Non-Interventional Study (NIS) Protocol

Document Number:	c38026921-01
BI Study Number:	1237-0121
BI Investigational Product(s):	Tiotropium bromide + Olodaterol
Title:	Comparison of Exacerbation Risk and Health Outcomes in Maintenance Treatment Naïve COPD patients using Stiolto vs. Trelegy.
Brief lay title:	Outcomes in COPD patients using Stiolto Respimat vs. Trelegy Ellipta.
Protocol version identifier:	1.0
Date of last version of protocol:	10/25/2021
PASS:	No
EU PAS register number:	Study not registered
Active substance:	Tiotropium and Olodaterol
Medicinal product:	Stiolto® Respimat®
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorization holder(s):	Not applicable
Joint PASS:	No
Research question and objectives:	***Primary objective:*** • To characterize the COPD patient population who are maintenance treatment naïve and initiated Trelegy or Stiolto as the first line therapy.

	• To compare the effectiveness of Stiolto (new treatment initiation) with Trelegy (new treatment initiation) for time to the first COPD exacerbation (moderate/severe) in COPD patients who are maintenance treatment naïve. • To compare COPD exacerbations following initiation of Stiolto (new treatment initiation) with initiation of Trelegy (new treatment initiation) ***Secondary objectives:*** • To compare the effectiveness of Stiolto (new treatment initiation) with Trelegy (new treatment initiation) for time to the first hospitalization of community acquired pneumonia in COPD patients who are maintenance treatment naïve. • To assess differences between Stiolto vs Trelegy in, "all-cause" and "COPD and/or pneumonia-related", HCRU and HCRU cost (total population and sub-groups by care setting).
Country(-ies) of study:	United States
Author:	[redacted] Address: [redacted] Tel.: + [redacted]
Marketing authorisation holder(s):	[redacted] Address: [redacted] Tel.: + [redacted]
In case of PASS, add: **MAH contact person:**	Not applicable as it is not a PASS study
In case of PASS, add: **<EU-QPPV:>**	Not applicable as it is not a PASS study
In case of PASS, add: **<Signature of EU-QPPV:>**	Not applicable as it is not a PASS study
Date:	10/25/2021

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2. LIST OF ABBREVIATIONS

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

3. RESPONSIBLE PARTIES

NIS[redacted]:

Address:
Tel.: +

BI Team

Address:
Tel.: +

[redacted] Team: [redacted] and [redacted]

External Scientific Experts: [redacted] and [redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Stiolto/Spiolto			
Name of active ingredient: Tiotropium bromide + Olodaterol			
Protocol date: *25 October 2021*	**Study number:** 1237.0121	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Title of study:	Comparison of Exacerbation Risk and Health Outcomes in Maintenance Treatment Naïve COPD patients using Stiolto vs. Trelegy.		
Rationale and background:	Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality throughout the world.[1] COPD has risen to become the third leading cause of death in the United States (US). [2,3] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 report and the American Thoracic Society 2020 report recommends dual bronchodilator therapy (DBT) with long-acting muscarinic antagonists (LAMAs) plus long-acting beta2-agonists (LABAs) for patients with COPD who have persistent symptoms and/or exacerbations on LAMA or LABA monotherapy. [4,5] Consideration of escalation to triple therapy (TT; LAMA+LABA+inhaled corticosteroids [ICS]) is recommended in case of further exacerbation (≥2 moderate exacerbations or 1 severe exacerbation) and after assessing the risks/benefits. An important consideration is the trade-off between preventing exacerbations and the increased risk of pneumonia associated with addition of ICSs. [6] There are recommendations to restrict TT use further, to only patients who are likely to respond to ICS (such as ≥2 moderate exacerbations or 1 severe exacerbation in the previous year, to those with asthma-COPD overlap or elevated blood eosinophils. [7]		

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Rationale and background:	Several trials compared a single-inhaler fixed dose combination (FDC) TT with an open combination of TT (ICS/LABA plus LAMA) respectively and found a small degree of greater benefit with FDC TT. [8] Several Randomized Controlled Trials (RCTs) assessing the comparison of DBT LAMA-LABA to TT FDC of LAMA-LABA-ICS inhalers reported fewer exacerbations over one year with TT FDC. [9,10,11] However, these findings are complicated by methodologic issues related to the withdrawal of maintenance treatment at randomization, inclusion of patients with history of asthma and around at least 40% -70% utilizing ICS before entering the clinical trials. [12, 13,14] TT is associated with 53% greater risk of pneumonia compared to DBT and is frequently used inappropriately, including overuse in certain COPD patients. [15,16,17,18,19] Approximately 13% - 15% of maintenance treatment naïve patients are prescribed FDC TT as first line long-acting maintenance medication (Data on File) contradicting guideline recommendations and irrespective of the safety concerns. We believe a major reason of that practice pattern is just out of convenience as FDC TT are now available in the market. and certain pharmaceutical companies are encouraging early prescribing of triple therapy, including amongst primary care physicians. Any deviation in pharmacological management, particularly maintenance treatment initiation of COPD patients that is different from GOLD 2020 or ATS 2020 strategy document for the management of COPD may have both clinical and economic consequences. [20]		

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Rationale and background:	Given the high-cost side effect associated with long-term use of ICS and inconsistent evidence concerning whether there is a clinically relevant benefit of ICS combination therapy in terms of COPD disease control, it is important to assess differences between subsets of COPD patients in terms of the effectiveness and cost of FDC TT versus other non-ICS options, such as FDC DBT (e.g., Tiotropium+Olodaterol). In view of all the above findings which represent a limited view of the patients who could potentially use these FDC TT treatments we intend to conduct an observational study in a real-world clinical practice setting. There is a clear unmet need for better evidence on specific patient populations upon which to base FDC TT treatment recommendations. We propose to assess the effectiveness of Trelegy Ellipta, a FDC TT and compare it with Stiolto, a FDC DBT in patients who are maintenance treatment naïve and measure the incidence of COPD exacerbation, the incidence of community acquired pneumonia, health care resource utilization (HCRU) and associated HCRU costs. Trelegy Ellipta is a FDC of TT (Fluticasone Furoate + Umeclidinium + Vilanterol, 100/62.5/25 mcg) approved by the FDA in September 2017 for once-daily, maintenance treatment of COPD. Stiolto Respimat is a FDC of DBT (tiotropium bromide + olodaterol, 5/5 mcg), approved by FDA in May 2015 for once-daily, maintenance treatment of COPD).		

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Research question and objectives:	The goal of this study is to investigate the risk of COPD exacerbations, community acquired pneumonia, and health care utilization in maintenance treatment naïve patients treated as first line therapy with Fixed Dose Combination (FDC) of Tiotropium + Olodaterol (Stiolto, 5/5 mcg), in comparison to maintenance treatment naïve patients treated with first line therapy, FDC of Fluticasone Furoate + Umeclidinium + Vilanterol (Trelegy, 100/62.5/25 mcg). Primary objective: ▪ To characterize the COPD patient population who are maintenance treatment naïve and initiated Trelegy or Stiolto as the first line therapy. ▪ To compare the effectiveness of Stiolto (new treatment initiation) with Trelegy (new treatment initiation) for time to the first COPD exacerbation (moderate/severe) in COPD patients who are maintenance treatment naïve. ▪ To compare COPD exacerbations following initiation of Stiolto (new treatment initiation) with initiation of Trelegy (new treatment initiation) Secondary objectives: ▪ To compare the effectiveness of Stiolto (new treatment initiation) with Trelegy (new treatment initiation) for time to the first hospitalization of community acquired pneumonia in COPD patients who are maintenance treatment naïve		

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Title of study:	Comparison of Exacerbation Risk and Health Outcomes in Maintenance Treatment Naïve COPD patients using Stiolto vs. Trelegy.		
Study design	This is a non-interventional study with existing data. It will be a retrospective, observational, non-interventional, new user design, real world study of Commercial Insurance and Medicare beneficiaries, using administrative claims data for the period of 15th September 2016 through 31st March 2020. Patients initiating Stiolto, or Trelegy will be identified using pharmacy claims ([redacted] database). The date of the first prescription claim (on or after 15th September 2017) will be defined as the index date. Patients will be required to have a diagnosis of COPD (ICD-9-CM: 491.xx, 492.xx, 496.xx; ICD-10-CM: J41-J44) on two separate medical claims. Patients 40 years or older will be included in the study. Patients will be required to have continuous enrolment for 12 months prior to the index date. Patients will be excluded if they show any use of COPD maintenance medications (ICS, LABA or LAMA in any combination), during the baseline period of six months pre-index date. This will satisfy the criteria for being considered as treatment naive. Patients with two separate medical claims with a diagnosis of asthma, lung cancer, interstitial lung disease, or cystic fibrosis during the study period will be excluded. Using propensity score matching (PSM) technique, we will develop matched cohorts of patients between Stiolto initiators and Trelegy initiators. We will conduct 1:1 matching using nearest neighbor matching approach. Exacerbation will be defined as a COPD hospitalization (severe exacerbation) or Emergency Department (ED) visit (severe exacerbation) with COPD, or use of approved respiratory antibiotics (e.g., Azithromycin) ± Oral CorticoSteroids (OCS) medications within ±7 days of the office/outpatient visit (moderate exacerbation) as the primary diagnosis. Multiple exacerbations occurring within 14 days of each other will be considered as a single exacerbation and will be per the higher severity.		

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Title of study:	Comparison of Exacerbation Risk and Health Outcomes in Maintenance Treatment Naïve COPD patients using Stiolto vs. Trelegy.		
Population:	Comparison of Exacerbation Risk and Health Outcomes in Maintenance Treatment Naïve COPD patients using Stiolto vs. Trelegy.*Inclusion Criteria:* 1. ≥40 years of age as of the year of the index date 2. At least one pharmacy claim for Stiolto Respimat or Trelegy Ellipta between 15 September 2017 and 31st March 2020. a. For Stiolto Respimat users, the first pharmacy claim of FDC of Tiotropium + Olodaterol (5/5 mcg) will be defined as the index date. b. For Trelegy Ellipta users, the first pharmacy claim of FDC of Fluticasone Furoate + Umeclidinium + Vilanterol (100/62.5/25 mcg), will be defined as the index date. 3. Two medical claims (at least one claim on index date or before in the baseline period) with an ICD-9/10 diagnosis code(s) for COPD in any position during the study period (baseline ± post index date). 4. At least one year of continuous medical and pharmacy health plan eligibility prior to the index date is required (to allow a baseline period for the covariates and characterizing the study population).		

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Population:	*Exclusion Criteria:* 1. To increase the likelihood of a true diagnosis of COPD, we will exclude all patients with two medical claims of asthma, cystic fibrosis, lung cancer, or interstitial lung disease in any position on separate dates of service during the study period. 2. To restrict the cohort to first line maintenance therapy of Stiolto Respimat or first line maintenance therapy of Trelegy Ellipta we will exclude; patients on LAMA. monotherapy; LABA monotherapy; ICS monotherapy; free or FDC of ICS+LABA, LAMA+LABA, ICS+LABA+LAMA therapy within six months prior to index date. 3. Pharmacy claims for multiple index medications on the index date. 4. Pharmacy claims for non-index COPD maintenance medications on the index date.		
Variables:	Moderate and Severe COPD exacerbation, Pneumonia (time to and counts), HCRU for COPD and Pneumonia; both related and attributable costs.		

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Title of study:	Comparison of Exacerbation Risk and Health Outcomes in Maintenance Treatment Naïve COPD patients using Stiolto vs. Trelegy.		
Data sources:	We will utilize medical and pharmacy claim records for COPD patients included in the [redacted] database (previously named [redacted] 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.		
Study size:	~3000 patients in each cohort are sufficient for ≥80% power of		
Data analysis:	Summary measures will include standard descriptive statistics (e.g., mean, standard deviation, median and range for continuous variables; counts and percentages for categorical variables).		
Milestones:	Data collection will begin in Nov 2021, interim results will be available in Dec 2021, data collection will end in Dec 2021, and the final report will be completed and be made available in Jan 2022.		

5. AMENDMENTS AND UPDATES

None

Number	Date	Section of study protocol	Amendment or update	Reason
1				
2				

6. MILESTONES

Milestone	Planned Date
Start of data collection	NOV 2021
End of data collection	DEC 2021
<Registration in the EU PAS register>	NOV 2021
Final report of study results:	FEB 2022

7. RATIONALE AND BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality throughout the world.[1] COPD has risen to become the third leading cause of death in the United States (US). [2,3] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 report and the American Thoracic Society 2020 report recommends dual bronchodilator therapy (DBT) with long-acting muscarinic antagonists (LAMAs) plus long-acting beta2-agonists (LABAs) for patients with COPD who have persistent symptoms and/or exacerbations on LAMA or LABA monotherapy. [4,5] Consideration of escalation to triple therapy (TT; LAMA+LABA+inhaled corticosteroids [ICS]) is recommended in case of further exacerbation (≥2 moderate exacerbations or 1 severe exacerbation) and after assessing the risks/benefits. An important consideration is the trade-off between preventing exacerbations and the increased risk of pneumonia associated with addition of ICSs. [6] There are recommendations to restrict TT use further, to only patients who are likely to respond to ICS (such as ≥2 moderate exacerbations or 1 severe exacerbation in the previous year, to those with asthma-COPD overlap or elevated blood eosinophils. [7]

Several trials compared a single-inhaler fixed dose combination (FDC) TT with an open combination of TT (ICS/LABA plus LAMA) respectively and found a small degree of greater benefit with FDC TT. [8] Several Randomized Controlled Trials (RCTs) assessing the comparison of DBT LAMA-LABA to TT FDC of LAMA-LABA-ICS inhalers reported fewer exacerbations over one year with TT FDC. [9,10,11] However, these findings are complicated by methodologic issues related to the withdrawal of maintenance treatment at randomization, inclusion of patients with history of asthma and around at least 40% -70% utilizing ICS before entering the clinical trials. [12,13,14] TT is associated with 53% greater risk of pneumonia compared to DBT and is frequently used inappropriately, including overuse in certain COPD patients. [15,16,17,18,19] Approximately 13% -15% of maintenance treatment naïve patients are prescribed FDC TT as first line long-acting maintenance medication (Data on File) contradicting guideline recommendations and irrespective of the safety concerns. We believe a major reason of that practice pattern is just out of convenience as FDC TT are now available in the market. and certain pharmaceutical companies are encouraging early prescribing of triple therapy, including amongst primary care physicians. Any deviation in pharmacological management, particularly maintenance treatment initiation of COPD patients that is different from GOLD 2020 or ATS 2020 strategy document for the management of COPD may have both clinical and economic consequences.[20]

Given the high-cost side effect associated with long-term use of ICS and inconsistent evidence concerning whether there is a clinically relevant benefit of ICS combination therapy in terms of COPD disease control, it is important to assess differences between subsets of COPD patients in terms of the effectiveness and cost of FDC TT versus other non-ICS options, such as FDC DBT (e.g., Tiotropium+Olodaterol).

In view of all the above findings which represent a limited view of the patients who could potentially use these FDC TT treatments we intend to conduct an observational study in a real-world clinical practice setting. There is a clear unmet need for better evidence on specific patient populations upon which to base FDC TT treatment recommendations. We propose to assess the effectiveness of Trelegy Ellipta, a FDC TT and compare it with Stiolto, a FDC DBT in patients who are maintenance treatment naïve and measure the incidence of COPD exacerbation, the incidence of community acquired pneumonia, health care resource utilization (HCRU) and associated HCRU costs.

Trelegy Ellipta is a FDC of TT (Fluticasone Furoate + Umeclidinium + Vilanterol, 100/62.5/25 mcg) approved by the FDA in September 2017 for once-daily, maintenance treatment of COPD. Stiolto Respimat is a FDC of DBT (tiotropium bromide + olodaterol, 5/5 mcg), approved by FDA in May 2015 for once-daily, maintenance treatment of COPD).

8. RESEARCH QUESTION AND OBJECTIVES

The goal of this study is to investigate the risk of COPD exacerbations, community acquired pneumonia, and health care utilization in maintenance treatment naïve patients treated as first line therapy with Fixed Dose Combination (FDC) of Tiotropium + Olodaterol (Stiolto, 5/5 mcg), in comparison to maintenance treatment naïve patients treated with first line therapy, FDC of Fluticasone Furoate + Umeclidinium + Vilanterol (Trelegy, 100/62.5/25 mcg). Primary and Secondary analyses will be conducted for the total population and [redacted]

Primary objective:

- To characterize the COPD patient population who are maintenance treatment naïve and initiated Trelegy or Stiolto as the first line therapy.

- To compare the effectiveness of Stiolto (new treatment initiation) with Trelegy (new treatment initiation) for time to the first COPD exacerbation (moderate/severe) in COPD patients who are maintenance treatment naïve.

- To compare COPD exacerbations following initiation of Stiolto (new treatment initiation) with initiation of Trelegy (new treatment initiation)

Secondary objectives:

- To compare the effectiveness of Stiolto (new treatment initiation) with Trelegy (new treatment initiation) for time to the first hospitalization of community acquired pneumonia in COPD patients who are maintenance treatment naïve.

- To assess differences between Stiolto vs Trelegy in, “all-cause” and “COPD and/or pneumonia-related”, HCRU and HCRU cost (total population and sub-groups by care setting).

9. RESEARCH METHODS

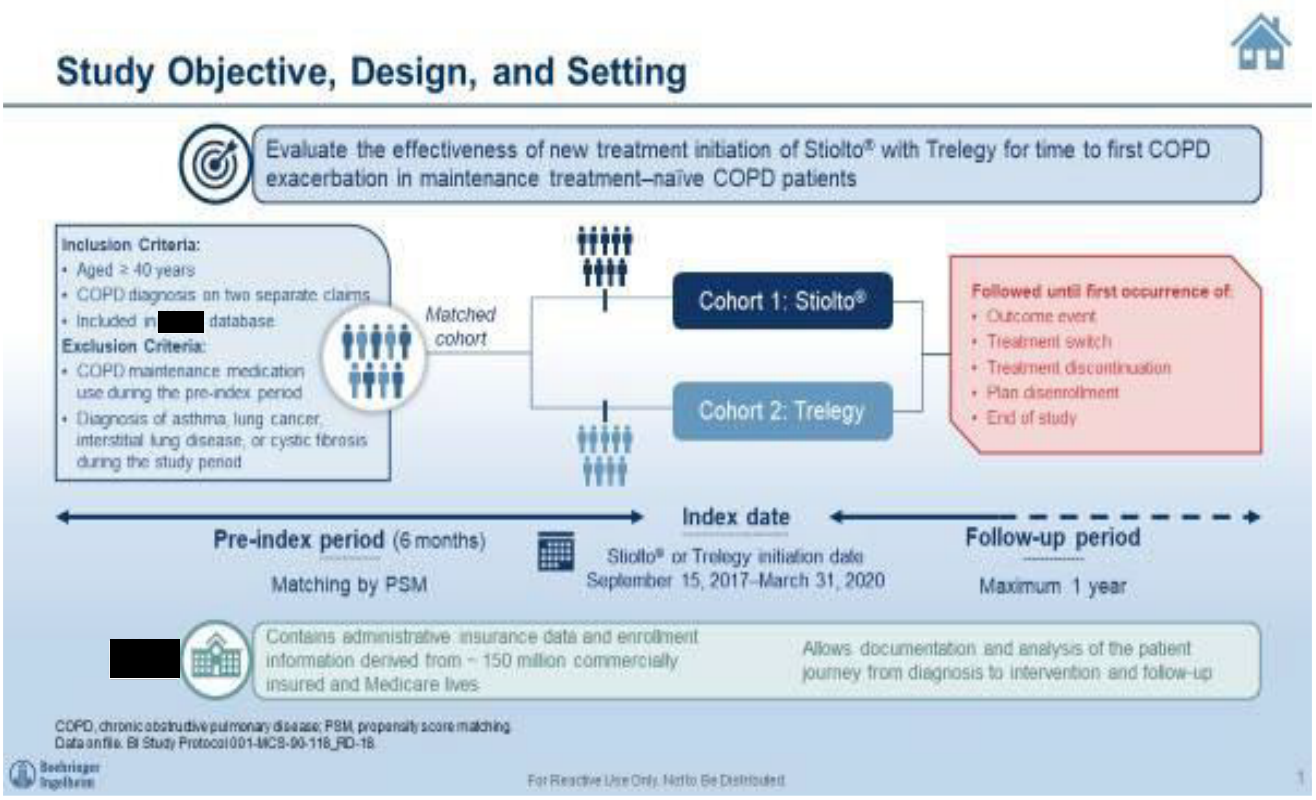
9.1 STUDY DESIGN

This is a non-interventional study with existing data. It will be a retrospective, observational, non-interventional, new user design, real world study of Commercial Insurance and Medicare beneficiaries, using administrative claims data for the period of 15th September 2016 through 31st March 2020.

Patients initiating Stiolto, or Trelegy will be identified using pharmacy claims [redacted] database). The date of the first prescription claim (on or after 15th September 2017) will be defined as the index date. Patients will be required to have a diagnosis of COPD (ICD-9-CM: 491.xx, 492.xx, 496.xx; ICD-10-CM: J41-J44) on two separate medical claims. Patients 40 years or older will be included in the study. Patients will be required to have continuous enrolment for 12 months prior to the index date. Patients will be excluded if they show any

use of COPD maintenance medications (ICS, LABA or LAMA in any combination), during the baseline period of six months pre-index date. This will satisfy the criteria for being considered as treatment naive. Patients with two separate medical claims with a diagnosis of asthma, lung cancer, interstitial lung disease, or cystic fibrosis during the study period will be excluded. Using propensity score matching (PSM) technique, we will develop matched cohorts of patients between Stiolto initiators and Trelegy initiators. We will conduct 1:1 matching using nearest neighbour matching approach with a caliper of 0.2. Exacerbation will be defined as a COPD hospitalization (severe exacerbation) or Emergency Department (ED) visit (severe exacerbation) with COPD, or use of approved respiratory antibiotics (e.g., Azithromycin) ± Oral CorticoSteroids (OCS) medications within ±7 days of the office/outpatient visit (moderate exacerbation) as the primary diagnosis. Multiple exacerbations occurring within 14 days of each other will be considered as a single exacerbation and will be per the higher severity. A schematic of the study design is presented below in Figure 1.

Figure 1 Study Design



Patients will be followed the index date to record time to first incidence of exacerbations, record time to first incident case of pneumonia, and HCRU. The analysis will be, "on treatment", analysis. Patients will be followed from the index date until the earliest of the first occurrence of outcome event, switch in index treatment (Stiolto or Trelegy), discontinuation of index treatment (Stiolto or Trelegy), the end of the study period, the end of continuous health plan eligibility, or (for main analyses) one year after index date. Hazard ratios and their 95% CI from proportional hazards models will be used to assess differences in the risk of COPD exacerbation and pneumonia. [redacted]

9.2 SETTING

We will utilize medical and pharmacy claim records for COPD patients included in the [redacted] database (previously named [redacted]). 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.

9.2.1 Study sites

There are no specific trial sites in this study. We will utilize medical and pharmacy claim records for COPD patients included in the [redacted] database (previously named [redacted] 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.

9.2.2 Study Population

Patients initiating Stiolto, or Trelegy will be identified using pharmacy claims ([redacted] database). The date of the first prescription claim (on or after 15th September 2017) will be defined as the index date. Patients will be required to have a diagnosis of COPD (ICD-9-CM: 491.xx, 492.xx, 496.xx; ICD-10-CM: J41-J44) on two separate medical claims. Patients 40 years or older will be included in the study. Patients will be required to have continuous enrolment for 12 months prior to the index date. Patients will be excluded if they show any use of COPD maintenance medications (ICS, LABA or LAMA in any combination), during the baseline period of six months pre-index date. This will satisfy the criteria for being considered as treatment naive. Patients with two separate medical claims with a diagnosis of asthma, lung cancer, interstitial lung disease, or cystic fibrosis during the study period will be excluded. Using propensity score matching (PSM) technique, we will develop matched cohorts of patients between Stiolto initiators and Trelegy initiators. We will conduct 1:1 matching using nearest neighbour matching approach with a caliper of 0.2. Exacerbation will be defined as a COPD hospitalization (severe exacerbation) or Emergency Department (ED) visit (severe exacerbation) with COPD, or use of approved respiratory antibiotics (e.g., Azithromycin) ± Oral CorticoSteroids (OCS) medications within ±7 days of the

office/outpatient visit (moderate exacerbation) as the primary diagnosis. Multiple exacerbations occurring within 14 days of each other will be considered as a single exacerbation and will be per the higher severity.

Patients will be followed after the index date to record time to first incidence of exacerbations, record time to first incident case of pneumonia, and HCRU. The analysis will be, "on treatment", analysis. Patients will be followed from the index date until the earliest of the first occurrence of outcome event, switch in index treatment (Stiolto or Trelegy), discontinuation of index treatment (Stiolto or Trelegy), the end of the study period, the end of continuous health plan eligibility, or (for main analyses) one year after index date. Hazard ratios and their 95% CI from proportional hazards models will be used to assess differences in the risk of COPD exacerbation and pneumonia. [redacted]

Inclusion Criteria:

- ≥40 years of age as of the year of the index date
- At least one pharmacy claim for Stiolto Respimat or Trelegy Ellipta between 15 September 2017 and 31st March 2020.
    - For Stiolto Respimat users, the first pharmacy claim of FDC of Tiotropium + Olodaterol (5/5 mcg) will be defined as the index date.
    - For Trelegy Ellipta users, the first pharmacy claim of FDC of Fluticasone Furoate + Umeclidinium + Vilanterol (100/62.5/25 mcg), will be defined as the index date.
- Two medical claims (at least one claim on index date or before in the baseline period) with an ICD-9/10 diagnosis code(s) for COPD in any position during the study period (baseline ± post index date).
- At least one year of continuous medical and pharmacy health plan eligibility prior to the index date is required (to allow a baseline period for the covariates and characterizing the study population).

Exclusion Criteria:

- To increase the likelihood of a true diagnosis of COPD, we will exclude all patients with two medical claims of asthma, cystic fibrosis, lung cancer, or interstitial lung disease in any position on separate dates of service during the study period.
- To restrict the cohort to first line maintenance therapy of Stiolto Respimat or first line maintenance therapy of Trelegy Ellipta we will exclude; patients on LAMA. monotherapy; LABA monotherapy; ICS monotherapy; free or FDC of ICS+LABA, LAMA+LABA, ICS+LABA+LAMA therapy within six months prior to index date.
- Pharmacy claims for multiple index medications on the index date.
- Pharmacy claims for non-index COPD maintenance medications on the index date.

9.2.3 Study Visits

9.2.4 Study Discontinuation

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

1. In the overall population, Stiolto initiators from September 2017 – March 2020 will be matched using Propensity Score Matching (PSM) with Trelegy initiators from September 2017 – March 2020 on a prespecified list of covariates listed in section 10.2.2. to ensure that the two cohorts are well balanced (i.e., standardized difference ≤10%) across all characteristics. However, for any baseline characteristics with significant differences (Standardized differences (SD) greater than 0.10 (10%)) after PSM matching, these characteristics will be included as covariates in the regression models, or we will develop interaction terms to match on or discontinue the study if major channeling (SD>10%) is observed.

2. Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a research collaborator, disturbing the appropriate conduct of the study

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

9.3 VARIABLES

The definitions for exacerbations are as below.

- A severe exacerbation will be defined as follows:
  - An inpatient admission or an ER visit with a COPD diagnosis code in the primary position; or
  - An inpatient admission or an ER visit with a diagnosis code for acute respiratory failure in the primary position and a COPD diagnosis code in any position; or
  - An inpatient admission or an ER visit with a diagnosis code for acute respiratory failure in the primary position + an inpatient admission or an ER visit within ±7 days with a COPD diagnosis code in any position.
- A moderate exacerbation will be defined as follows:
  - An ambulatory (office or outpatient) visits with a COPD diagnosis code in any position + a pharmacy claim for an oral corticosteroid (OCS) prescription within ±7 days of the office/outpatient visit; or

- An office or outpatient visit with a COPD diagnosis code in any position + a pharmacy claim for respiratory antibiotic prescription within ±7 days of the office/outpatient visit; or
- An office or outpatient visit with a COPD diagnosis code in any position + a pharmacy claim for an OCS + a pharmacy claim for respiratory antibiotic prescription within ±7 days of the office/outpatient visit.

- Pneumonia diagnosis: Binary indicators will be created to identify patients with a diagnosis of 1) pneumonia (Appendix 1). The time to first pneumonia diagnosis, and time to first pneumonia, during follow-up will also be captured.
- Pneumonia-related hospitalization: Binary indicators will be created to identify patients with an acute hospitalization with diagnosis of 1) pneumonia in any position (Appendix 1) The time to first pneumonia-related hospitalization during follow-up will also be captured.
- COPD exacerbation and/or pneumonia diagnosis: Binary indicators will be created to identify patients with each of the following composite outcomes: severe COPD exacerbation or an acute hospitalization with a diagnosis of pneumonia in any position, severe COPD exacerbation or a hospitalization with a diagnosis of pneumonia in any position, any COPD exacerbation or pneumonia diagnosis in any position, and any COPD exacerbation or pneumonia diagnosis in any position. Time to event variables will be created for each composite outcome during the follow-up period.

The following outcomes will be measured in the baseline and follow-up periods. The baseline period will include claims occurring on the index date, except for the index medication claims, which will be included in the follow-up period.

- All-cause health care resource utilization: Indicator variables and counts of physician office visits, hospital outpatient visits, ED visits, "other" (non-inpatient) visits, inpatient stays, and pharmacy claims will be created. Other medical visits are a residual category that includes, but is not limited to, services rendered at independent laboratories, assisted living facilities, and by home health providers. An indicator variable will be created to identify inpatient stays with an acute stay during the inpatient admission. The length of inpatient stays will also be captured. The time to first inpatient stay, the time to first inpatient stay with an acute stay, and the time to first ED visit during follow-up will be captured.
- COPD and/or pneumonia-related health care resource utilization: This utilization will be calculated analogously to all-cause utilization, but restricted to medical claims with a diagnosis for COPD and/or pneumonia, in any position (Appendix 1) and pharmacy claims for a COPD-related treatment (Appendix 2), including COPD-guideline recommended antibiotics (Appendix 3).

- COPD-related health care resource utilization: This utilization will be calculated analogously to all-cause utilization, but restricted to medical claims with a diagnosis for COPD in any position (Appendix 1) and pharmacy claims for a COPD-related treatment (Appendix 2), including COPD-guideline recommended antibiotics (Appendix 3)
- Pneumonia-related health care resource utilization: This utilization will be calculated analogously to all-cause utilization but restricted to medical claims with a diagnosis for pneumonia in any position (Appendix 1).
- COPD or pneumonia-attributable health care resource utilization: This utilization will be calculated analogously to all-cause utilization, but restricted to medical claims with a diagnosis for COPD or pneumonia in the primary position or a diagnosis for acute respiratory failure in the primary position and a diagnosis for COPD or pneumonia in a non-primary position (Appendix 1) and pharmacy claims for a COPD-related treatment (Appendix 2), including COPD-guideline recommended antibiotics (Appendix 3)
- All-cause health care costs (insurer + patient paid amounts): Health care costs will be computed from the payer and patient perspective together. This is the actual amount paid to the provider by the health plan plus the patient co-pay and/or coinsurance amounts, rather than an estimated cost. Total costs will be calculated and presented as the combined pharmacy costs and medical costs. Medical costs will be presented and will include sub-categories of physician office costs, hospital outpatient costs, emergency services costs, inpatient costs, and other costs.
    - Costs will be adjusted to 2019 dollars using the medical care component of the Consumer Price Index (CPI) to reflect inflation between the date of the claim and 2019.[22] The final report will include additional columns with the latest available 2020 mid-year CPI adjustment applied to costs for scaling the results as needed. [22]
    - Costs from other payers may be important, particularly for studies involving older patients dually eligible for commercial and Medicare coverage. In consultation with [redacted] this study will NOT incorporate the amounts estimated to be paid by other payers for a total paid or allowable amount. [23]
- COPD and/or pneumonia-related health care costs (insurer + patient paid amounts): These costs will be calculated analogously to the all-cause costs, but restricted to medical claims with a diagnosis for COPD, pneumonia, or acute bronchitis/bronchiolitis in any position (Appendix 1) and pharmacy claims for a COPD-related treatment (Appendix 2), including COPD-guideline recommended antibiotics (Appendix 3).
- COPD-related health care costs (insurer + patient paid amounts): These costs will be calculated analogously to the all-cause costs, but restricted to medical claims with a diagnosis for COPD in any position (Appendix 1) and pharmacy claims for a COPD-related treatment (Appendix 2), including COPD-guideline recommended antibiotics (Appendix 3).

- Pneumonia-related health care costs (insurer + patient paid amounts): These costs will be calculated analogously to the all-cause costs but restricted to medical claims with a diagnosis for pneumonia in any position (Appendix 1).
- COPD or pneumonia-attributable health care costs (insurer + patient paid amounts): These costs will be calculated analogously to the all-cause costs, but restricted to medical claims with a diagnosis for COPD or pneumonia in the primary position or a diagnosis for acute respiratory failure in the primary position and a diagnosis for COPD or pneumonia in a non-primary position (Appendix 1) or pharmacy claims for a COPD-related treatment (Appendix 2), including COPD-guideline recommended antibiotics (Appendix 3).

Clinical characteristics will be measured in the baseline period. The baseline period will include claims occurring on the index date, except for the index medication claims, which will be included in the follow-up period.

- Quan-Charlson comorbidity score: A comorbidity score will be calculated based on the presence of diagnosis codes (in any position) on medical claims in the baseline period.[24,25,26] The score is calculated based on a weighted sum of 12 comorbid conditions. The score represents the cumulative likelihood of one-year mortality and serves as a proxy for comorbidity burden. The Quan-Charlson comorbidity score also will be categorized into the following groups: zero, one, two, three, four, and five or more.
- Oxygen therapy: Evidence of oxygen use will be captured in the baseline period based on diagnosis (ICD-9, ICD-10), procedure (HCPCS, CPT, ICD-9) and revenue codes for oxygen therapy (Appendix 1).
- Baseline respiratory medication utilization: Indicator variables for respiratory medication classes and selected individual respiratory medications will be based on both pharmacy and medical claims (nebulizer treatments may appear in medical claims). Medication classes will include: LAMAs (alone; overall and separately), LABAs (alone), ICS (alone), ICS/LABA single inhaler combination medications, SAMAs (alone), SABAs (alone), SAMA/SABA single inhaler combination medications, any rescue (SAMA alone, SABA alone, or SAMA/SABA single inhaler combination medications), methylxanthines, phosphodiesterase-4 (PDE-4) inhibitors and oral corticosteroids (OCS). Baseline medication use variables will exclude claims which make up the index therapy assignment. Number of fills by class will also be captured. Indicator variables will be created to identify patients who are naïve to long-acting bronchodilators (free or fixed dose LAMAs or LABAs) and to long-acting bronchodilators plus inhaled corticosteroids (free or fixed dose LAMAs, LABAs, and ICSs) at index.
- Index provider specialty: The specialty of the provider on the index prescription fill will be captured. If no provider specialty is recorded on the index prescription fill, the provider specialty from the most recent COPD-related visit on or prior to the index date will be captured. An indicator variable will identify if the provider specialty was determined from the index pharmacy claim. Provider specialty will be classified as one of the following: pulmonology, primary care [family practice, general practice, and

geriatrics], internal medicine, allied health professional, cardiology, other specialty, and unknown specialty. If claims for more than one provider occur on the date used to classify the provider's specialty, the hierarchy of categories listed above will be used to pick a single provider specialty.

- Pulmonology visits within 30 days of index date: An indicator variable will be created to identify patients with a pulmonologist visit within 30 days prior to and excluding the index date.
- Spirometry testing: If available, indicator and count variables will be created to identify patients with lung function testing (Appendix 1). A count of spirometry tests during the baseline period will be created. Multiple spirometry tests within a 30-day period will be counted as one test.

Patient characteristics will be measured as of the index date, or the first available claim after the index date with valid values for each of the characteristics. It may be necessary to modify or remove some variables or analytic table templates to preclude identification of individual patients and protect proprietary health plan information.

- Index year: The year of the patient's index date will be identified.
- Seasonality: The month of the patient's index date will be identified and classified as fall (September, October, November), winter (December, January, February), spring (March, April, May), or summer (June, July, August).
- Age: Age will be defined as of the index year
- Age groups: Patients will be assigned to one of the following age groups: 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 and 80+
- Gender: Gender will be captured from enrolment data; patients with undefined gender will be removed from the study sample
- Race/ethnicity: Race/ethnicity information will be captured if available in the [redacted] database, no further linking with any additional consumer sociodemographic data will be attempted, but if data is available it will be categorized as follows: White, African American/Black, Asian, Hispanic, or unknown (unknown includes missing). This variable depends on the availability of data and will be missing for some or all patients.
- Insurance type: Whether the patient was covered under a commercial or Medicare Advantage health plan will be captured
- Plan type: Plan type will be categorized as Exclusive Provider Organization (EPO), Health Maintenance Organization (HMO), Point of Service (POS), Preferred Provider Organization (PPO), Individual and Other
- Geographic region: The US region in which the study patient is enrolled in a health plan will be determined and reported and states will be categorized into five geographic regions in accordance with the US Census Bureau's region designations; the four health plan regions are presented in the table 1 below. Patients categorized into "other" will be excluded from the study.

Table 1 Health Plan Regions

Region	State
Northeast	CT, MA, ME, NH, RI, VT, NJ, NY, PA
Midwest	IL, IN, MI, OH, WI, IA, KS, MN, MO, ND, NE, SD
South	DC, DE, FL, GA, MD, NC, SC, VA, WV, AL, KY, MS, TN, AR, LA, OK, TX
West	AZ, CO, ID, MT, NM, NV, UT, WY, AK, CA, HI, OR, WA

9.3.1 Exposures

Patients will be assigned to one of the following mutually exclusive study cohorts based on the index pharmacy claim: Stiolto Respimat or Trelegy Ellipta. Exposure measures will be based on pharmacy dispensing of the two medications under study, namely Stiolto Respimat or Trelegy Ellipta, over a follow-up period, beginning the index date and lasting up to one year from index date. Discontinuation for index medication will be defined as a gap in index medication of ≥45 days (sensitivity analysis with ≥30 days can be included) following the runout of days' supply (discontinuation date = runout prior to the gap in therapy). Switch in index medication will be defined as a pharmacy fill for ≥30 consecutive days of a non-index maintenance medication (switch date = first date of the new treatment regimen). Switch includes any other change in use of index medication by active ingredient, inclusive of a change to a different combination therapy (ICS/LABA FDC, different LAMA/LABA or LAMA/LABA/ICS FDC) change from a FDC to a free form combination therapy with mono LAMA plus mono LABA, or mono ICS plus mono LABA, or mono LAMA plus mono LABA plus mono ICS or a change to a monotherapy.

Individuals in the study cohort will be followed from the index date until the earliest of the date of a switch in treatment, addition of an ICS for the Stiolto Respimat group, discontinuation of the index COPD maintenance treatment, the end of the study period, or the end of continuous health plan eligibility. Main analyses will be further limited to the first 12 months after index date, with sensitivity analyses considering all available data.

All patients will be required to be continuously enrolled in the health plan for a minimum of 12 months. The 12 months prior to and including the index date (index date – 364 through index date) will be used to assess baseline characteristics. The period starting the day after the index date, up to a maximum of 12 months duration (index date +1 through index date +365) will be used to assess exacerbation, pneumonia, HCRU and cost outcomes. Patients will be censored at the earliest of the following: discontinuation of the index medication (Stiolto or Trelegy), switch to a non-index medication, disenrollment from the health plan, 12-months following the index date, or the end of the study period.

9.3.2 Outcomes

9.3.2.1 Primary Outcomes

The primary outcome event for effectiveness is time to first COPD exacerbation after cohort entry. The event is defined as follows:

- Severe exacerbation:
  - Hospitalization with a principal discharge diagnosis of COPD and/or
  - An emergency department (ED) visit with a discharge diagnosis of COPD
  - An inpatient admission or an ER visit with a diagnosis code for acute respiratory failure in the primary position and a COPD diagnosis code in any position

- Moderate exacerbation:
  - An antibiotic for a respiratory condition dispensed ± an OCS

Time to the first COPD exacerbation will be measured from index date until the occurrence of a hospitalization for COPD (severe exacerbation) or ED visit for COPD (severe exacerbation) or prescription of an antibiotic ± an OCS on the same day (moderate exacerbation). Severe and moderate exacerbations were considered as a composite for main analyses. Sensitivity analyses will include stratification by exacerbation severity.

Exacerbations will be categorized as moderate or severe and a count of any (severe or moderate), severe, and moderate will be provided.

9.3.2.2 Secondary Outcome(s)

The secondary outcome is time to first hospitalization for community-acquired pneumonia (serious pneumonia). Pneumonia was defined using ICD-9-CM diagnoses 481.x-486.x; 487.0, 507.x, 507.0, 507.1, 507.8, 510.0, 510.9, 511.0, 513.0, 514.x, 517.1, 519.8, 530.84, and ICD-10 diagnosis codes J10.0; J11.0; J12-J18; J22; J69; J85.0; J85.1; J86. This definition has been previously used in COPD. [27,28]

- COPD and/or pneumonia related HCRU (including acute inpatient stays and their length of stay, emergency department visits, ambulatory [Physician office visits, hospital outpatient visits], and other medical visits)
- COPD-related HCRU
- Pneumonia-related HCRU
- COPD-attributable HCRU
- All-cause HCRU

HCRU is defined as total inpatient, emergency department, and outpatient care episodes. Estimates will be presented both overall and for COPD and/or pneumonia-related care, defined as claims where a diagnosis of COPD or pneumonia is present. Medications used, defined as total number of distinct medication subclasses dispensed (e.g., 4-digit level of the Generic Product Identifier) and total number of dispensing for medications per year. COPD-related medication utilization included all COPD medications, OCS, and guideline-recommended antibiotics

Annual HCRU costs (including costs paid by the patient, health plan, and any third party via coordination of benefits) will be then calculated as total costs, medical costs, pharmacy costs, ambulatory costs, ED costs, inpatient costs, and other costs. Costs were defined as related to COPD if the claim has a diagnosis for COPD in any position or is a pharmacy claim for a medication used to treat COPD. The sum of all costs from all care settings and pharmacy dispensing will be assessed overall, for COPD and/or pneumonia-related care.

[redacted]

9.3.3 Covariates

Patient characteristics at baseline will be assessed for Stiolto and Trelegy users overall and stratified by history of exacerbation.

The covariates included in the Propensity Score Matching (PSM) will include all the below covariates including the ones defined during the 12-month pre-index baseline period and chronic comorbid conditions.

- Gender
- Age group (years, categorical and a continuous variable)
- Calendar year of cohort entry
- Region
- Insurance type (e.g., Commercial, Medicare)
- Season of index date (winter, spring, summer, fall)

Additional characteristics that will be defined during the 12-month pre-index baseline period:

- Previous acute COPD exacerbation (measured both overall and in the 30 days prior to cohort entry), categorized as 0, 1, or ≥2.
    - All exacerbations (Moderate+Severe)
    - Hospitalizations (Severe)
- Use of other respiratory drugs in the 12-month pre-index period:
    - Short-acting beta-agonists
    - Short-acting Anticholinergics
    - Methylxanthines
    - LAMA
    - LABA

  - ICS
  - ICS/LABA
- Use of antibiotics commonly prescribed for a respiratory condition (e.g., azithromycin)
- Use of OCS
- Oxygen Use
- Pulmonary Rehabilitation

Chronic comorbidities were defined using diagnoses identified during all available data prior to the index date, and included

- Quan-Charlson Comorbidity Index score/individual comorbidities
- Cardiovascular disease
- Diabetes
- Renal failure
- GERD
- Arthritis
- Osteoporosis
- Cancer (excluding basal cell carcinoma)
- Baseline pneumonia diagnosis
- Baseline acute bronchitis diagnosis
- Diagnosis of dyspnea during baseline identified using ICD 9 786.0x and ICD 10 R06.0x
- Diagnosis of obesity during baseline identified using ICD 9 278.xx and ICD 10 E66.xx
- Diagnosis of alcohol dependence during baseline identified using ICD 9 303.xx, 305.0x and ICD 10 F10.xx
- Smoking dependence during baseline identified using ICD 9 305.1 and ICD 10 F17.xx
- Tobacco use or cessation counselling*

*We anticipate limited capture of lifestyle variables known to be risk factors and potential confounders, including obesity, smoking status, and excessive alcohol consumption.

[redacted]

9.4 DATA SOURCES

We will utilize medical and pharmacy claim records for COPD patients included in the [redacted] database (previously named [redacted]).

9.5 STUDY SIZE

Considering the study design being non-interventional study with existing data, retrospective, new user design and treatments being: Stiolto Respimat (active treatment) vs. Trelegy Ellipta (comparator), primary endpoint of time to first exacerbation (moderate/severe) and COPD population being maintenance treatment naïve, we didn't find any such study that exactly matches these criteria in literature.

We looked at two retrospective, observational, non-interventional studies in the literature. Suissa et al published in Chest (CHEST 2020; 157(4):846-855) a real-world study of COPD treatment, the triple combination of LAMA, LABA, and ICS inhalers and compared its effectiveness to combining LAMA and LABA inhalers in preventing COPD exacerbations.[23] Suissa et al had a sample size of ~2000 patients on LAMA and LABA.[23] They reported that the adjusted hazard ratio (HR) of a COPD exacerbation associated with LAMA-LABA-ICS initiation compared with LAMA-LABA initiation was 0.97 (95% CI, 0.87-1.08). For patients with blood eosinophil counts > 6%, the HR was 0.66 (95% CI, 0.46- 0.94). For patients with two or more prior exacerbations, it was 0.83 (95% CI, 0.70-0.98). [29] The incidence of severe pneumonia requiring hospitalization was increased with LAMA-LABA-ICS initiation (HR, 1.46; 95% CI, 1.03-2.06). [29] The second study, by Palli et al compared health plan-paid costs, COPD exacerbations, and pneumonia diagnoses among patients newly treated with a LAMA + LABA regimen composed of tiotropium (TIO) + olodaterol (OLO) in a fixed-dose combination inhaler (TIO + OLO) or TT in a U.S. Medicare Advantage Part D insured population.[24] This study was published in Journal of Managed Care & Specialty Pharmacy 2020 26:10, 1363-1374 and had a sample size of ~1500 patients on Stiolto.[30] Palli et al reported longer time to first severe COPD exacerbation (P = 0.020) and first pneumonia diagnosis (P = 0.002) for TIO + OLO versus TT and a lower percentage of TIO + OLO patients experiencing these events (severe COPD exacerbation: 9.0% vs. 16.1%; pneumonia: 14.5% vs. 19.3%).[30]

Feasibility Assessment: Using [redacted] database we identified 15,538 and 35,686 patients who initiated first line treatment with Stiolto or Trelegy, respectively, between 15th September 2017 and 31st March 2020. These patients had 12-months of baseline with both medical and pharmacy coverage. After applying the inclusion/ exclusion criteria the sample size is reduced to 3996 patients in the Stiolto group and 5121 in the Trelegy group and post PSM our final sample size is 3018 in each group, which gives sufficient power when compared to earlier studies (Suissa et al (~2000 patients with LAMA-LABA) and Palli et (~1500 patients per cohort) as mentioned above). Based on these two studies from the literature and the feasibility numbers for the current study we are confident that we will have enough patients to ensure ≥80% power.

9.6 DATA MANAGEMENT

All established security and confidentiality procedures will be observed by BI and/or [redacted] personnel who are assigned appropriate access to the data. Enrolment data, medical claims, and prescription claims will be accessed from the administrative claims' dataset. The analyses will be performed on limited data sets that are void of

member protected health information and all results were shared in aggregate form only.

9.7 DATA ANALYSIS

Summary measures will include standard descriptive statistics (e.g., mean, standard deviation, median and range for continuous variables; counts and percentages for categorical variables). However, for any baseline characteristics with significant differences (Standardized differences (SD) greater than 0.10 (10%)) after PSM matching, these characteristics will be included as covariates in the regression models, or we will develop interaction terms to match on or discontinue the study if major channeling (SD>10%) is observed. Basically, a two-step approach: The first step will be to characterize the patients after PS matching to see whether balance can be achieved (based on SD) and at least 2000 patients from the Stiolto cohort can be matched with at least 2000 patients in the Trelegy cohort before proceeding to the second step of doing the comparative analysis. Sensitivity analyses may be performed on a select set of covariates considered to be prognostic factors. In the event of study discontinuation, partial results (all analysis leading up to and including PSM) will be provided in a final report.

A Cox proportional hazards models will be used on the time to first COPD exacerbation with treatment as a covariate. Comparisons will be made between treatment cohorts using HR and will be presented with associated 95% CI. To account for variable lengths of follow-up observation time, population annualized results will be provided (annualized costs [e.g., Sum of total costs/Sum of total follow-up patient years for each cohort]). The annualized cost may be modelled as dependent variable in a Generalized Linear Model with treatment cohort as a covariate and the follow-up patient years as an offset for each cohort.
Comparisons will be made between treatment cohorts and will be presented with associated 95% CI. Additionally, descriptive techniques that account for the length of observation time measure will be used appropriately. Per patient per month calculations will not be performed because of bias concerns. Appropriate tests comparing the Stiolto cohort and the Trelegy cohort (e.g., standardized differences, McNamara's tests, paired t-tests, sign tests) will be used based on the distribution of the measure. Patients not matched will be excluded from the post-match analysis.

9.7.1 Main analysis

Analyses will be presented comparing Stiolto vs Trelegy overall after PSM matching and stratified as follows if the sample size allows (at least 15% in each strata):

- Low history of exacerbation: 0 inpatient (i.e., severe exacerbations) and 0-1 outpatient events (i.e., moderate exacerbations)

- High history of exacerbation: ≥1 inpatient (i.e., severe exacerbations) or ≥2 outpatient events (includes ED)

We will describe the formation of the study cohort. Patient characteristics at baseline in patients treated with Stiolto and patients treated with Trelegy will be assessed separately using standard descriptive statistics.

Propensity scores including both pre-specified and data-derived variables will be then calculated. Balance of patient characteristics between the cohorts will be described before and after propensity score application and compared using standardized differences. For each Stiolto patient, a Trelegy patient with the closest available propensity score will be selected. Nearest neighbor matching method with a caliper of 0.2 will be utilized. Standardized differences greater than 0.10 (10%) will be taken to indicate imbalance, and these variables will also be included in outcome models, categorized as appropriate.

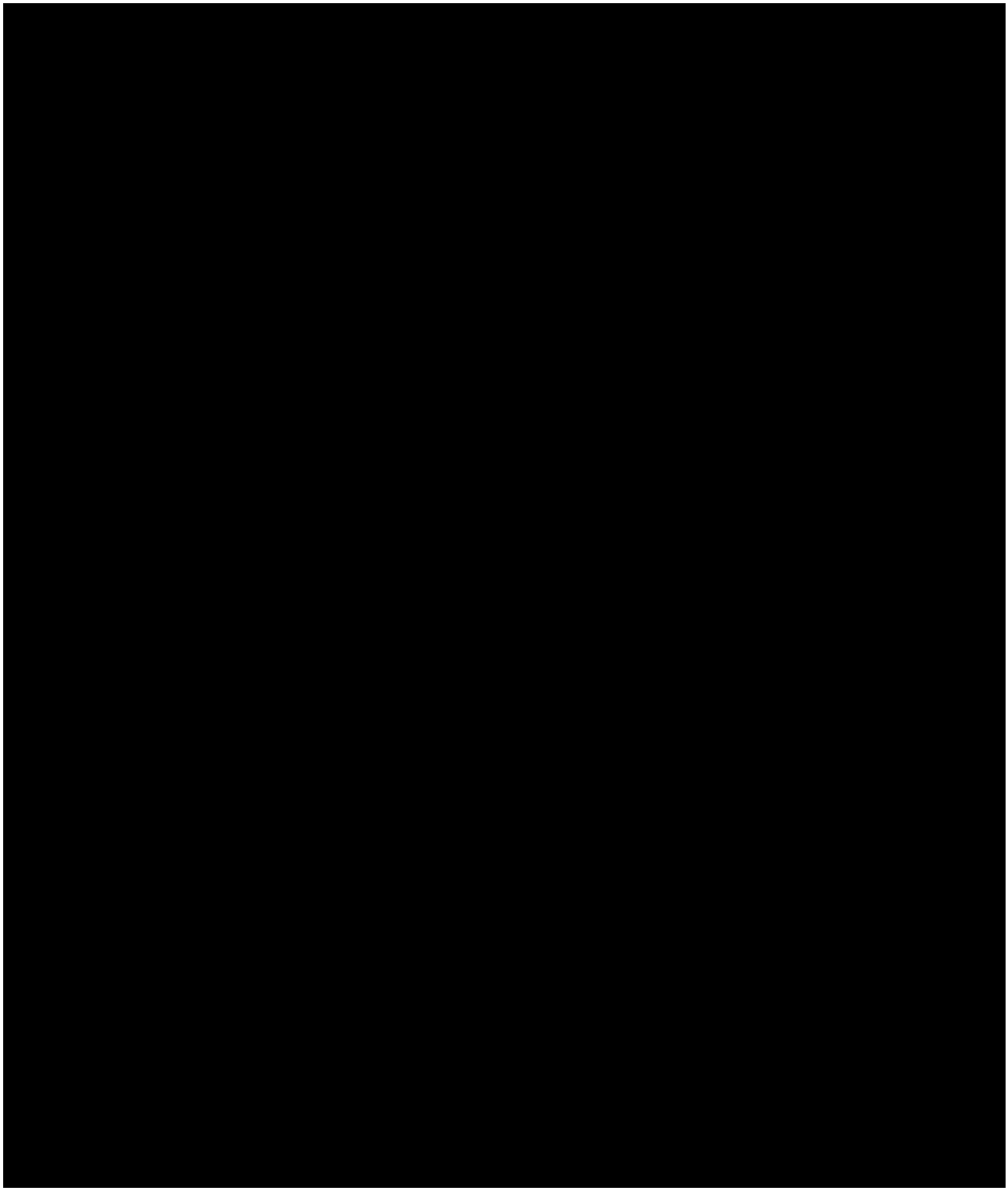
For the analysis of the primary objective, a Cox proportional hazard regression model will be used to perform an as-treated analysis that assesses the effect of first line maintenance medication with Stiolto versus the first line maintenance medication with Trelegy on the time to first COPD exacerbation. This estimates the HR of a COPD exacerbation associated with Stiolto use relative to Trelegy use, along with 95% CI. Based on the days' supply post index date, allowing a grace period of 45 days following the end of days' supply to account for intermittent use.

Stratified analyses will be using the same approach as the main analysis. Calculation of propensity scores will be repeated within the subset of the cohort with available results to create weighted populations suitable for these stratified analyses.

The analysis of the secondary objective related to the risk of pneumonia will also be assessed using Cox proportional hazard regression models with an as-treated approach, like that of the primary analysis.

In terms of HCRU, we will be presenting continuous and categorical variables using standard descriptive statistics to describe total visits and total costs related to inpatient, outpatient, and emergency care as well as distinct medications used, and pharmacy costs. Utilization and costs will be stratified to facilitate comparison between Stiolto and Trelegy and presented by individual setting and cost will also be presented as a composite. All-cause and COPD and/or pneumonia specific cost and utilization characteristics will be described separately.

[redacted]



9.7.3 Safety Analysis

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.

9.8 QUALITY CONTROL

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

[redacted] develops study approaches of sound scientific design that meet clinically stringent review. Researchers develop detailed protocols that include definitions, codes, analyses, and table shells. The coding strategy is then reviewed by a clinical team member for validity and relevance to ensure potential outlying issues are identified and addressed. The protocol further provides [redacted] and [redacted] an opportunity to solidify research questions and address any potential gaps in information
[redacted] incorporates meticulous quality assurance checks during data set construction to generate the most accurate data set. Our analysts perform record-level verification of all data elements, double-program certain portions of the data set, program data edit checks, visually review raw claims data against the constructed data elements and review the analysis to assess the validity of results.
Results will be verified by the [redacted] and BI research team assigned to the study.

9.9 LIMITATIONS OF THE RESEARCH METHODS

As with all studies utilizing claims data, there are certain limitations that should be noted. 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. Medications filled over the counter or provided as samples by the physician will not be observed in the claims data. Patients with commercial health insurance may be different from those with non-commercial or without (commercial) health insurance, and hence study results may not be generalizable to the overall population. Population aged 65 years and older might be underrepresented, which may affect external validity in the case of Medicare, Medicare Advantage or Medicaid patients. Socioeconomic data is not available. Smoking status information during the study period is not available in this data source. 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.
This real-world evidence study lacks controls available with RCTs. Patient misclassification, missing data, objective and reliable measurement of patient outcomes, and lack of detailed information regarding subjects' clinical history or clinical status during the study timeframe may undermine the accuracy of our study results. In the absence of randomization, confounding by indication could be an issue. Controlling via PSM should limit this bias but can control only for measured covariates and may produce estimates that are impacted by residual confounding. This is of particular importance in the case of lifestyle factors that are less critical to insurance billing and thus poorly captured in claims data.
There is the possibility of information bias due to misclassification of the outcomes or exposure or missing data as prescriptions dispensed by a pharmacy but not taken by patients could lead to misclassification of exposure. Pharmacy dispensing data does bring us one step closer to patient use than physician prescribing given that the patient has taken the effort to obtain the medication as instructed, however, information such as indication can only be inferred based on diagnostic patterns.
Finally, we cannot exclude the possibility of unmeasured differences in exacerbation risk across exposure groups. Data on several relevant confounders (e.g., Body mass index, smoking habits, symptom scores), as well as data from spirometry on lung function will not be available for analysis. Although certain bias analysis can be planned but they are limited by the strength of the assumptions they rely on. An impact of residual confounding caused by these unmeasured factors cannot be ruled out. Further, we cannot exclude the possibility that patients may have gone on to develop outcomes later beyond the study period. We will conduct bias analysis as appropriate to address these concerns.

9.10 OTHER ASPECTS

Not applicable.

10 PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant BI Standard Operating Procedures (SOPs).

The rights of the investigator and of the sponsor about publication of the results of this study are described in the investigator contract. As a rule, no study results should be published prior to finalization of the study report.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This NIS is a retrospective database analysis of existing data and is IRB exempt as there is no patient informed consent required for the study.

10.2 STATEMENT OF CONFIDENTIALITY

No patient's identity or medical records will be disclosed for the purposes of this study except in compliance with applicable law.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

The rights of the investigator and of the sponsor regarding publication of the results of this study are described in the investigator contract. As a rule, no study results should be published prior to finalization of the study report.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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13.2 UNPUBLISHED REFERENCES

NA

APPENDIX 1: CODE LISTS

Code	Code Type	Description
518.81	ICD-9 Dx	Acute respiratory failure
518.82	ICD-9 Dx	Other pulmonary insufficiency, not elsewhere classified
518.84	ICD-9 Dx	Acute and chronic respiratory failure
799.1	ICD-9 Dx	Respiratory arrest
J9600	ICD-10 Dx	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia
J9601	ICD-10 Dx	Acute respiratory failure with hypoxia
J9602	ICD-10 Dx	Acute respiratory failure with hypercapnia
J80	ICD-10 Dx	Acute respiratory distress syndrome
J9620	ICD-10 Dx	Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia
J9621	ICD-10 Dx	Acute and chronic respiratory failure with hypoxia
J9622	ICD-10 Dx	Acute and chronic respiratory failure with hypercapnia
R092	ICD-10 Dx	Respiratory arrest

APPENDIX 2: COPD-RELATED RESPIRATORY MEDICATIONS AND CLASSES

Drug Class	Subclass	Medication
Maintenance medications	Inhaled long-acting anti-muscarinic agents (LAMA)	aclidinium glycopyrrolate revefenacin tiotropium umeclidinium
	Long-acting β-agonists (LABA)	arformoterol formoterol indacaterol olodaterol salmeterol
	Inhaled corticosteroids (ICS)	beclomethasone budesonide (both inhaler and nebulizer) ciclensonide flunisolide fluticasone mometasone triamcinolone

Drug Class	Subclass	Medication
	Inhaled LAMA/LABA combination	aclidinium/formoterol glycopyrrolate/formoterol indacaterol/glycopyrrolate tiotropium/olodaterol umeclidinium/vilanterol
	Inhaled ICS/LABA combination	budesonide/formoterol fluticasone/salmeterol fluticasone/vilanterol mometasone/formoterol
	Inhaled ICS/LABA/LAMA combination	Budesonide/glycopyrrolate/formoterol fumarate[1] Fluticasone/umeclidinium/vilanterol
	Methylxanthines (intravenous, oral)	aminophylline dyphylline theophylline
	PDE-4 inhibitor (oral)	roflumilast
Rescue medications	Short-acting β-agonists (SABA) (inhalation, oral)	albuterol bitolterol isoetharine isoproterenol levalbuterol metaproterenol pirbuterol
	Short-acting anti-muscarinic Agents (SAMA) (inhalation)	ipratropium
	SAMA/SABA (inhalation)	ipratropium/albuterol
	Oral corticosteroids (OCS)[2]	betamethasone dexamethasone hydrocortisone methylprednisolone prednisolone prednisone

[1]This medication was FDA approved for maintenance treatment of COPD on 24 July 2020, which is outside of the study time period, and will not be included in this study.
[2]Including tablets, oral solutions, elixirs, etc. Injectable corticosteroid medications will not be included.

APPENDIX 3: COPD GUIDELINE-RECOMMEND ANTIBIOTIC MEDICATIONS

Drug Category	Drug Class	Medication
COPD Guideline-recommended Antibiotics[1]	Cephalosporins	cefaclor cefdinir cefditoren cefepime cefpodoxime cefprozil ceftibuten ceftriaxone cefuroxime
	Macrolides	azithromycin clarithromycin
	Penicillins	amoxicillin amoxicillin/potassium piperacillin/tazobactam
	Quinolones	levofloxacin moxifloxacin
	Sulfonamide combinations	sulfamethoxazole/trimethoprim
	Tetracyclines	doxycycline

[1]The American Thoracic Society (2017) and Global Initiative for Chronic Obstructive Lung Disease (2020) guidelines recommend that antibiotics for acute exacerbation of chronic bronchitis be selected based on local sensitivity patterns. For more specific recommendations, The Sanford Guide to Antimicrobial Therapy (2020) was referenced.

COPD Exacerbation Definition

- **Exacerbation Hierarchy:** Exacerbation events will be classified as severe or moderate according to the highest severity contributing event.
- **Exacerbation Episodes:** Exacerbations occurring within 14 days of each other will be considered a single exacerbation episode and will be classified according to the highest severity contributing event.
- **Episode Length:** The start date of the exacerbation episode will be the service date of the first event (medical encounter or pharmacy fill for an OCS or antibiotic). The end date of the exacerbation episode will be defined as the last observed exacerbation event date (or discharge date if an inpatient event) + 14 days.

- **Single Event Episode**
- In a single event episode, the exacerbation begins with the earliest occurrence of these events: COPD exacerbation defined inpatient admission, ER visit, ambulatory visit, or corticosteroid or antibiotic dispensing as defined in Section 9.3.2.1. In a single event episode, the exacerbation ends 14 days from the start of the event, hospital discharge, or following the OCS or antibiotic dispensing, whichever is later.
- ***Episode Start date*** = service date of a qualifying event (inpatient admission, ED visit, ambulatory visit, or OCS or antibiotic dispensing).
    - If the qualifying event is a hospitalization, the start date is the admission date.
    - If the qualifying event is an ED visit, the start date is the service date.
    - If the qualifying event is an ambulatory visit or an OCS or antibiotic dispensing, the start date is the earliest of the associated medical visit or medication dispensing date.

Episode End Date

- If the qualifying event is a hospitalization: discharge date + 14 days
- If the qualifying event is an ER visit: start date + 14 days
- If the qualifying event is an ambulatory visit or an OCS or antibiotic dispensing: Fthe latest of the medical visit or medication dispensing + 14 days

- If the Episode End Date is after the end of follow-up, then set an additional flag **CENSORED**=1.
- NOTE: Under this definition, it is possible for the runout of a medication to exceed the End Date.
- **MULTIPLE EVENT EPISODES**
- If another qualifying event occurs before the episode End Date, then the episode is extended. The date of the second event is used to reset the End Date per the definition above, using information from this second event. The process continues until a 14-day period with no exacerbation qualifying events occur. The End Date is set (as defined above).
- ***Episode Length:*** (End date – Start date) + 1

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

NA

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

NA

ANNEX 3. ADDITIONAL INFORMATION

ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol must be sent for review to the following individuals **prior to approval**.

Reviewer	**NIS involving BI product(s)**	**NIS not involving BI product(s)**	
		Global NIS	**Local NIS**
NIS Lead	X	X	X
Global TM Epi	X	X	X
Global TMM / TMMA / TM Market Access	X	X	
Global Project Statistician	X	X	
Global TM RA	X		
Global PVWG Chair	X		
GPV SC	X	X	X
Global CTIS representative	X		
Local Medical Director	X (if local study)		X
Local Head MAcc / HEOR Director	X (if local study)		X
Global TA Head Epi*	X	X	
Global TA Head Clinical Development / Medical Affairs / Market Access*	X	X	
Global TA Head PV RM*	X		
RWE CoE	X	X	
PSTAT / PSTAT-MA (for NISnd only)	X	X	X
NIS DM	X	X	X
Local Head MA/Clinical Development			X (does not apply to NISed without chart abstraction)

* *After review by Global TM for function*

Study Title: Comparison of Exacerbation Risk and Health Outcomes in Maintenance Treatment Naïve COPD patients using Stiolto vs. Trelegy.

Study Number: 1237.0121 Protocol Version:1.0