3 VARIABLES

9.3.1 Exposures

The exposure variables in this study include Tio initiation, and ICS/LABA dose increase or an additional prescription/refill of high-dose-ICS/LABA following the first prescription of baseline high dose ICS/LABA for at least 3 months.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

(*Datbase I/II combined)*
The primary outcome measure is time to first exacerbation per person.
Exacerbations will be defined as either a hospitalization with a primary diagnosis of asthma, an ER visit with a primary diagnosis of asthma, an asthma exacerbation diagnosis recorded (ICD 493.02, 493.12, 493.22, 493.92, J45.21, J45.31, J45.41, J45.51, J45.901).
The primary endpoint analysis will be of patients aged 12 years and above.

9.3.2.2 Secondary outcomes

Databases I/II combined
Secondary endpoints will include,
Rate of exacerbation,

Health Care Resource Utilization (HCRU)
HCRU is defined as frequency of hospitalizations, ER visits, and outpatient visits during follow-up, all-cause and asthma related, and the associated costs (medical and pharmacy).

Additional Secondary outcomes Database II

Where Tio patients and their matched subgroup of NonTio patients both have available lung function test results at baseline and in the follow up period, we will utilize change in lung function (trough FEV1) as a secondary outcome.

Where Tio patients and their matched subgroup of NonTio patients both have available ACT score results at baseline and in the follow up period, we will utilize change in ACT score.

9.3.3 Covariates

Other covariates are described in Table 1, including demographic information as available in the dataset as recorded at index date. Comorbidities included in the CCI will be identified during the pre-index period. Other and specific comorbidities such as cardiovascular conditions, cerebrovascular diseases, hypertension, diabetes, metabolic and endocrine comorbidities, anxiety and depression, gastro-esophageal reflux disease, cancer and obesity will also be identified during baseline. Additionally, polypharmacy at baseline, will be identified in the pre-index period. Finally, a composite measure of asthma control status will be made as defined in Table 1, classified as Well and Poor. Asthma Control Test score and eosinophil blood count levels as available, will also be identified at baseline for Cohort II only. We will also record exacerbation rate, resource use parameters, and cost during baseline.

Table 1: Matching Parameters

Variable Name and Type	**Description**	**Applicable to Study Cohort: 1=IMS, 2=EMRClaims+**
ICS/LABA dose on ICS/LABAi date	The dose level of the first prescription on the ICS/LABAi date (low, medium, or high)	1 and 2
Demographics (categorical and continuous variables)	Age (10-year increments) and Gender Male/Female), Region (if available, Northeast, Midwest, South, West)	1 and 2
CCI (continuous variable)	Charlson Comorbidity Index score	1 and 2
Specific comorbidities (categorical variables)	Cardiovascular conditions, cerebrovascular diseases, hypertension, diabetes, metabolic and endocrine comorbidities, anxiety and depression, gastro-esophageal reflux disease, cancer and obesity identified using appropriate ICD codes. All above measures will be coded as binary (yes/no) variables.	1 and 2
Medications (categorical variable)	Polypharmacy level matched within a range of 2 drugs (for example, 0-2,3-5,6-8,8-10 and so on).	1 and 2
Asthma Control Status: Well Control or Poor Control (categorical variable)	'Well Controlled' if patient has no prescriptions for an OCS, and no asthma-related emergency department visits or hospitalizations other than the first diagnosis recorded in the data extracted (Ref: Stempel JACI 2005). Categories will include Well Controlled and Not Well Controlled.	1 and 2
Hospital admissions Outpatient visits ER visits and OCS use (categorical variables)	Poorly Controlled patients ("Not Well Controlled") will further be matched based on the presence of asthma-related admissions, outpatient visits, and ER visits or use of OCS during the pre-index period.	1 and 2
Eosinophil levels (EMRClaims+ database only) (categorical variables)	Eosinophil level categories: <150 cells/µL,151-300cells/µL, 301-400 cells/µL, ≥400 cells/µL (as available)	2
Asthma Control Test (ACT) results (EMRClaims+ database only) (categorical variables)	ACT score categories developed based on data distribution (as available)	2

9.4 DATA SOURCES

Two separate databases will be appended to create the analytic dataset to obtain sufficient power for the primary endpoint analysis. This approach will provide both comprehensive geographic representation from national claims, and important asthma clinical measures available through electronic medical records (EMR). Both databases have been widely published in the academic asthma literature.

As a general note, this study protocol attempts to anticipate availability of detailed data elements of the two real-world data sets listed below. Consistent with accepted research standards using retrospective administrative data, evaluation of missing data and study variables is often required to ultimately finalize the study protocol as it relates to inclusion of covariates as well as secondary outcome measures.

IMS Pharmetrics (IMS or Database I)
We will establish Database 1 using medical and pharmacy claim records from IMS Pharmetrics data. Data from January 2015-2018 will be extracted, with the first patient follow-up period for tiotropium 1.25 mcg dose patients starting January 2016. This database contains administrative insurance data and enrolment information derived from approximately 150 million commercially insured and Medicare lives. This longitudinal database allows documentation and analysis of the patient journey from diagnosis to intervention and follow-up. It is nationally representative covering 90% of US hospitals and compliant with current HIPAA (Health Insurance Portability and Accountability Act) regulations.

EMRClaims+ (Database II)
We will establish database II using EMRClaims+®, which will offer lung function results, Asthma Control Test (ACT) scores, as well as eosinophil counts for asthma patients in addition to administrative data. EMRClaims+® is an integrated health services database containing more than 20 million EMR across seven states in the Midwestern region of the United States. The database includes administrative insurance claims of approximately 690,000 lives linked to an overlapping healthcare provider database of EMR, including laboratory values, and provider billing files.

The above two databases will be combined for the analysis of endpoints common to both databases.

9.5 STUDY SIZE

The expected number of asthma patients aged 12 years and above, without concurrent COPD, and continuous enrollment for 12 months prior to the Tiotropium Respimat® date is estimated to be approximately 2,100 to be matched to double (4200 patients) the number of NonTio patients resulting in a total N =6,300. Power calculation was conducted for the primary endpoint, time-to-first exacerbation by the end of the follow-up time. The calculation was based on detecting a significant treatment effect using Cox proportional hazard model. Estimates were obtained from the MEZZO trial comparing tiotropium 2.5 µg vs. salmeterol (P15-01655). Assuming 6.4% of patients in the control group followed

up for 5.5 months will have an exacerbation (based on the salmeterol group in the MEZZO study) and assuming a constant hazard rate, equating to an exponential rate parameter of 0.012 per month for the control group and 0.0096 per month for the Tio group, the power is calculated to be 77%. Using the Primo study, assuming 26.9% of patients in the control group followed up for 11 months will have an exacerbation (based on the Tio R 5 group in the 48-week study Primo) and assuming a constant hazard rate, equates to an exponential rate parameter of 0.028 per month in the control group and 0.0224 per month in the Tio group, the power is 98%. The Mezzo-derrived power calculation likely underestimates the power since our study design includes sicker patients that required a step-up in ICS treatment (not required in the Mezzo Study). While we expect that the actual power will lie between the two estimates (assuming that the patient population is similar to the less severe Primo patients and the more severe MEZZO patients), the estimated power is greater than 77%.

9.6 DATA MANAGEMENT

All established security and confidentiality procedures will be observed by BI and/or personnel who are assigned appropriate access to the data. Enrolment data, medical claims, and prescription claims will be accessed from this 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

We will provide the sample attrition at each step of the inclusion-exclusion criteria as well as a baseline demographic and comorbidity breakdown. We will provide a comparative breakdown in baseline measures for the unmatched and matched cohorts to assess if PSM eliminated baseline differences. For the primary endpoints analysis, we will calculate the time to first exacerbation per patient and compare it between the two groups (Tio vs. NonTio). For secondary endpoint analyses we will compare the rate of exacerbation, proportion of patients with exacerbations after 6 months and one year (based on Kaplan Meier estimates), HCRU and average cost during follow-up and compare them between the two groups (Tio vs. NonTio).
The primary outcome of the study will be analyzed using Cox proportional hazard modelling. The secondary outcome of rate of exacerbation per patient will be analyzed using negative binomial regression. This technique works on the assumption that the rate of exacerbation varies among every subject in the study (P16-06846). Also this model accounts for overdispersion of data which is likely to happen due to variability between the patients. Balance in covariates will be checked after matching. If PSM was able to balance all observed baseline characteristics, the regression models for outcomes will be limited to the databases (IMS and EMR) and to the key independent variable of interest (namely Tio use vs. ICS/LABA dose increase) and model overfitting is not, therefore, of concern. However, if there are unbalanced baseline characteristics, we will include these characteristics in the regression as covariates. For regression model covariate selection we

will also estimate the multicollinearity of covariates by assessing their correlations of independent variables. For example, if comorbidities from the specific list are also included in CCI, they will only be included in the CCI.

In order to handle missing data, in the PSM we will create a category variable ('missing data") for each covariate to ensure that patients with that variable and without that variable are respectively matched. Patients with missing prescription data required for classification of the treatment groups will be excluded. Patients with missing lung function scores and ACT scores at baseline and in the follow up period will be excluded from these respective secondary analyses.

9.8 QUALITY CONTROL

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

9.9 LIMITATIONS OF THE RESEARCH METHODS

Claims and EMR data are subject to certain limitations. The presence of a claim for a filled prescription or prescription absent a claim does not indicate that the medication was consumed or that it was taken as prescribed, and any medications filled over-the-counter or provided as samples by the physician will not be observed in the claims data. Finally, as with all claims-based analyses, study results may not be generalizable to the overall population as patients who have commercial health insurance may be different from those with non-commercial or without (commercial) health insurance. Database I underrepresents the population aged 65 years and older, which may affect external validity in the case of Medicare, Medicare Advantage or Medicaid patients. 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. Not all patients in Database II will have lung function results or ACT scores, therefore, the sample size for related secondary endpoints or sub-group analyses may produce results for these analyses that are not generalizable. While duplication analyses will make double counting the same patient across both datasets negilible, it should be noted that the same patient may be present in both cohorts.

Including patients with persistent use of high-dose ICS/LABA(as opposed to an increase in ICS/LABA dose) in the NonTio group, may complicate the interpretation of the results, as patients with a deterioration in their asthma necessitating an increase in asthma medication (Tio group) will be matched to patients continuing on the same medication (high-dose ICS/LABA).

No claims regarding the effectiveness of Tio should be made on the basis of this study. This real-world evidence study lacks controls available with randomized controlled trials. Patient misclassification, missing data, objective and reliable measurement of patient outcomes, and lack of detailed information regarding subjects' cinical history or clinical status during the study timeframe may undermine the accuracy of our study results.

9.10 OTHER ASPECTS

The IMS® PharMetrics Plus database is comprised of adjudicated claims for more than 150 million unique enrollees across the US. Enrollees with both medical and pharmacy coverage in 2012 represented 40 million active lives. Patients in the majority of three-digit zip codes and in every metropolitan statistical area of the US are represented, with coverage of data from 90% of US hospitals, 80% of all US doctors, and representation from 85% of the Fortune 100 companies. Because the database is constructed from a variety of geographic regions and employer groups, the database 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.

EMRClaims+®, will offer lung function results, Asthma Control Test (ACT) scores, as well as eosinophil counts for asthma patients in addition to administrative data. EMRClaims+® is an integrated health services database containing more than 20 million EMR across 7 states in the Midwestern region of the United States. The database includes administrative insurance claims across approximately 690,000 lives linked to an overlapping healthcare provider database of EMR, including laboratory values, and provider billing files. This data source uniquely provides a strong-level of internal validity since two separate sources (EMR and administrative data) cross reference unique patient identifiers. In the event of discrepancies between administrative files and EMR data (or for uncertainty about disease classification), manual evaluation of the individual patients' medical records is conducted to provide resolution based on access to the complete patient medical history in the EMR.

The databases do not have the capability to uniquely identify members who disenroll and re-enroll; consequently, these individuals are assigned a new identifier and may be represented in the data as two unique subjects. It is also possible that a patient may be in both cohorts. Both possibilities will be checked using zip codes. If two patients are suspected of being the same, only the data with the longer follow-up period will be used.

9.11 SUBJECTS

1. Patients with least one asthma diagnosis in the inpatient setting or at least two separate instances of asthma diagnosis (separated by at least 30 days) recorded in the outpatient or emergency room setting will be included (ICD 9 CM: 493.xx or ICD 10: J45-J45.999).
2. Patients will be required to be already on ICS/LABA.
3. Patients below the age of 6 years on the ICS/LABAi date will be excluded.
4. Patients will be required to have available records 12 months prior to the index date (6 months will be used if patient exclusions due to this criteria adversely affect the study sample size).
5. Patients with a diagnosis of COPD at any time during the study period will be excluded.
6. Those who are on biologics at baseline will be removed.
7. After the PSM process, unmatched patients will be excluded.

9.11.1 Cases

NA

9.11.2 Controls

NA

9.12 BIAS

Channeling Bias Mitigation

Introduction of channeling bias in this study is highly likely using retrospective claims data based on asthma medication use; patients between the two cohorts may differ in baseline control and severity levels. On aggregate, patients for whom Tiotropium Respimat® 1.25 mcg was added (vs NonTio) are likely to be less well-controlled and more severe both at baseline and and during the follow up period. Absent a method to control for this channeling bias, it is likely that placing sicker patients in the Tiotropium Respimat® 1.25mcg group will confound an accurate comparison of cost, resource use, and other outcomes between the groups. Two design features of our study will help mitigate this bias. First, our comparison (NonTio) group will be required to step-up their baseline ICS/LABA dose or have an additional prescription/refill of high-dose-ICS/LABA following the first prescription of baseline high dose ICS/LABA within the study period. Second, we will use Propensity Score Matching (PSM) to match patients on key measures of disease control and severity as listed in Table 1, such as demographics, Charlson Comorbidity Index (CCI) score, specific comorbidities, number of prescriptions (overall and asthma-related medications). This baseline matching strategy will be particularly important to ensure that patients in the TIO group who have a corresponding increase in their ICS dose at or prior to the date of their TIO prescription (for example, if the patient has an exacerbation), will be matched to a corresponding NonTIO patient in terms of increased ICS dose or additional ICS prescription. It should be noted that after the prescription index date for both Tio and NonTio patients, we anticipate changes in ICS medication for patients in both cohorts. These ICS medication changes reflect patient

outcomes in the follow-up period, where patients who encounter exacerbation in either group are likely to see a change in the ICS dose.

As a result, post-index period ICS medication changes will not alter the classification of patient groups nor will it be the basis for exclusion of these patients.

We will conduct 1:2 matching using a nearest neighbour matching approach with a radius of 0.2*SD(log(P)). This will be conducted in both databases (IMS: Cohort I and EMRClaims+: Cohort II) separately.

10. PROTECTION OF HUMAN SUBJECTS

All data are HIPAA compliant to protect patient privacy.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

Data is anonymized and extracted, analyzed, validated 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 where adverse events is identified during data compilation, data reporting or data analysis.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

TBD

13. REFERENCES

13.1 PUBLISHED REFERENCES

P14-03600 Chung KF et al. International ERS/ATS Guidelines on definition evaluation and treatment of severe asthma. Eur Respir J 43, 343-373 (2014)

P15-01655 Kerstjens HA et al. Tiotropium and salmeterol as add-on therapies to inhaled corticosteroids for patients with symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. Lancet Respir Med. 2015 May;3(5):367-76

P16-06846 Keene ON, Calverley PMA, Jones PW, Vestbo J, Anderson JA. Statistical Analysis on exacerbation rates in COPD, TRISTAN, and ISOLDE revisited. Eur Respir J 32 (1) 17-24 (2008)

P19-00715 Braido F. Failure in Asthma control: Reasons and Conseuqences. Scientifica 2013. 549252 (2013)

R11-4318 Guidelines for Good Pharmacoepidemiology Practices (GPP) (revision 2: April 2007). http://www.pharmacoepi.org/resources/guidelines_0827.cfm (access date: 13 September 2011) ; Bethesda: International Society for Pharmacoepidemiology (ISPE); 2007.

R16-0701 Peters SP, Jones CA, Haselkorn T, Mink DR, Valacer DJ, Weiss ST. Real-world Evaluation of Asthma Control and Treatment (REACT): findings from a national web-based survey. J Allergy Clin Immunol 119 (6) 1454-1461 (2007)

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

NA

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

NA