Doc. No.: c23740530-01

# *Randomized Pragmatic Clinical Trial in a Community-Based Setting Comparing STIOLTO® RESPIMAT® vs. ICS-LABA plus LAMA in Patients with COPD*

**The AIRWISE Study: Assessment In a Real World setting of the effect of Inhaled Steroid-based triple therapy versus the combination of tiotropium and olodaterol on reducing COPD Exacerbations**

## Protocol No. 1237-0064

[redacted]

[redacted]

**Fax:** [redacted]

**May 9, 2018**
Version 2.0

**STUDY APPROVALS**
Protocol No: 1237-0064
May 9, 2018

**Sponsor Approval:**

**Name:** [redacted]
**Title:** Executive [redacted]

**Signature:** [redacted] **Date:** 5/9/18

**Name:** [redacted]
**Title:** Senior Associate [redacted]

**Signature:** [redacted] **Date:** 5/9/18

**Name:** [redacted]
**Title:** Principal Statistician, [redacted]

**Signature:** [redacted] **Date:** 5/9/18

**Study Physician Agreement:**

I have read the protocol "*Randomized Pragmatic Clinical Trial in a Community-Based Setting Comparing STIOLTO® RESPIMAT® vs. ICS-LABA plus LAMA in Patients with COPD*" and agree to ensure that all staff members involved in the conduct of this study are informed of their obligations in meeting the commitments in accordance with it.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described pragmatic trial.

**Signature:** _____ **Date:** _____

**Print Name:** _____

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# SYNOPSIS

**Title:** Randomized Pragmatic Clinical Trial in a Community-Based Setting Comparing STIOLTO® RESPIMAT® vs. ICS-LABA plus LAMA in Patients with COPD

**Study Name/Brief Title:** Assessment In a Real World setting of the effect of Inhaled Steroid-based triple therapy versus the combination of tiotropium and olodaterol on reducing chronic obstructive pulmonary disease (COPD) Exacerbations [AIRWISE]

**Sponsor:** Boehringer Ingelheim

**Treatment:** Stiolto® Respimat®

**Active Ingredient**: Tiotropium bromide & olodaterol

**Comparator Product:** Inhaled Corticosteroid plus Long-acting beta agonists combination plus Long-acting muscarinic antagonists (ICS plus LABA plus LAMA) (Triple Therapy)

**Protocol No.:** 1237-0064

**Study Physicians:** Approximately 400 physicians who actively manage adult patients in the target indication, chronic obstructive pulmonary disease (COPD).

**Country:** United States (US)

**Patients:** Adults (40 years of age or older) with COPD who are currently on long-acting muscarinic antagonist (LAMA) or long-acting beta agonist (LABA) or inhaled corticosteroid (ICS)/LABA maintenance therapy, and whose treatment is not controlled on the current medication regimen as determined by the physician.

Anticipated enrollment for this study is approximately 3200 patients, with approximately 1600 patients enrolled in each group. Patients will be randomized to either Stiolto Respimat or ICS plus LABA plus LAMA (triple therapy) made up of the combination of any approved drugs that their physician chooses.

**Study Objectives**: The objectives of this study are as follows:

1.) The primary objective of this pragmatic study is to compare the time to first moderate or severe COPD exacerbation in patients, not controlled on their current therapy, randomized to Stiolto Respimat versus triple therapy over 12 months of treatment.

2.) The secondary objectives of this study are:

   a. To compare the annual rate of moderate or severe COPD exacerbations for patients on Stiolto Respimat with patients on triple therapy.

   b. To compare the time to first severe COPD exacerbation in both treatment arms.

   c. To compare the annual rate of severe COPD exacerbations in both treatment arms.

   d. To compare the proportion of patients with moderate or severe COPD exacerbations in both treatment arms.

[redacted]

[redacted]

**Study Endpoints:**

Primary endpoint: time to first moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation over 12 months of treatment

Secondary endpoints:

- Annual rate of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations
- Time to first severe chronic obstructive pulmonary disease (COPD) exacerbation over the 12 month observation period
- Annual rate of severe chronic obstructive pulmonary disease (COPD) exacerbations
- Proportion of patients with moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations over the 12 month observation period

[redacted]

**Study Design:** This is a pragmatic randomized open label active controlled parallel group design trial conducted in a real-world, community-based practice setting for a fixed duration of 12 months of treatment. All participating patients will already be on LAMA, LABA or ICS/LABA for COPD, but will have been determined by their physician to not be controlled on their current therapy. Patients enrolled in the study will be randomized to either Stiolto Respimat or ICS plus LABA plus LAMA (triple therapy) and provided with a prescription for the assigned treatment.

Inclusion and exclusion criteria are minimally restrictive and there are few study-specific evaluations. Study physicians will follow and treat patients according to their routine clinical practice and judgment. Clinical and healthcare claims data will be collected from study patients for 12 months. [redacted]

It is anticipated that patients who are being treated for COPD will, as part of usual care, likely undergo medical evaluation at regular intervals over the course of the study. Physicians will collect study data during patient office visits and other patient contact (e-mail, phone, contact with another treating physician, receipt of records) that occur as part of standard clinical practice over the course of the study. However, the only required study visits are a baseline visit and a final end of study (EOS) visit at 12 months.

**Patient Selection:**

Inclusion Criteria:

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

Priority will be given to patients actively enrolled in an [redacted] affiliated health plan.

- COPD diagnosis as defined by the study physician
- Currently on one of the following maintenance therapies:
  - LAMA monotherapy

- LABA monotherapy
- ICS/LABA (Fixed Dose Combination (FDC))

- Physician determination that patient is not controlled on current pharmacotherapy
- Adult patient 40 years of age or older at time of study enrollment
- Willingness and ability to understand and provide documented Informed Consent Form (ICF) and Health Insurance Portability and Accountability Act (HIPAA) Authorization Form prior to commencement of any study required assessments, either directly or through Legally Authorized Representative.

Exclusion Criteria:

Patients presenting with any of the following exclusion criteria will not be eligible for enrollment into the study:

- Currently on LAMA/LABA (free or FDC) or triple therapy (ICS plus LABA plus LAMA)
- Contraindication to any study medications (LAMA, LABA or ICS)
- Documented diagnosis of current asthma
- Pregnant or nursing women

**Study Procedures**:

- Study physicians will identify eligible patients for participation.
- Study physicians will obtain written informed consent and patients will be randomized to either Stiolto Respimat or triple therapy upon enrollment.
- Study physicians will collect demographic, clinical and COPD history data on electronic Case Report Forms (eCRFs) at baseline.
- A complete blood count (CBC) including differential white cell count will be drawn at baseline. In the event that a CBC is not available at baseline, laboratory results within 12 months of baseline will be accepted.
- The COPD Assessment Test™ (CAT) symptom score will be assessed at baseline.
- Study physicians will collect patient data (exacerbations, targeted medication changes, selected adverse events (AEs) (AEs leading to study treatment discontinuation, dose modification, or trial withdrawal)) during any patient office visits or other patient contact during the 12 months the patient is on study and enter it via an electronic data capture (EDC) system. Any Serious Adverse Events (SAEs), including COPD exacerbation SAEs, will be collected via paper system.
- Clinical data collection at the EOS visit at 12 months will include exacerbations, targeted medication changes, selected AEs and any SAEs.
- [redacted]

**Study Duration:** Patients will be on study and followed for 12 months by the physician to collect clinical data. [redacted]

**Patient Reported Outcomes (PROs):** The CAT will be administered at baseline to provide a simple and reliable measure of health status in COPD and assist patients and their physicians in quantifying the impact of COPD on the patient's health at baseline.

| |
|---|
| **Effectiveness Analysis:** The primary effectiveness analysis will assess time to first moderate or severe COPD exacerbation (as prospectively collected in the eCRF) of Stiolto Respimat compared to triple therapy. A Cox proportional hazards model will be used to compare treatments. |
| **Secondary/Sensitivity Analyses:** As a secondary effectiveness objective, the annual rate of moderate or severe exacerbations will also be calculated and compared between treatment groups. Other secondary analyses include evaluation of severe COPD exacerbations for time to first exacerbation and annual rate, proportion of patients with moderate or severe COPD exacerbations, sensitivity analyses relating to exacerbation definition and source data, and sensitivity analyses relating to generalizability of the study population. |
|  |
| **Safety:** All SAEs reported by the patients during the study period are required to be documented on the appropriate SAE reporting form. Selected AEs, e.g. AEs leading to study treatment discontinuation, dose modification, or trial withdrawal, will be collected on the eCRF during the study. During extraction of data from the claims database, any identified SAEs will be reported if not already collected on SAE form. |

## LIST OF ABBREVIATIONS

| Abbreviation or Special Term | Definition |
|---|---|
| AE | Adverse Event |
| AIRWISE | Assessment In a Real World setting of the effect of Inhaled Steroid-based triple therapy versus the combination of tiotropium and olodaterol on reducing COPD Exacerbations |
| CAT | COPD Assessment Test |
| CBC | Complete Blood Count |
| eCCGs | Electronic Case Report Form Completion Guidelines |
| CDM | Clinical Data Manager |
| CFR | Code of Federal Regulations |
| CMH | Cochran-Mantel-Haenszel |
| COPD | Chronic Obstructive Pulmonary Disease |
| eCRF | Electronic Case Report Form |
| DMP | Data Management Plan |
| ECG | Electrocardiogram |
| EDC | Electronic Data Capture |
| EMA | European Medicines Agency |
| EOS | End of Study |
| ER | Emergency Room |
| FDA | Food and Drug Administration |
| FDC | Fixed Dose Combination |
| FEV1 | Forced Expiratory Volume in One Second |
| FVC | Forced Vital Capacity |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| HCRU | Healthcare Resource Utilization |
| HIPAA | Health Insurance Portability and Accountability Act |
| [redacted] | [redacted] |

| Abbreviation or Special Term | Definition |
|---|---|
| HR | Hazard Ratio |
| ICD-10 | International Classification of Disease, 10th Revision |
| ICF | Informed Consent Form |
| ICS | Inhaled Corticosteroid |
| ID | Identifier |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| ITT | Intent to Treat |
| LABA | Long-Acting Beta Agonist |
| LAMA | Long-Acting Muscarinic Antagonist |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PP | Per Protocol |
| PRO | Patient Reported Outcome |
| PT | Preferred Term |
| PV | Pharmacovigilance |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SM | Service Mark |
| SMQ | Standardized Medical Queries |
| SOC | System Organ Class |
| T2DM | Type 2 Diabetes Mellitus |
| TM | Trademark |
| US | United States |
| WISDOM | Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management |

# 1 INTRODUCTION

## 1.1 Background and Rationale

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by progressive airflow limitation and airway inflammation leading to a gradual loss in lung function.[1] COPD is one of the most prevalent chronic diseases and the third leading cause of deaths in the United States (US) in 2011.[2] However, a majority of the patients (>50%) with low pulmonary function are unaware of their COPD condition.[3] This under diagnosis poses challenges in community clinical practice, resulting in inappropriate patient management.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends classifying patients for treatment based on assessment of existing symptoms, severity of airflow limitation, and history of exacerbations.[4] Airflow obstruction is measured by spirometry, which is considered as the gold standard for accurate and repeatable measurement of lung function. The presence of post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <0.70 confirms the presence of persistent airflow limitation and hence COPD diagnosis. However, spirometry is significantly underutilized by primary care physicians to confirm the diagnosis of COPD.[5]

For patients who are diagnosed with COPD, treatments include maintenance medication with mono- and combination bronchodilator therapies. Treatment with both a long-acting muscarinic antagonist (LAMA) and a long-acting beta agonist (LABA) has been recommended in patients whose COPD is not sufficiently controlled with mono- bronchodilator therapy. Clinical trials examining combination treatment with LAMA and LABA have shown long term improvements in lung function, symptom scores, and exacerbations in patients with moderate to very severe COPD.[6,7] Further, the convenience of fixed dose combination (FDC) products might provide an improved patient-centered approach that enhances patient acceptance and adherence to dual

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[1] Dewar M, Curry W. Chronic Obstructive Pulmonary Disease: Diagnostic Considerations. Am Fam Physician. 2006 Feb 15;73(4):669-676.
[2] Hoyert DL, Xu JQ. Deaths: preliminary data for 2011. *Natl Vital Stat Rep*. 2012; 61(6):1-65. Hyattsville, MD: National Center for Health Statistics. 2012
[3] Center for Disease Control and Prevention. What is COPD? Available at http://www.cdc.gov/copd/index.htm. Accessed on January 20, 2015.
[4] Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org. Accessed on March 4, 2017.
[5] Mapel DW, Dalal AA, Johnson P, et al. A clinical study of COPD severity assessment by primary care physicians and their patients compared to spirometry. Am J Med. 2015. doi: 10.1016/j.amjmed.2014.12.018.
[6] Vogelmeier C, Kardos P, Harari S, et al. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6 month study. Respir Med. 2008;102:1511-1520.
[7] Tashkin DP, Pearle J, Iezzoni D, et al. Formoterol and tiotropium compared with tiotropium alone for treatment of COPD. COPD. 2009;6:17-25.

bronchodilator therapy and reduces copay burden to the patient. Stiolto® Respimat® is an FDC containing tiotropium (a LAMA) and olodaterol (a LABA) that was approved by the Food and Drug Administration (FDA) in May of 2015. Multiple randomized controlled trials have demonstrated that the Stiolto Respimat is superior to either monotherapy.

GOLD 2017 does not recommend the use of triple combination therapy (LABA/inhaled corticosteroid (ICS) + LAMA) except potentially in a subset of patients in group D (high risk for exacerbation/high symptom scores). On the other hand, long-acting bronchodilators, including the combination of LAMA and LABA, are recommended as options in groups B (low risk for exacerbation/high symptoms scores), C (high risk for exacerbation/low symptoms scores) and D. However, multiple observational analyses of real-world data, including the preparatory analyses performed by [redacted] in the [redacted] population, continue to show a high proportion of COPD patients being prescribed ICS-containing regimens, including triple therapy. The magnitude of ICS prescribing seems to be contrary to the recommendations provided by GOLD 2017, and provides the impetus to perform the proposed study.

While the benefits of ICS therapy are well documented across a broad spectrum of patients with asthma, their benefits in the COPD population appear to be more targeted to select patient phenotypes. Specifically, the benefit appears to be most robust in patients with severe COPD with a history of frequent exacerbations or with an inflammatory/allergic component to their disease. In addition, ICS therapy is associated with localized symptoms such as voice hoarseness and thrush, as well as systemic diseases such as upper respiratory tract infections and osteoporosis.

The Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM)[8] trial explored the impact of withdrawing ICS in patients concurrently receiving LAMA/LABA combination therapy. In this randomized, double-blind, non-inferiority designed study the risk of moderate or severe exacerbations was similar between those who had their ICS withdrawn versus those who continued. A logical follow-up research question from the WISDOM study is to assess patients who are not controlled on their current therapy of ICS-LABA, LABA alone or LAMA alone, to see if change in therapy to LAMA/LABA FDC therapy is similar in effect to triple therapy. Studying the question in a manner that assesses patients as therapy is "stepped-up" is reflective of usual clinical practice and would provide valuable and relevant real-world evidence to both practicing clinicians and health care payers. In addition, the GOLD 2017 update specifically states that "more evidence is needed to draw conclusions on the benefits of triple therapy LABA/LAMA/ICS compared to LABA/LAMA." To this end, the proposed study, AIRWISE: Assessment In a Real World setting of the effect of Inhaled Steroid-based triple

[8] Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD. N Engl J Med. 2014;317:1285-94.

therapy versus the combination of tiotropium and olodaterol on reducing COPD Exacerbations, is a non-inferiority trial of community-based COPD patients randomized to either Stiolto Respimat or triple therapy following a physician decision to escalate therapy. The decision to escalate therapy will be at the discretion of the treating physician. Patients will be treated according to routine clinical practice and followed for clinical (exacerbations, etc.) [redacted]

# 2 STUDY OBJECTIVES

## 2.1 Primary Objectives

The primary objective of this pragmatic study is to compare the time to first moderate or severe COPD exacerbation in patients, not controlled on their current therapy, randomized to Stiolto Respimat versus triple therapy over 12 months of treatment.

### 2.1.1 Primary Objective Definitions

For the purpose of this study, a COPD exacerbation is defined as a complex of lower respiratory events/symptoms (increase or new onset) related to the underlying COPD, with duration of three days or more, requiring a prescription of antibiotics and/or systemic steroids and/or hospitalization.

A complex of lower respiratory events/symptoms is defined as at least two of the following:

- Shortness of breath
- Sputum production (volume)
- Change in sputum color
- Cough
- Wheezing
- Chest tightness

"Onset of exacerbation" will be defined by the onset of first recorded symptom. The "end of exacerbation" will be decided by the investigator based on clinical judgment.

Exacerbations will be classified as follows:

Moderate: Exacerbation requiring receipt of an exacerbation-related prescription of oral corticosteroids and/or antibiotic, but not requiring hospitalization

Severe: Exacerbation requiring COPD-related hospitalization

For hospitalizations associated with COPD exacerbation, the information collected should include the start date of all COPD-related hospitalizations, as well as the discharge date from the hospital or equivalent.

## 2.2 Secondary Objectives

The secondary objectives of this study include:

1) To compare the annual rate of moderate or severe COPD exacerbations for patients on Stiolto Respimat with patients on triple therapy.
2) To compare the time to first severe COPD exacerbation in both treatment arms.
3) To compare the annual rate of severe COPD exacerbations in both treatment arms.
4) To compare the proportion of patients with moderate or severe COPD exacerbations in both treatment arms.

[redacted]

## 3 STUDY ENDPOINTS

The primary endpoint of this study is time to first moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation over 12 months of treatment.

Secondary endpoints include:

- Annual rate of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations
- Time to first severe chronic obstructive pulmonary disease (COPD) exacerbation over the 12 month observation period
- Annual rate of severe chronic obstructive pulmonary disease (COPD) exacerbations
- Proportion of patients with moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations over the 12 month observation period

[redacted]

# 4 STUDY DESIGN

## 4.1 Overview

This is a pragmatic non-inferiority trial conducted in a real-world, community-based practice setting for a fixed duration of 12 months of treatment. All participating patients will already be on LAMA, LABA or ICS/LABA for COPD, but will have been determined by their physician to not be controlled on their current therapy. No definition of 'controlled' will be offered by the trial protocol in order to allow physicians to make real-world autonomous decisions. Patients enrolled in the study will be randomized to either Stiolto Respimat or ICS plus LABA plus LAMA (triple therapy) and provided with a prescription for the assigned treatment. Study treatments will be open-label.

In keeping with the study objective to evaluate Stiolto Respimat in a real-world setting, this study is naturalistic in design. Inclusion and exclusion criteria are minimally restrictive and there are few study-specific evaluations. Study physicians will follow and treat patients according to their routine clinical practice and judgment. Patients who enroll in the study agree to the release of health information and to answer questions about their health during the course of the study. Clinical and healthcare claims data will be collected from study patients for approximately 12 months. [redacted]

Consistent with the naturalistic design, this study does not have a rigid visit schedule. It is anticipated that patients who are being treated for COPD will, as part of usual care, likely undergo medical evaluation at regular intervals. Physicians will collect study data during patient office visits and other patient contact (e-mail, phone, contact with another treating physician, receipt of records) that occur as part of standard clinical practice over the course of the study. The only required study visits are a baseline visit and a final end of study (EOS) visit at 12 months post enrollment.

## 4.2 Practice and Participant Selection

### 4.2.1 Physician Practice Eligibility

Enrollment of approximately 400 physician sites with an adequate COPD population in the US is anticipated.

### 4.2.2 Participant Recruitment and Eligibility

Eligible participants include active COPD patients whose physicians determine that their COPD is not controlled on their current therapy (LAMA or LABA monotherapy or ICS/LABA). Patient recruitment and eligibility study procedures reflect the study's goal of evaluating Stiolto Respimat in a real-world setting. As such, patients will be recruited from the physician's patient population in a manner that is representative of the real-world population who are currently receiving care within their practice.

The determination that the patient is not controlled on their current therapy, and therefore eligible for the study, is at the discretion of the physician. Once an eligible patient is enrolled, they will be randomized in sequence.

It is anticipated that participants will be recruited from patients who are actively enrolled in an [redacted] of [redacted] or [redacted] health plan (hence forth referred to as [redacted] health plans). To meet enrollment goals recruitment will allow non-[redacted] patients within enrolled physician practices, which may include Medicare/Medicaid patients. [redacted]

### 4.2.3 Participant Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

Priority will be given to patients actively enrolled in an [redacted] affiliated health plan.

- COPD diagnosis as defined by the study physician
- Currently on one of the following maintenance therapies:
  - LAMA monotherapy
  - LABA monotherapy
  - ICS/LABA (FDC)
- Physician determination that patient is not controlled on current pharmacotherapy
- Adult patient 40 years of age or older at time of study enrollment
- Willingness and ability to understand and provide documented Informed Consent Form (ICF) and Health Insurance Portability and Accountability Act (HIPAA) Authorization Form prior to commencement of any study required assessments, either directly or through Legally Authorized Representative.

### 4.2.4 Participant Exclusion Criteria

Patients presenting with any of the following exclusion criteria will not be eligible for enrollment into the study:

- Currently on LAMA/LABA (free or FDC) or triple therapy (ICS plus LABA plus LAMA)
- Contraindication to any study medications (LAMA, LABA or ICS)
- Documented diagnosis of current asthma
- Pregnant or nursing women

Women of childbearing potential are not restricted in this trial, however it is expected that the investigator will assess the risks and benefits of the assigned treatment as per the product label(s) and discuss this with any women of childbearing potential prior to providing the patient with the prescription for the assigned treatment.

#### 4.2.5 Participant Enrollment

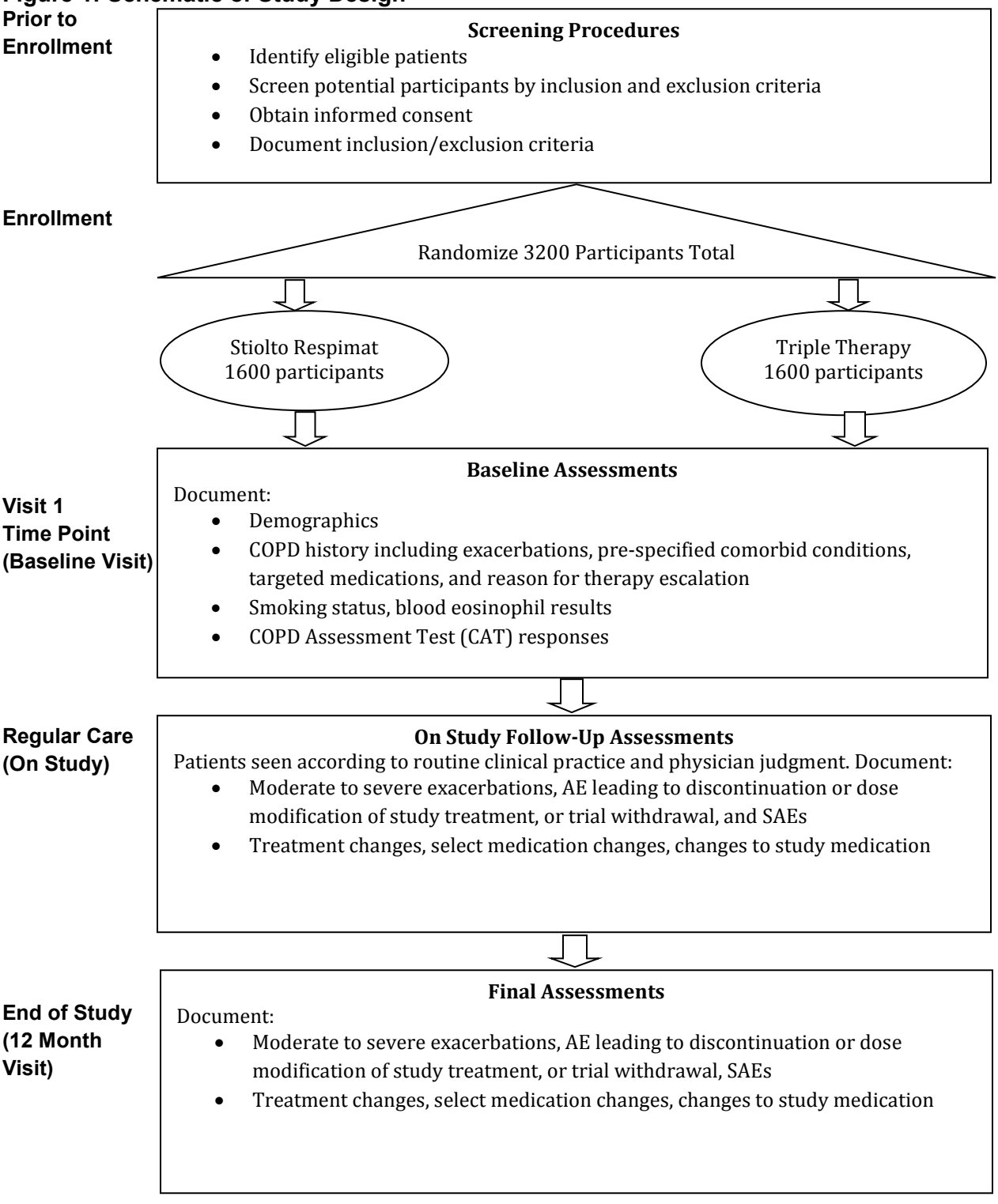
Anticipated enrollment for this study is approximately 3200 patients, with approximately 1600 patients enrolled in each group.

#### 4.2.6 Patient Randomization

Enrolled study patients will be randomized to either Stiolto Respimat or triple therapy in a 1:1 ratio. Once the study physician has determined patient eligibility and has enrolled them into the study in the Electronic Data Capture (EDC) system, the physician will receive the randomization assignment (Stiolto Respimat or triple therapy) for that patient.

Patient eligibility and randomization is depicted in the study schematic (Figure 1).

**Figure 1: Schematic of Study Design**




The only required study visits are Baseline and EOS at 12 months. Data will be collected at routine clinical visits and other patient contact in between Baseline and EOS if available per standard clinical practice. See Table 1 for additional detail.

# 5 STUDY PROCEDURES

## 5.1 Enrollment Procedures

Once potential physician sites have been identified, physicians who agree to participate in the study will be enrolled. Following Institutional Review Board (IRB) approval of a site and study training, sites will begin patient enrollment. The physician will make the decision regarding the patient's suitability for the study, and in order to maintain the real-world nature of the study, patients will be approached for potential enrollment into the study during routine office visits or other patient contact as part of their standard care.

## 5.2 Baseline Visit

Eligible patients interested in participating will provide written informed consent and be randomized to either Stiolto Respimat or triple therapy at their baseline visit. Data collection at baseline will include inclusion/exclusion criteria as well as the data outlined in the sections below. A blood sample will be drawn at the baseline visit for a complete blood count (CBC) including differential white cell count. In the event that a CBC is not available at baseline, laboratory results within 12 months of baseline will be accepted.

### 5.2.1 Participant Characteristics

Study physicians or trained site personnel will collect patient characteristics at each office visit as summarized in Table 1, either directly from the patient or abstracted from the patient's chart, and enter them into the electronic Case Report Form (eCRF). Baseline assessments will include demographic data, baseline clinical data (selected pre-specified comorbid conditions, CBC including a required baseline blood eosinophil count, and smoking status) as well as COPD and exacerbation history.

### 5.2.2 Treatments

Upon enrollment, patients will be randomized to receive either Stiolto Respimat or triple therapy. Treatment details will be recorded in the eCRF.

## 5.3 PROs

Symptomatology will be assessed at baseline via the COPD Assessment Test™ (CAT) to enable classification of patients by the 2017 GOLD A-D criteria in conjunction with exacerbation history data. Patients will complete the CAT and site study personnel will enter the completed forms into the eCRFs.

### 5.3.1 COPD Assessment Test ™ (CAT)

The CAT is a short (8-item), simple, patient-completed questionnaire that measures the impact of COPD on a patient's well-being and daily life.[9] Patients rate the following items on a 6-point (0-5) scale, where higher scores indicate worse symptoms: Cough, Phlegm, Chest Tightness, Breathlessness, Activities at Home, Confidence Leaving Home, Sleep and Energy. Scores from individual items are summed, yielding CAT scores ranging from 0-40, with higher scores indicating worse COPD-related health status.

The CAT instrument is attached in Appendix A.

## 5.4 Study Period

Patients will be followed from baseline to EOS at 12 months. [redacted] Patients will be followed for the full 12 months regardless of study treatment changes or discontinuation during the study period. Only if a patient withdraws consent will data collection be discontinued.

Consistent with the naturalistic design, this study does not have a rigid visit schedule. Patients will be followed for 12 months according to their treating physician's routine clinical practice and judgment. On-study data collection during routine clinical visits or other contacts with patient, such as by phone or e-mail, contact with another treating physician, or receipt of records, will include exacerbations, COPD targeted concomitant medications, changes to study treatment, adverse events (AEs) leading to study treatment discontinuation, dose modification, or trial withdrawal and any Serious Adverse Events (SAEs). It is anticipated that patients who are being treated for COPD will undergo medical evaluation at regular intervals; however, the only required study visits are baseline and EOS at 12 months.

The study is anticipated to take 36 months from commencement of enrollment through data analysis and reporting.

## 5.5 Final Visit/EOS

The EOS visit will be 12 months after baseline. Data collection at EOS will include exacerbations, COPD concomitant medications, changes to study treatment, AEs leading to study treatment discontinuation or dose modification, or trial withdrawal, and any SAEs. Post-study treatment is at the discretion of the physician.

The study visit schedule is summarized in Table 1.

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[9] Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34:648-654.

### 5.7 Withdrawals

#### 5.7.1 Physician Practices

Boehringer Ingelheim and/or the IRB reserve the right to terminate the study or participation of the study physicians at any time. In such cases, data collection will end. After the collected data is received, the participating study physicians will be compensated as contractually agreed.

#### 5.7.2 Participants

Discontinuation will be based upon physician clinical determination and/or by patient decision. Participation in this study is voluntary, and all patients are free to terminate their participation at any time. In the event of early termination of study participation, details regarding the discontinuation will be recorded. Patients will be followed for the full 12 months regardless of treatment changes or discontinuation during the study period. Only if a patient withdraws consent will data collection be discontinued. The study physician will record the reason for withdrawal and continue follow-up with the patient for any unresolved SAEs.

## 6 STATISTICAL METHODS

### 6.1 Analysis Overview

This is a randomized, open-label, parallel-group, non-inferiority design pragmatic study, with a fixed duration of 12 months. Patients are randomized to Stiolto Respimat or triple therapy. The primary endpoint is the time to first moderate or severe COPD exacerbation.

Null hypothesis for non-inferiority

The null hypothesis of this non-inferiority trial is that the hazard ratio (HR) of time to first moderate or severe COPD exacerbations in the Stiolto Respimat arm compared to the triple therapy arm is larger than 1.2. The non-inferiority margin of 20% was based on practical considerations and kept consistent with the margin used in the WISDOM study.[10]

H0: HR(Stiolto Respimat/Triple Therapy) >= 1.2

versus

H1: HR(Stiolto Respimat/Triple Therapy) < 1.2

This will be addressed by comparing the upper bound of the 95% two-sided confidence interval for the HR with the non-inferiority margin of 1.2.

## 6.2 Study Populations

The following populations will be defined for analysis and reporting.

### 6.2.1 Analysis Populations

#### *6.2.1.1 Intent to Treat (ITT) Population*

The ITT population will include all randomized patients allocated to their original randomized treatment group, even if they switched or discontinued study treatment.

#### *6.2.1.2 Per Protocol (PP) Population*

No per-protocol set is defined and no analysis is planned. A sensitivity analysis using on-treatment exacerbations is described in Section 6.4.

[redacted]

### 6.2.2 Safety Population

The safety population will include all randomized patients who received a prescription of any study treatment (Stiolto Respimat or triple therapy).

[10] Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD. N Engl J Med. 2014;317:1285-94.

## 6.3 Sample Size Determination

### 6.3.1 Power and Sample Size for Primary Objective

Table 2 presents several scenarios considered for sample size. The sample size for this study is 3200 patients, with 1600 in each treatment group. This sample size was calculated using Addplan 6.1 software based on a non-inferiority test for survival analysis (with Schoenfeld's formula for calculating the number of events), under the following assumptions:

- Expected HR of moderate or severe COPD exacerbations of 1.0 between Stiolto Respimat and triple therapy
- 20% non-inferiority margin, with HR boundary of 1.20
- 42.5% of patients in the triple therapy arm have at least one moderate or severe COPD exacerbation in 12 months
- 90% power
- One-sided Type I error rate of 0.025
- Randomization ratio 1:1 between treatment arms
- Fixed trial duration with 12 month follow up
- 15% drop-out rate during 12 months in both treatment arms

### 6.3.2 Randomization and Blinding

A [redacted] statistician independent from the study will create the randomization schedule to be loaded into the EDC system. Randomization will be validated by an independent statistician for the 3200 sample size plus 25% overrun. Patients will be randomized in equal ratio to the two treatment arms and blocked randomization will be used. The block size will be documented in the study report.

This is an open-label randomized phase 4 trial, which is designed and conducted as a pragmatic trial, i.e. as a study in a real-world setting with minimal inclusion/exclusion criteria and few study-specific visits and procedures. Blinding for this open-label pragmatic trial is not feasible; however selection bias will be eliminated via concealed treatment allocation through the EDC system. The database for this pragmatic trial will not be blinded.

### 6.3.3 Interim Analysis

There is no interim analysis planned for this trial.

## 6.4 Effectiveness Analysis

The effectiveness analysis will address the primary objective of this study: to determine whether Stiolto Respimat is non-inferior to triple therapy as measured by time to first moderate or severe exacerbation. For the primary endpoint, COPD exacerbation defined as moderate or severe as collected in the eCRF will be used.

The primary analysis for the primary endpoint will be performed using the ITT population. Patients will be analyzed using the treatment arm to which they are randomized to, even if they switched or discontinued study treatment. Patients will be censored at the time of last contact or death, if they did not experience a moderate or severe COPD exacerbation before. The exacerbation data from eCRF will be used for the primary analysis.

For the primary endpoint, i.e. time to first moderate or severe COPD exacerbation, the Cox proportional hazards model with baseline ICS prior use as a covariate will be used to estimate the HR and the two-sided 95% Wald confidence interval.

[redacted]

The primary endpoint will also be analyzed for moderate or severe COPD exacerbations from different data sources: (1) claims data only and (2) integrated eCRF/claims data.

The details of all analyses will be fully described in the Statistical Analysis Plan (SAP).

### 6.5 Patient Reported Outcome (PRO) Analysis

The impact of COPD on patients' health and quality of life will be assessed at baseline via the CAT. PRO analysis will be descriptive in nature and will not involve any statistical testing. Rather, summary statistics will be used to describe patient perceived health status impairment associated with COPD at baseline, as well as potentially as an explanatory variable in any multivariate analyses or in subgroup analyses.

### 6.6 Safety Analysis

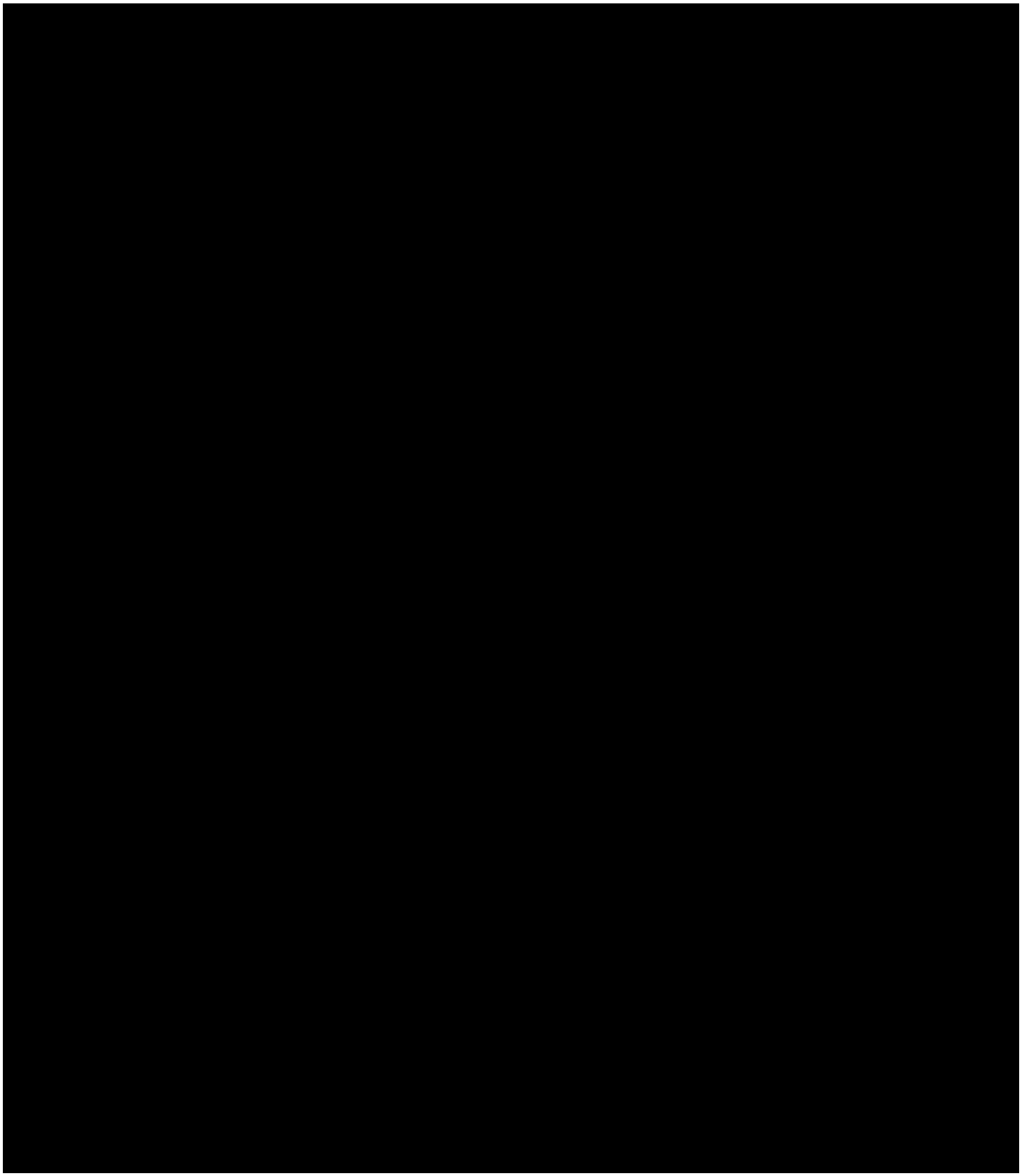
Collection of AEs in the study eCRF will be limited to AEs leading to study treatment discontinuation or dose modification, or trial withdrawal. All SAEs will be reported by the investigator via a dedicated SAE report form directly to Boehringer Ingelheim Global Pharmacovigilance as described in section 7.2. As hospitalization SAEs are reflected in claims records, a patient-level review comparing hospitalization claims entries with reported SAEs for each respective patient will take place after completion of the 12-month visit in order to identify any hospitalizations of which the investigator was potentially unaware. The investigator will receive information of any SAE identified through this process and report it using the standard SAE reporting process (See section 7.2).

SAE data for analysis will be drawn from the Boehringer Ingelheim Safety Database.

Analysis of non-serious AEs (leading to study treatment discontinuation or dose modification, or trial withdrawal) will be performed on the study database, as these are entered in the eCRF only.

Safety analyses will be descriptive in nature. No hypothesis testing is planned prospectively.

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary at the time of reporting, and recoded to the MedDRA version current at the time of database integration. Summary tables and listings will be produced to compare the incidence of AEs across treatment groups, by Preferred Term (PT)/System Organ Class (SOC) and also by medical concept (MedDRA Standardized Medical Queries (SMQ) or custom Boehringer Ingelheim searches termed Pharmacovigilance (PV) endpoints). All AEs with an onset after the first dose of trial medication and up to 21 days after the last dose of trial medication will be assigned to the on-treatment period. Other AEs will be assigned either to the screening period, post-treatment period or the post-study period as appropriate.



[redacted]

### 6.8 Missing Data

Missing data for exacerbation endpoints will not be imputed.

## 7 AE REPORTING

The study physician is responsible for monitoring the safety of participating patients. All SAEs reported by the patients during the study period are required to be documented on the appropriate SAE reporting form. Selected AEs, e.g. AEs leading to study treatment discontinuation, dose modification, or trial withdrawal, will also be collected on the eCRF during the study. SAEs identified in patient-level review of hospitalization data extracted from claims will be notified to the investigators and then reported by these on the SAE reporting form (cf. section 6.6).

### 7.1 AEs

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Only selected non-serious AEs will be collected in eCRF: events leading to study treatment discontinuation, dose modification, or trial withdrawal.

Causal relationship of AEs

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug.
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced.
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of **dose-response** (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

### 7.2 SAEs

A SAE is defined as any AE which fulfils at least one of the following criteria:

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalization, or
- Requires prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity, or
- Is a congenital anomaly or birth defect, or
- Is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

**AEs considered "Always Serious"**

In accordance with the European Medicines Agency (EMA) initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above. The investigators will be notified of any AE that is entered in the eCRF that meets criteria as an Important Medical Event per Always Serious List. The investigator will promptly complete the SAE form with all available information about the AE(s) and report to the sponsor's unique entry point as described in the Investigator Site File (ISF) immediately (within 24 hours).

All SAEs will be reported via Boehringer Ingelheim SAE reporting forms to the Global Pharmacovigilance Database. If patient-level review of claims versus site entries reveals any hospitalization SAE in claims not already captured by the investigator, the investigator will be contacted providing information and asking for completion of an SAE form with those details known to him/her.

#### 7.2.1 Reporting Period of SAEs

AEs and SAEs will be reported from the time a patient signs consent until the final visit at 12 months or until the patient discontinues the trial. After the patient completes or discontinues the trial, the investigator does not need to actively monitor the patient for AEs but should only report related SAEs of which the investigator may become aware of by any means of contact with the patient, e.g. phone call.

SAE reporting procedure will follow usual Boehringer Ingelheim forms and processes and will be further described in the ISF. The investigator must report SAEs on a Boehringer Ingelheim SAE form via the fax form immediately (within 24 hours of investigator's awareness of the

event) as described in the ISF. The same timeline applies if follow up information becomes available.

Healthcare Claims Database SAE reporting process

If patient level review of claims database versus site entries at'12+3 month mark' (3 months after the 12 month follow-up visit) reveals any hospitalization in claims database that is not already captured by the investigator as an SAE, the investigator will be contacted with this information. The investigator will promptly complete the SAE form with all available information about the patient's hospitalization and report to the sponsor's unique entry point as described in the ISF immediately (within 24 hours).

Information required

For each AE, the Investigator should provide the information requested on the appropriate eCRF pages (if applicable) and Boehringer Ingelheim SAE Report form. The Investigator should determine the causal relationship to the trial medication.

The following should also be recorded as S(AE) in the eCRF and SAE form (if applicable):

- Worsening of pre-existing conditions,
- Changes in vital signs, electrocardiograms (ECGs), physical examinations, and laboratory test results, if they are judged clinically relevant by the Investigator.

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions.

### 7.3 Pregnancy

Once a female subject has been enrolled into the trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day, whichever is shorter, of the pregnancy becoming known to the investigator) to the defined unique entry point for SAE forms by means of Pregnancy Monitoring Form A (pregnancy monitoring forms and contact details will be provided in the ISF).

The outcome of the pregnancy associated with the drug exposure must be followed up and reported by means of Pregnancy Monitoring Form B.

In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed.

## 8 DATA COLLECTION

### 8.1 Data Sources

Data sources include demographic and clinical data collected prospectively by study sites, patient-completed PRO data and administrative claims data from patients on [redacted] health

plans ([redacted] and targeted non-[redacted] health plans. In order to maintain patient confidentiality, each patient will be assigned a unique patient study ID upon enrollment to use in place of patient name or any other identifying information (e.g., medical record number). Clinical study data, PROs and claims-derived variables will be integrated into one analysis dataset via this confidential patient ID.

The study physician has the ultimate responsibility for the collection and reporting of all clinical and patient data through the eCRFs as well as ensuring that they are accurate and complete.

### 8.2 eCRFs/EDC

All clinical study data will be collected at the physician office and entered into eCRF by trained site study personnel through a fully validated, 21 CFR 11 and HIPAA compliant EDC system. Patients will complete PRO questionnaires (i.e., CAT) by paper and pen and the site study personnel will enter the completed forms into the EDC system.

All study personnel involved in data entry will be trained on patient confidentiality and the EDC system prior to beginning data entry. Site users will be provided eCRF Completion Guidelines (eCCGs) to assist with study data collection and entry. Study personnel will access the EDC system through a secure study website.

### 8.3 Database Development

All prospectively collected study data will reside in a 21 CFR 11 and HIPAA compliant secure database, developed and managed by [redacted] EDC vendor. Patient-level study data will be downloaded from the EDC system to secure [redacted] servers for linkage to claims derived variables via a unique patient ID.

A Clinical Data Manager (CDM) will manage the study database and act as the system administrator, creating and maintaining users and database access privileges. Standard user-type privileges will be configured and implemented to ensure privacy and security compliance policy requirements. Patient confidentiality will be strictly maintained.

A Data Management Plan (DMP) will be developed at the beginning of the study to describe all functions, processes and specifications for collection, cleaning and validation of study data from study start up to database lock.

### 8.4 Data Quality Assurance

The DMP will describe structures, processes, policies and procedures employed to ascertain the quality of the data and to ensure against errors in data entry, transfer or transformation accuracy throughout the study. Data quality oversight will involve a multi-tiered process that includes electronic edit check specifications, manual checks, self-evident corrections, listing reviews and electronic data transfer agreement summaries. Electronic edit checks will be programmed to show discrepancies online at the time of data entry, giving the operator the option to confirm acceptance of the discrepant data or change the data. Manual review and listing reviews will be run as outlined in the DMP, either at predetermined intervals or as necessary. The CDM will

open queries to resolve any discrepancies either within the database or directly with study personnel. All changes to existing data will be fully tracked, maintaining an audit trail report of every transaction.

# 9 STUDY MANAGEMENT

## 9.1 Regulatory and Ethical Consideration

All study activities will be conducted in accordance with regulatory guidelines for real-world, pragmatic research. Study personnel at physician sites will be provided training on the study protocol, the ICF, data collection and data entry to ensure both the protection of potential study patients as well as the scientific integrity of the study. A hybrid approach of both remote and onsite monitoring will be employed.

### 9.1.1 IRB/Independent Ethics Committee (IEC)

The study physician will have prospective approval of the study protocol, ICF and any patient information or recruiting materials, if applicable, prior to commencement of any study activities. In the case of a protocol amendment, the study physician must sign the revised protocol and submit the amendment to the IRB/IEC for review and approval prior to implementation of any changes specified in the protocol amendment. All changes in research activity and all unanticipated problems involving risk to human patients or others must be reported promptly to the IRB/IEC.

The study physician will obtain continued review of the study at intervals not to exceed one year or otherwise specified by the IRB/IEC.

### 9.1.2 Informed Consent

An ICF fully describing the purpose, procedures and potential risks and benefits of the study will be developed and approved by the IRB/IEC prior to study initiation. The study physician must ensure that each study patient is fully informed of the study and authorizes release of health information prior to study enrollment. The study physician, or study personnel designated by the study physician, will obtain written informed consent from each patient prior to initiation of any study-related procedures. Each patient will be given a copy of the signed ICF. The study physician will retain the original signed ICF for each patient.

The IRB/IEC must prospectively approve the ICF and any changes to the ICF during the course of the study before use. If a protocol amendment alters the study design or increases the potential risk to the patient, the ICF must be revised and submitted to the IRB/IEC for review and approval prior to implementation. The revised ICF must then be used to obtain consent from new patients entering the study. The revised ICF must also be used to obtain consent from currently enrolled patients if they are affected by the amendment.

### 9.2 Dropouts

Patient participation is strictly voluntary and patients may refuse to participate or withdraw from the study at any time and for any reason. As such, patients may voluntarily withdraw prior to completing the final visit. In such cases, the study physician will document the specific reason for the incomplete information (e.g., withdrawal of consent, lost to follow-up) on the eCRF. The physician should continue follow-up with the patient for any unresolved SAEs.

### 9.3 Record Retention and Access

This study may be subject to audits or evaluations by regulatory authorities or Boehringer Ingelheim (or its designee). To enable such evaluations and/or audits, the study physician must agree to maintain and allow reasonable access to required patient and study records. The study physician agrees to keep the identity of all participating patients (sufficient information to link records, e.g., hospital records), all original signed ICFs, SAE Forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls, reports). The study physician should retain records according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

## 10 PUBLICATION OF STUDY RESULTS

All information related to this study is considered confidential information belonging to Boehringer Ingelheim and [redacted] A final study report will be generated following completion of data collection and analysis. Results and findings will be submitted to conferences and for publication in peer-reviewed scientific journals.

**Table 1: Time and Events Schedule**

| | *Study Visits* | | |
|---|---|---|---|
| **Assessment or Procedure** | **Baseline** | **On Study Follow-Up**[1] | **EOS 12 Months** |
| Written Informed Consent | X | | |
| Eligibility Criteria | X | | |
| Randomization | X | | |
| Demographics | X | | |
| Selected pre-specified comorbid conditions | X | | |
| CBC (Baseline Blood Eosinophil Count Required)[2] | X | | |
| Smoking Status | X | | |
| COPD Diagnosis Date | X | | |
| COPD Exacerbation History (number and severity of exacerbations in last year) | X | | |
| Pre-Study COPD Therapy | X | | |
| Reason for therapy escalation | X | | |
| COPD Concomitant Medications | X | X | X |
| CAT™ | X | | |
| Study Treatment | X | X | X |
| COPD Exacerbations | | X | X |
| Selected AEs[3] | | X | X |
| SAEs[3] | | X | X |

[1]The only required study visits are Baseline and EOS. Data will be collected at routine clinical visits and other patient contact in between Baseline and EOS if available per standard clinical practice.

[2]In the event that a CBC is not available at baseline, laboratory results within 12 months of baseline will be accepted.

[3]All SAEs and selected AEs will be collected from Baseline through EOS or early termination of study participation. Selected AEs are AEs leading to study treatment discontinuation, dose modification or trial withdrawal.

**Table 2: Sample size calculations (with number of events) under different assumptions for p1, HR and power, 20% non-inferiority margin, one-sided alpha 0.025 and 15% drop-out rate during 12 months.**

| Scenario | P1 (proportion of patients with >=1 moderate /severe COPD exacerbation during 12 months in Triple Therapy arm) | P2 (proportion of patients with >=1 moderate/ severe COPD exacerbation during 12 months in Stiolto arm) | Expected HR of moderate/ severe COPD exacerbations between Stiolto and Triple Therapy | Power | Number of events (moderate/ severe COPD exacerbations) | Sample size (total) |
|---|---|---|---|---|---|---|
| 1 | 40% | 39.07% | 0.97 | 95% | 1147 | 3120 |
| **2** | **42.5%** | **42.5%** | **1** | **90%** | **1264** | **3200** |
| 3 | 45% | 46% | 1.03 | 80% | 1358 | 3204 |

These sample size calculations were completed using Addplan 6.1 software based on a non-inferiority test for survival analysis.

## APPENDIX A: COPD Assessment Test™ (CAT)

Your name:

Today's date:

CAT
COPD Assessment Test

### How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

**Example:** I am very happy 0 X 2 3 4 5 I am very sad

| | | | SCORE |
|---|---|---|---|
| I never cough | 0 1 2 3 4 5 | I cough all the time | |
| I have no phlegm (mucus) in my chest at all | 0 1 2 3 4 5 | My chest is completely full of phlegm (mucus) | |
| My chest does not feel tight at all | 0 1 2 3 4 5 | My chest feels very tight | |
| When I walk up a hill or one flight of stairs I am not breathless | 0 1 2 3 4 5 | When I walk up a hill or one flight of stairs I am very breathless | |
| I am not limited doing any activities at home | 0 1 2 3 4 5 | I am very limited doing activities at home | |
| I am confident leaving my home despite my lung condition | 0 1 2 3 4 5 | I am not at all confident leaving my home because of my lung condition | |
| I sleep soundly | 0 1 2 3 4 5 | I don't sleep soundly because of my lung condition | |
| I have lots of energy | 0 1 2 3 4 5 | I have no energy at all | |
| | | TOTAL SCORE | |

**Summary of Amendments and Updates**

**Summary of Changes**
**1237-0064 Protocol Version 2.0, dated 09May2018**

| Number | Section/Page | Change | Rationale |
|---|---|---|---|
| 1 | Global Change | May 9, 2018~~June 7, 2017~~<br><br>Version ~~1~~2.0 | Updated protocol date and version. |
| 2 | Study Approvals, page 2 | **Sponsor Approval:**<br><br>**Name:** [redacted]<br>**Title:** [redacted] of Clinical Development & Medical Affairs, Primary Care - Respiratory~~COPD & Asthma~~<br>[redacted] | Updated sponsor Principal Investigator for study approval signature. |
| 3 | Synopsis Study Procedures, page 9 | • A complete blood count (CBC) including differential white cell count will be drawn at baseline. In the event that a CBC is not available at baseline, laboratory results within 12 months of baseline will be accepted. | Added language to relax the timing required for a baseline CBC. This change increases the flexibility of study requirements and is consistent with the pragmatic design. |
| 4 | Section 4 Study Design<br>4.2.2 Participant Recruitment and Eligibility, page 17-18 | ~~To maintain the real-world nature of the study, patients will be recruited for enrollment when they interact with their physician as part of their standard care.~~ | Removed sentence to allow additional patient outreach at study sites to increase study enrollment. |
| 5 | Section 4 Study Design | ~~To enhance enrollment at trial initiation, up to 500 non-~~[redacted] | Deleted sentences to remove any restriction from |

| | | | |
|---|---|---|---|
| | 4.2.2 Participant Recruitment and Eligibility, page 18 | ~~patients will be allowed to enroll, following which enrollment will be restricted to~~ [redacted] ~~patients only if possible. In such event that additional non-~~ [redacted] ~~patients are needed to complete enrollment, the decision to re-open enrollment to non-~~ [redacted] ~~patients will be made jointly between~~ [redacted] ~~and Boehringer Ingelheim.~~ | enrollment of non-[redacted] patients to increase study enrollment. |
| 6 | Figure 1: Schematic of Study Design, page 20 | • Identify ~~E~~eligible patients ~~interacts with physician in course of normal care~~ | Modified sentence to allow additional patient outreach at study sites to increase study enrollment, consistent with change #4 in 4.2.2 above |
| 7 | Section 5 Study Procedures<br>5.2 Baseline Visit, page 21 | A blood sample will be drawn at the baseline visit for a complete blood count (CBC) including differential white cell count. In the event that a CBC is not available at baseline, laboratory results within 12 months of baseline will be accepted. | Added language to relax the timing required for a baseline CBC. This change increases the flexibility of study requirements and is consistent with the pragmatic design. |
| 8 | Table 1: Time and Events Schedule, page 36 | CBC (Baseline Blood Eosinophil Count Required)[2]<br><br>[2]In the event that a CBC is not available at baseline, laboratory results within 12 months of baseline will be accepted. | Added footnote to relax the timing required for a baseline CBC. This change increases the flexibility of study requirements and is consistent with the pragmatic design, and consistent with changes #3 and #7 in Study Procedures above. |
| 9 | Table 1: Time and Events Schedule, page 36 | Selected AEs[23]<br>SAEs[23]<br><br>[23]All SAEs and selected AEs will be collected from Baseline through EOS or early termination of study | Updated footnote numbering to accommodate addition of footnote in change #8. |

| | | | |
|---|---|---|---|
| | | participation. Selected AEs are AEs leading to study treatment discontinuation, dose modification or trial withdrawal. | |

**APPROVAL / SIGNATURE PAGE**

**Document Number: c23740530** **Technical Version Number:1.0**

**Document Name:** clinical-trial-protocol-version-2

**Title:** Randomized Pragmatic Clinical in Trial in a Community-Based Setting Comparing STIOLTO RESPIMAT vs. ICS-LABA plus LAMA in Patients with COPD The AIRWISE Study: Assessment In a Real World setting of the effect of Inhaled Steroid based triple therapy versus the combination of tiotropium and olodaterol on reducing COPD Exacerbations

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Author-Clinical Monitor | [redacted] | 08 Jun 2018 12:41 CEST |

**(Continued) Signatures (obtained electronically)**

| **Meaning of Signature** | **Signed by** | **Date Signed** |
|---|---|---|