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Author: [redacted]

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As specified in the protocol, feasibility was conducted prior to analysis to determine precision of the pre-specified study design. The event rate and number of pneumonia events was lower than expected based on feasibility and prior work. As a result, most of the following adjustments were made to the protocol to improve precision regarding estimates of pneumonia.

- The protocol feasibility sections were updated following selection of the new user cohort and development of algorithms to identify episodes of pneumonia and censoring periods. Preliminary feasibility had not adjusted for the protocol inclusion/exclusion criteria or analysis requirements.
- The analysis period was expanded from 2005-2010 to 2002-2010 to increase precision to examine pneumonia via identification of additional new users and pneumonia events.
- Severe pneumonia events, hospital-acquired pneumonia (HAP) and severe community-acquired pneumonia (CAP), were combined rather than analyzed separately due to the low number of HAP events.
- The primary endpoints for modeling were clarified to be severe pneumonia events (HAP and severe CAP combined) and all pneumonia events combined rather than HAP, severe CAP and non-

severe CAP separately. These individual endpoints needed to be defined in order to evaluate pneumonia by severity; however, there is more efficiency in combining all events together and then subsetting by severe events than analyzing separately.

- The secondary analysis comparing severe and non-severe CAP was adjusted to include comparisons of patients with pneumonia versus patients without pneumonia on demographics, COPD history, and co-morbid conditions. The original objective was to compare between severe and non-severe pneumonia, however, the small number of events limit the ability to perform multiple logistic regression of severe and non-severe pneumonia.
- Minor clarification on table shell populations and analyses to improve clarity.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
BMI	Body Mass Index
CAP	Community Acquired Pneumonia
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSC	Fluticasone Propionate/Salmeterol Combination
FEV_1	Forced Expiratory Volume in One Second
FF	Fluticasone Furoate
GOLD	Global Initiative for Chronic Obstructive Lung Disease
CPRD-GOLD	GP OnLine Database
GP	General Practitioner
GSK	GlaxoSmithKline
HAP	Hospital-Acquired Pneumonia
HES	Hospital Episode Statistics
ICS	Inhaled Corticosteroid
ICD	International Classification of Diseases
IPTW	Inverse Probability of Treatment Weighting
LABA	Long Acting Beta Agonist
LAMA	Long-Acting Anti-Muscarinic
LABD	Long-Acting Bronchodilator
MRC	Medical Research Council
OCS	Oral Corticosteroids
PS	Propensity Score
SABA	Short-Acting Beta-Agonist
SAL	Salmeterol
THIN	The Health Improvement Network
QOF	Quality Outcomes Framework
UK	United Kingdom
VI	Vilanterol

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1. INTRODUCTION

An association has been observed between pneumonia and currently marketed ICS-containing medications relative to non-steroid containing medications among patients with COPD [Ernst, 2007, Crim, 2009; Drummond, 2008; Spencer, 2011; Singh, 2010]. The risk factors for development of pneumonia, including serious pneumonia requiring hospitalization, have been well-characterized in clinical and observational studies and include older age, current smoking, low BMI, certain chronic co morbid conditions (e.g. dementia), higher levels of dyspnoea, and markers of COPD disease severity [Calverley, 2011; Crim, 2009; Mannino, 2009; Müllerova, 2012].

In clinical trials, serious pneumonia was defined as any pneumonia that resulted in death, immediate risk of death (investigator judgment), or hospitalization or prolonged existing hospitalization. In the fluticasone furoate (FF)/vilanterol (VI), an increased incidence of pneumonia, including serious pneumonia was observed with the use of FF/VI compared with VI monotherapy in two one-year-long exacerbation studies (study HZC102970 and study HZC102871). In addition, there were reports of fatal pneumonia in the FF/VI 200/25 treatment group.

In previous studies within the same class of medicines, there was approximately a 1.5 to 2-fold increase in the risk of serious pneumonia, the ICS-containing medication as compared to long-acting beta-agonist (LABA) monotherapy (30 vs. 55 pneumonia episodes per 1,000 person years for 500/50 fluticasone propionate / salmeterol combination [SFC] and 50 salmeterol, respectively [Crim, 2009]. There was no increase in the risk of pneumonia fatality, and results suggested a reduction in mortality in patients taking FSC relative to placebo, but did not achieve statistical significance [Calverley, 2007]. A similar two-fold increase was seen in the two, one-year long studies of FSC vs. SAL studies (data not shown).

In the FF/VI development program, the risk of serious pneumonia was almost three-fold greater for the FF/VI relative to the VI treatment groups (34.9, 37.0, and 33.6 per 1,000 person years for 50/250, 100/25, and 200/25 FF/VI versus 12.1 per 1,000 person years in 25 VI). In addition, inconsistencies in incidence of fatal pneumonia events between the two FF/VI exacerbation studies were noted; however, the low absolute number of fatal events precludes an accurate assessment of the risk or an evaluation of a dose response relationship due to low precision.

2. RATIONALE

Based on the increased risk of serious pneumonia observed in patients randomized to FF/VI, GSK seeks to gain a better understanding of the rates and risk factors for serious pneumonia in patients with COPD using retrospective observational studies of the class of inhaled corticosteroid (ICS)-containing medications.

In addition to quantifying the magnitude of association between ICS and serious pneumonia, this study aims to provide additional information to the previous studies of COPD and pneumonia through examination of risk factors for pneumonia requiring hospitalization (e.g. body mass index [BMI], lung function, current smoking status, dyspnea) not measured in previous observational data sources. Further, it will evaluate statistical interaction between ICS and other risk factors for serious pneumonia. Finally, it will evaluate characteristics of patients with pneumonia who are more likely to be admitted to hospital.

The results will be used to identify patients at greatest risk of pneumonia requiring hospitalization and may identify where risk minimization and/or medical recommendations may be appropriate to prevent pneumonia or improve pneumonia treatment leading to reduced morbidity and mortality.

3. TARGET AUDIENCE

This study will be used by GSK, clinicians, and regulatory agencies to inform on risk factors for pneumonia in patients with COPD for the purposes of risk minimization. The results will be disseminated in a form of manuscripts and scientific presentations. The results are slated to complete in February 2013 to be provided to regulatory agencies. The results will be provided to the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

4. OBJECTIVES

The overall objectives of this retrospective observational COPD cohort study are:

- to estimate the magnitude of association between risk factors and pneumonia requiring hospitalization, including ICS-containing medications
- to evaluate if ICS-containing medications modify the effect of risk factors for severe pneumonia (i.e. evaluate statistical interaction between ICS × other risk factors)
- among patients with pneumonia, to evaluate any differences in clinical characteristics between patients who have severe pneumonia (requiring hospitalization or contracted in hospital) relative to those with non-severe community acquired pneumonia that did not require hospitalization in the one-year prior following new user Cohort Entry
- to evaluate any differences in clinical characteristics between patients who develop pneumonia or severe pneumonia vs. those who do not develop pneumonia in the one year period following new user Cohort Entry

5. METHODOLOGY

5.1. Feasibility Assessment

Prior to conducting this study, two feasibility assessments were conducted to support the study objectives including a preliminary feasibility assessment and more refined assessment following cohort selection. The feasibility informs on the number of patients in each pre-defined group of new users of respiratory medications and the number of patients meeting different definitions of pneumonia. These figures will allow for an assessment of the available statistical precision to examine treatment group differences.

Mannino and colleagues found a rate of pneumonia requiring hospitalization to be 22.7 per 1,000 person years among patients with advanced disease (GOLD stage airflow limitation III or IV) [Mannino, 2009]. A previous study of community-acquired pneumonia (CAP) in a primary care population of patients with COPD in the GPRD [Müllerova, 2012], there were approximately 40,000 patients with prevalent COPD in CPRD-GOLD between 1996-2006 with ~8% experiencing pneumonia (CAP without restricting to those requiring hospitalization) during the study period with a CAP rate of 22.4 per 1000 person years. The authors included a highly sensitive definition of pneumonia, resulting in 1,469 cases of CAP in their case-control study.

Feasibility results on the 2005-2010 study period included approximately 12,000 new users and 185 pneumonia events. When expanding to include the study period 2002-2010, there will be approximately 18,742 new users of ICS-containing medications (n=12,065) or long-acting bronchodilators (LABD) based on requiring CPRD-GOLD linkage to HES, and hospitalization data 12-mo prior to the new user prescription as presented in Table 1. These totals include the application of all inclusion/exclusion criteria; however, additional subjects may get excluded in the final analysis based on censoring and on-going pneumonia at the time of cohort entry.

Table 1 Feasibility Results: New User Cohort

Number of New Users	Year of Cohort Entry									Total
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
LABD	354	513	703	765	715	723	972	938	994	6,677
ICS-containing[a]	1,828	1,499	1,633	1,369	1,310	1,207	1,244	1,100	875	12,065
Total by Year	2,182	2,012	2,336	2,134	2,025	1,930	2,216	2,038	1,869	18,742

a. ICS-Containing=inhaled corticosteroid-containing medications, LABA=long-acting beta-agonists, LAMA=long-acting antimuscarinics

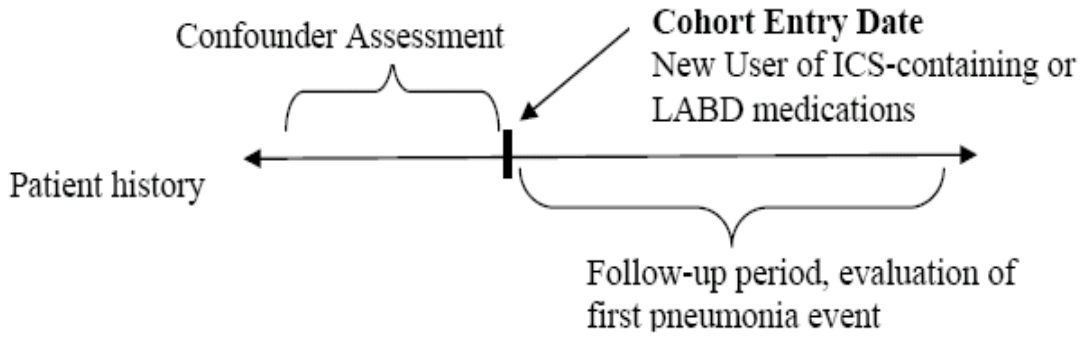
5.2. Study Design

This will be a retrospective cohort design.

CPRD-GOLD data will be used to identify a 'new-user' COPD cohort to evaluate a relationship between an exposure to respiratory medications, long-acting bronchodilators (LABD) or ICS-containing medications and the first episode of the pneumonia types of interest.

New users of ICS-containing medications or long-acting bronchodilator (LABD) would be evaluated in a cohort design for the occurrence of pneumonia following their designation as new users. Specific medications are described in Section 5.2.1. To adjust for anticipated differences in confounding by severity between the two treatment groups, important patient characteristics relating to COPD severity and pneumonia would be evaluated in the patient history in the period prior to and including the new user date. Propensity scores (PS) would be generated using these characteristics. The study schematic is presented in Figure 1.

Figure 1 Study Schematic: New User Cohort Design 2002-2010



A strength of the new-user design is that patient follow-up starts with the initial medication prescription written by the healthcare provider for all treatment groups and avoids potential biases that result from examining prevalent users relating to survivor bias and changes in their covariates based on exposure to treatment [Ray, 2003].

5.2.1. New User Study Population

Based on the treatment guidelines, we expect the potential for differences in COPD severity between treatment groups that require adjustment in the analysis. For the treatment of COPD, there is a consensus document on the treatment paradigm for patients with COPD [GOLD, 2009]. A LABD is recommended as an initial maintenance treatment in patients with COPD, including long-acting antimuscarinics (LAMA) or long-acting beta-agonists (LABA). If the disease severity warrants, adding additional therapy (a second bronchodilator or ICS) is recommended. However, an internal unpublished analysis estimated that ~10% of patients at COPD diagnosis are prescribed triple therapy (LABA, LAMA, ICS) during the period 2008 -2009.

CPRD-GOLD data are available through December 22, 2011 with the 1Q2011 data load. HES data are available through August 2011 with the latest data load. Therefore, patients are examined to identify new users between January 2002 and December 31, 2010 to allow for time in the cohort after being identified as a new user and prior to censoring of available data. If the data availability changes, the study period will adjust accordingly in the analysis plan.

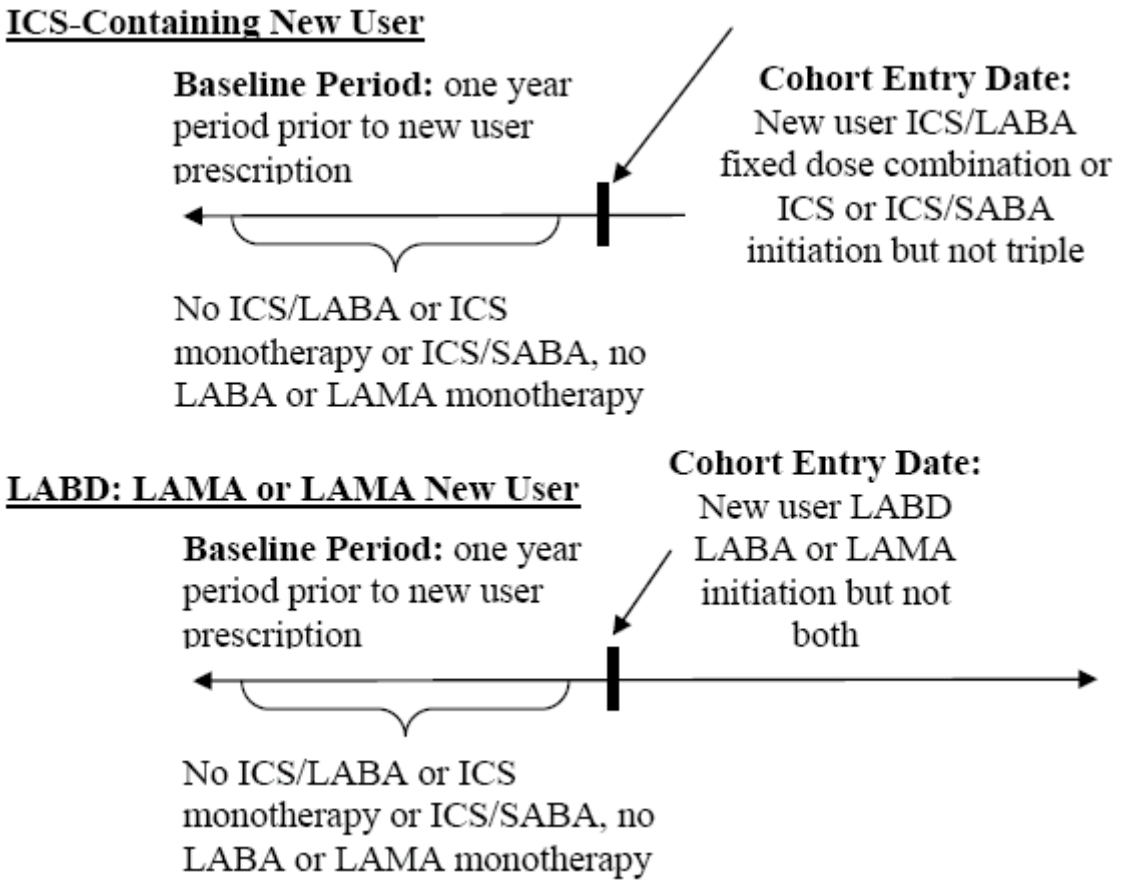
The **Baseline Period** is the one-year period prior to Cohort Entry Period to confirm new user status and evaluate patient characteristics of interest.

Identifying New Users
For the purposes of this study, a new user will be defined as someone who has not used medications of interest (ICS-containing or LABD containing medications) in the year prior to a new prescription of a medication of interest (ICS-containing of LABD). The one-year period of no use is referred to a washout period rather than requiring no use of these medications ever in the patient's history. New users of ICS-containing medications and new users of LABD would be identified separately, and are described in Figure 2.

The following patients would not be considered new users:

- New users of triple therapy (LABA/LAMA/ICS) in three single inhalers or ICS/LABA inhaler plus LAMA
- Patients who step up from LABD to ICS/LABA combination therapy in a single device (based on definition of a new user, they have LABD in the history)

Figure 2 Identification of New Users



ICS New Users. Patients will have at least one prescription for ICS-containing medications from January 2002 (the earliest use) until December, 2010 preceded by a year of no use of ICS-containing medications (ICS monotherapy or ICS/LABA fixed dose combination or ICS/SABA) or LABA or LAMA prior to the new user prescription. At Cohort Entry, Patients who are new users of ICS monotherapy or ICS+LABA or ICS+LAMA in separate inhalers could be included as new users. However, patients prescribed new use of triple therapy (ICS, LAMA, LABA) would be excluded from this analysis.

LABD New Users. Patients will have at least one prescription for LABA or LAMA (but not both) from January 2002 (the earliest use) until December, 2010 preceded by a year of no use of ICS-containing medications (ICS monotherapy or ICS/LABA fixed dose combination or ICS/SABA) or LABA or LAMA prior to the new user prescription.

By definition, patients prescribed new use of triple therapy (ICS, LAMA, LABA) would be excluded from this analysis.

Algorithm to Identify New Users. To identify new users, the following algorithm would be employed. First, patients will be evaluated to see if identify their first prescription of LABD in the analysis period (2002 through 2010). Next patients would be evaluated to see if they are new users of ICS-containing medications in a similar manner. Patients

will be included in the analysis only once. As patients could conceivably qualify as new users more than once during the study period or be on more than one medication during the study period, the first prescription defining a patient as eligible for the study (either as new user of LABD or new user of ICS) during the study period only would be evaluated. As patients generally tend to fill multiple prescriptions for COPD in a year and add therapies rather than switch therapies in COPD, subsequent prescriptions would not be evaluated for new use moving forward to the end of available data, as this is expected to yield few patients. In the case of data anomalies where a patient is prescribed ICS/LABA fixed dose combination with either LABA or ICS monotherapy, the patient will be considered as having an ICS/LABA new user prescription.

The date when patients become new users of LABD or ICS-containing medications is considered the **Cohort Entry Date**.

5.2.2. Inclusion / Exclusion Criteria

Inclusion Criteria

Patients are required to:

1. Have CPRD-GOLD data of acceptable research quality according to CPRD standards.
2. Be new users of LABD or ICS-containing medications from January 2002-December 2010
3. Have a COPD diagnosis at any time in the period prior to and including the Cohort Entry Date (to eliminate any patients with asthma only)
4. Have at least one year of data prior to Cohort Entry Date.
5. Be at least 45 years of age at Cohort Entry Date.
6. Have GPRD-HES linkage. (Note: these individuals need to be retained for basic demographics but are not part of the new user cohort).
7. Have HES coverage one year prior to the Cohort Entry Date

Exclusion Criteria

1. Patients with an occurrence of a code for a medical condition incompatible with COPD diagnosis any time in their history. This list contains conditions that are a related to lung or bronchial developmental anomalies, degenerative processes (cystic fibrosis, pulmonary fibrosis), bronchiectasis, pulmonary resection or other significant respiratory disorders other than COPD (but not including cancer) that can interfere with clinical COPD diagnosis or substantially change the natural history of the disease.

5.3. Data

This study will use the Clinical Practice Research Datalink's (CRPD)-GP OnLine Database (GOLD), a primary care research database in the United Kingdom. We will also include the following data with linkages to CPRD-GOLD:

- Hospital Episode Statistics through August, 2011 (http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=289)
- Office of National Statistics Mortality File or CPRD mortality information through March, 2011 (http://www.ons.gov.uk/ons/rel/subnational-health1/the-21st-century-mortality-files/2010/index.html) [Note: If we do not get access to ONS, we would use CPRD-GOLD algorithms for death in addition to the HES discharge status.]
- Townsend Deprivation Scores (http://www.communities.gov.uk/documents/communities/pdf/733520.pdf)

CPRD-GOLD data were formally referred to as the General Practice Research Database (GPRD). To prevent confusion between the database and the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which characterizes COPD severity and treatment guidelines, the protocol refers to the database as CPRD-GOLD. CPRD-GOLD contains computerized health care information entered by General Practitioners in the United Kingdom (UK). More than 600 General Practices have been contributing medical history data since 1987, with more than 6 million patients in the database. The database contains longitudinal data recorded by the GP on patient demographic and clinical characteristics, medical history including records of referrals to consultants and hospitalizations, primary care utilization, and prescription medication history over a period of up to 15 years. Descriptive and pharmacoepidemiological studies of patients with COPD have been conducted in CPRD-GOLD, including validation of physician-recorded COPD diagnosis [Soriano, 2001] and evaluation of COPD co-morbidities [Soriano, 2005]. Studies of pneumonia have also been conducted, including a study of CAP in CPRD-GOLD [Müllerova, 2012] and a validation study of CAP requiring hospitalization in The Health Improvement Network (THIN), which uses the same software as CPRD to capture primary care information [Meropol, 2012].

The database linkages are important to capture hospitalization information and mortality. In CPRD-GOLD, the GP enters information about hospitalizations, including serious pneumonia, from the discharge summary materials sent to their practice. HES includes hospitalization information for the majority of practices in the CPRD-GOLD. These data provide more information about the cause of hospitalization and length of stay than are otherwise available in the primary care record. Finally, we will use the Office of National Statistics linkage to mortality information. Mortality is an important competing risk for any COPD study, as patients are older and have co-morbid diseases due to aging and smoking history.

5.4. Outcome

5.4.1. Feasibility of Pneumonia

Pneumonia is difficult to define in database studies, and preliminary work was performed to better understand the number of pneumonias and coding trends in CPRD-GOLD and HES.

Note that most diagnoses of pneumonia in CPRD-GOLD do not assign an organism or cause based on the summary presented in Table 2.

Table 2 Preliminary Count of Community-Acquired Pneumonia Events in New User Cohort: CPRD-GOLD

		Number of Episodes			
			Pneumonia Definitions		
		All	Pneumonia	Other	Tuberculosis
All		583	564	11	8
GPRD Medical Code (Events)	Read Description				
572	Pneumonia due to unspecified organism	304	304	.	.
886	Bronchopneumonia due to unspecified organism	90	90	.	.
1849	Lobar (pneumococcal) pneumonia	59	59	.	.
16287	Chest infection - unspecified bronchopneumonia	23	23	.	.
3683	Basal pneumonia due to unspecified organism	21	21	.	.
10086	Pneumonia and influenza	15	15	.	.
9639	Lobar pneumonia due to unspecified organism	12	12	.	.
25694	Pneumonia due to other specified organisms	9	9	.	.
23095	Bacterial pneumonia NOS	9	9	.	.
5202	Viral pneumonia	8	8	.	.
635	Pulmonary tuberculosis	8	.	.	8
4910	Interstitial pneumonia	8	.	8	.
5324	Atypical pneumonia	3	3	.	.
14976	Viral pneumonia NOS	3	3	.	.
28634	Other bacterial pneumonia	3	3	.	.
11440	Pulmonary aspergillus disease	2	.	2	.
26287	Klebsiella pneumoniae/cause/disease classifd/oth chapters	1	1	.	.
30591	Pneumonia due to pseudomonas	1	1	.	.

		Number of Episodes			
			Pneumonia Definitions		
		All	Pneumonia	Other	Tuberculosis
34251	Pneumonia due to specified organism NOS	1	1	.	.
12573	Respiratory syncytial virus infection	1	.	1	.
40299	Pneumonia – candidal	1	1	.	.
12423	Pneumonia due to streptococcus	1	1	.	.

Preliminary coding trends were examined in HES and are presented in Table 3. Note that most diagnoses of pneumonia in CPRD do not assign an organism or cause.

Table 3 Preliminary Count of Pneumonia Events in New User Cohort: HES

		No Episodes	Col %
		N	%
All		2,327	100
An ICD10 diagnosis code	**ICD10 description**		
J18.1	Lobar pneumonia, unspecified	1,292	56
J18.9	Pneumonia, unspecified	782	34
J18.0	Bronchopneumonia, unspecified	124	5
J13	Pneumonia due to Streptococcus pneumoniae	31	1
J15.1	Pneumonia due to Pseudomonas	24	1
J14	Pneumonia due to Haemophilus influenzae	19	1
J15.0	Pneumonia due to Klebsiella pneumoniae	11	0
J15.2	Pneumonia due to staphylococcus	9	0
J17.2	Pneumonia in mycoses	7	0
J16.8	Pneumonia due to other specified infectious organisms	4	0
J18.8	Other pneumonia, organism unspecified	4	0
J10.1	Influenza with oth resp manifest influenza virus identified	4	0
J15.6	Pneumonia due to other aerobic Gram-negative bacteria	3	0
J15.7	Pneumonia due to Mycoplasma pneumoniae	3	0
J17.3	Pneumonia in parasitic diseases	3	0
J15.4	Pneumonia due to other streptococci	2	0
J11.1	Influenza with oth resp manifestation virus not identified	1	0
J11.0	Influenza with pneumonia, virus not identified	1	0
J15.9	Bacterial pneumonia, unspecified	1	0
J15.8	Other bacterial pneumonia	1	0
J15.5	Pneumonia due to Escherichia coli	1	0

Following the preliminary feasibility, subsequent feasibility on the total number of new users was evaluated as described in the protocol and presented in Table 4. This addressed the overlap between CPRD-GOLD and HES and definition of pneumonia episodes. The total number of pneumonia episodes available for the final analysis (e.g., time to first) are described in Table 4, including 283 pneumonia and 106 severe CAP, and 1 HAP. Based on concerns about statistical precision, the protocol analyses were adjusted prior to implementation of analysis.

Table 4 Count of First Pneumonia Events Including Adjustments for Episodes: New User Cohort

Pneumonia Events	Year of Cohort Entry									Total New Users
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Type of Pneumonia episode			.	.						
HAP	.	.			.	.	1	.	.	1
Severe CAP	16	22	13	11	18	7	11	5	3	106
Non-severe CAP	18	23	23	26	23	18	23	17	5	176
All Pneumonia	34	45	36	37	41	25	35	22	8	283

5.4.2. Considerations in Defining Pneumonia

No single definition of pneumonia severity would meet all needs [Brown, 2011]. In addition, there are challenges in accurately distinguishing the types and severity of pneumonia in the GP and hospital record without the confirmation of chest x-ray results, analysis of sputum sample for type of bacterial infection, etc. However, this information may not be collected depending on the healthcare setting and clinical presentation; on the other hand, COPD exacerbations can be associated with the identification of organisms in sputa without presence of pneumonia. The type of pneumonia and underlying organism may be critical to determining appropriate treatment and prognosis [Brown, 2011].

In addition, there are additional difficulties in identifying CAP using primary care, particularly using primary care databases. Several scenarios can occur to further complicate CAP diagnosis in primary care, e.g. (1) CAP will be diagnosed later than the real disease start and recorded only after the medical investigation confirms the working medical diagnosis; (2) CAP will be a consequence or a complication of a previous infectious disease or a COPD exacerbation, or (3) CAP will be later rejected by further clinical evidence. (4) health-care acquired pneumonia, including HAP, could be misdiagnosed as CAP, particularly in patients who seek healthcare frequently. It is not possible to fully address these caveats in a primary care database. But, these were considered when defining the CAP diagnosis and episode. A validation study of CAP requiring hospitalization [Meropol, 2012] and the availability of the CPRD-GOLD linkage to HES improves the ability to identify severe pneumonia (e.g., involving hospitalization).

Each pneumonia will be classified as an episode, with a start date and end date based on the type of pneumonia. In the case of CAP, treatment may precede diagnosis by up to 3

days. Defining the episode will allow distinction between pneumonia episodes that occur in the baseline period (prior to Cohort Entry Date) versus following cohort entry. Recurrent episodes will not be calculated in the study.

5.4.3. Pneumonia Definitions

Several pneumonia outcomes will be defined for this study based on what is recorded in HES and/or the GP record. Distinctions will be made between episodes of severe and non-severe pneumonia events as follows:

- Non-Severe CAP
- Severe pneumonia
  - Severe CAP (CAP requiring hospitalization or resulting in death)
  - Hospital-acquired pneumonia (HAP)

These are defined below. The above categories identify three main classification categories of pneumonia that differ in etiology, severity, and prognosis.

CAP episodes will be identified and classified as severe (requiring hospitalization) or non-severe.

CAP will be based on definitions used previously in CPRD-GOLD [Müllerova, 2012] and those published by others [Meropol, 2012], which have undergone extensive review and evaluation. For this study, a more specific definition will be applied to allow inclusion of only those pneumonia events (versus influenza or other respiratory infection) that occur in the community. As a secondary analysis, the more sensitive definition would be used in sensitivity analysis.

Non-Severe CAP will be classified as an episode of pneumonia that was treated in the community and did not result in hospitalization or death. It would be tabulated based on examining pneumonia episodes and subtracting away any severe CAP or HAP.

Severe CAP will be classified based on hospitalization or death due to pneumonia during the CAP episode. The following CAP would be considered as serious:

- Pneumonia episode that do not involve hospitalization and patient dies during the episode (CPRD-GOLD) OR
- Pneumonia episode that results in hospitalization, where pneumonia was recorded prior to hospitalization (CPRD-GOLD) or within the first 2 days of admission to hospital (HES). If recorded in HES, pneumonia could be recorded on any episode within a spell in any position (e.g., primary or secondary).

The codes denoting pneumonia include all ICD-10 codes for Influenza and pneumonia (J09 to J18) except J09, J10.1, J10.8, J11.1, and J11.8:

In HES, spells represent an admission to the hospital and are comprised of a series of care episodes. Each care episode has a primary diagnosis and secondary diagnosis, where the secondary diagnoses are a series of significant co-morbid conditions. Most hospital

admissions (>90%) have only one episode of care. Based on the nature of the care received, each spell has a healthcare related group (HRG) assigned to it that corresponds to the highest level of care needed.

Hospital-acquired pneumonia or HAP will be classified as a pneumonia episode that was not acquired in the community but was acquired in the hospital (based on HES). Typically, HAP is diagnosed in the hospital >2 days following admission. Pneumonia diagnosed within the first 2 days of hospitalization would be considered severe CAP.

For the purposes of pneumonia outcomes, we will examine all episodes of pneumonia within a spell. Pneumonia diagnoses that occur during any episode within a spell 3 or more days following admission would be considered HAP.

Unfortunately, there was only 1 HAP identified during the subsequent feasibility analysis prior to study conduct based on the date that pneumonia was recorded in the hospital. This raises concern about the ability to distinguish HAP from severe CAP in databases. Initial feasibility indicated the potential to identify HAP; however, a programming error was identified. Given the limited number of HAP, it could not be evaluated separately in the analyses and was combined with severe CAP.

Algorithms would be evaluated to prevent from double counting a single episode as one type of pneumonia. Pneumonia episodes would be classified first as HAP, then severe CAP, and the remaining would be considered CAP based on their relative severity and risk of mortality. It is acknowledged that coding anomalies may exist but be relatively infrequent, for example, there will be pneumonia episodes that may have codes suggested as CAP prior to hospital admission, but an individual patient may be diagnosed with HAP based on their HES information instead of CAP.

5.4.4. Pneumonia Episodes

As pneumonia could be recorded during the baseline period and/or following the Cohort Entry Date and last for a significant period of time, pneumonia will be identified using episodes in a similar manner to COPD exacerbations episodes (start and end dates). We base the assumptions on the definition of pneumonia episodes on prior work [Müllerova, 2012], and prior consultation regarding pneumonia clinical course and resolution patterns.

Although the focus in this study does not involve measuring recurrence as an endpoint, definitions of pneumonia episodes are important to distinguish between those that are in the baseline period (prior to being classified as a new user), on-going at the Cohort Entry Date, or in the cohort follow-up period. In addition, the number of prior pneumonia episodes in the baseline period may be an important factor relating to the risk of pneumonia in the analysis. Patients with on-going pneumonia episodes during cohort entry or with pneumonia that ended with 14 days of the cohort entry date would be excluded from the analysis. During the follow-up period, only the **FIRST** episode of pneumonia per person would be characterized Note: The entire first episode would be examined to distinguish between non-severe CAP, severe CAP, and HAP.

In a prior CAP study conducted by GSK using CPRD-GOLD [Müllerova, 2012], a pneumonia definition was postulated based on a prior consultation with Dr. Mark

Woodhead. The pneumonia episode length was estimated to last approximately 10 weeks (70 days) based on the following assumptions: 77% of COPD patients are expected to be managed at home to recover from CAP back to baseline clinical status within 42 days (6 weeks). Furthermore, it is expected that radiological changes would take longer, with 88% of patients exhibiting return to baseline chest X-ray by ten weeks following the CAP episode start. Therefore, an episode of pneumonia will be considered to last up to 70 days or longer (see below).

The **CAP pneumonia episodes** are defined as follows:

Start Date for CAP Episodes:

Non-severe CAP and severe CAP in the baseline period will be recorded as indicator variable s (yes/no) and the number of events based on the one-year period prior to Cohort Entry Date. The start of the first CAP episode is the 1st pneumonia event (diagnosis or antibiotics within 3 days prior to diagnosis) in the year prior to Cohort Entry Date. If antibiotics are provided in the 3 days prior to the pneumonia diagnosis, the start date will be the date of antibiotics prescription. The pneumonia end date will be at least 70 days with some exceptions (see below).

For all CAP episodes, we will look back to confirm if an episode is at least 14 days after the end of any prior pneumonia episode. In the follow-up period (after Cohort Entry), patients with CAP or HAP that has not ended at least 14 days prior to the Cohort entry Date will be excluded from the analysis.

End Date for CAP Episodes:

Applying to all CAP episodes, the **end of episode** was defined as 70 days after the start of the episode with some exceptions. The end date can shift under these scenarios: 1) if hospital discharge date for pneumonia CAP is after 70 days, end of the event is set to the discharge date 2) if the patient dies or available data in HES or CPRD-GOLD ends prior to 70 days, end date is set to date of death or data end date, or 3) if there is another pneumonia diagnosis or antibiotic prescribed 14 days following the 70-day end date, the end date is set to the date of antibiotics prescription or 4) if there is hospitalization for pneumonia within the 14-day period after the 70 days, the end date is set to the hospital discharge date,

This check is repeated until a period of 14 days is found, free of a pneumonia event and antibiotics prescription.

CAP episodes would then be classified based on severity (e.g., resulted in hospitalization) during the episode.

The **HAP pneumonia episodes** are defined as follows:

Start Date for HAP Episodes:

HAP in the baseline period will be recorded as indicator variables (yes/no) and the number of events based on the one-year period prior to Cohort Entry Date. The start of

the first HAP episode is the 1st non-CAP pneumonia event where pneumonia was diagnosed >2 days following admission to hospital. The pneumonia end date will be at least 70 days with some exceptions (see below).

For all HAP episodes, we will look back to confirm if the start of an episode is at least 14 days after the end of any prior pneumonia episode. In the follow-up period (after Cohort Entry), patients with CAP or HAP that has not ended at least 14 days prior to the Cohort entry Date will be excluded from the analysis.

End Date for HAP Episodes:

Applying to all HAP episodes, the **end of episode** was defined as 70 days after the start of the episode with some exceptions. The end date can shift under these scenarios: 1) if hospital discharge date for pneumonia CAP is after 70 days, end of the event is set to the discharge date 2) if the patient dies or available data in HES or CPRD-GOLD ends prior to 70 days, end date is set to date of death or data end, or 3) if there is another pneumonia diagnosis or antibiotic prescribed 14 days following the 70-day end date the end date is set to the end date of antibiotics prescription, or 4) if there is hospitalization for pneumonia within the 14-day period after the 70 days, the end date is set to the hospital discharge date.

This check is repeated until a period of 14 days is found, free of a pneumonia event and antibiotics events.

5.4.5. Created Pneumonia Variables

It is anticipated that the following variables would be created for all pneumonia episodes:

- Non-severe CAP (yes/no)
- Severe Pneumonia
  - Severe CAP (yes/no)
  - HAP (yes/no)
- Start Date of episode
- End Date of episode
- Episode in baseline period (yes/no)
- Episode in the follow-up period (yes/no)
- Note: Patients with an episode has not ended at least 14 days prior to the Cohort Entry Date (yes/no)- would be excluded from analysis

For each patient, the following variables would be created:

- Non-severe CAP at baseline? (Yes/No) During follow-up? (Yes/No)
- Severe CAP at baseline? (Yes/No) During follow-up? (Yes/No)
- HAP at baseline? (Yes/No) During follow-up? (Yes/No)

- Number of Non-severe CAP at baseline
- Number of Severe CAP at baseline
- Number of HAP at baseline
- Time to first pneumonia event or censoring days in follow-up period for each type of pneumonia separately

5.5. Exposure

The primary exposure of interest is ICS, evaluated in new user cohort of ICS-containing medications. The comparator exposure group of interest is LABD.

To account for poor adherence to respiratory medications, patients will be classified as exposed to study medication for the duration of prescribed therapy plus 30 days. When the duration of prescribed therapy cannot be determined due to missing information, it will be assumed to be a 30-day supply to correspond to the amount of medications in a single inhaler. In the case of a single inhaler, patients will allow for gaps of up to 90 days between prescriptions.

To identify a study population of long-term users, we will conduct a secondary analyses restricted to patients on treatment for greater than 6 months. The long-term users would allow for examination of cumulative doses. Gaps between each dispensing of up to 90 days will be allowed. A patient dispensed a single inhaler on the Cohort Entry Date would be censored at 90 days if they did not have another prescription. A patient dispensed a second prescription of a single inhaler on day 40 would experience 99 days of coverage (i.e., 39 days of coverage for the first inhaler and 90 days for the second inhaler).

The strength of the new user prescribed ICS medication on the Cohort Entry Date will be categorized into equipotent doses of low, medium, and high-dose ICS based on classification according to Figure 3-1 presented in the Global Initiative for Asthma (GINA) guidelines [GINA, 2011]. The strength of the new user prescription would be entered into the Cox model primary outcome models as low, medium, and high relative to LABD (e.g. dummy variables). The strength of the medication will be tabulated based on the prescription on the Cohort Entry Date.

The use of other medications during the one-year **Baseline Period** will be included in the model as a marker of disease severity.

Prescriptions (Yes/No) during the Baseline Period indicative of disease severity. In addition, the number of prescriptions (except oxygen use) for the following will be collected:

- short-acting bronchodilators (short-acting anticholinergics or short-acting beta-agonists, including combination inhalers)
- long-term oral corticosteroid use (>4 Rx in 12 months)
- theophyllines

- oxygen use. when recorded (changes in reimbursement censor this information during part of the analysis period, but we will capture what information is available)
- nebulized therapy (associated with severity / frailty)
- Daxas (roflumilast) if numbers are sufficient (approved in June 2010 (and may be 0 for most patients)

Exposure "counts" of medications will be categorized during analysis (e.g., tabular summaries, propensity score creation, Cox modeling).

5.6. Confounders

Key risk factors for pneumonia that may also relate to treatment will be measured in the one-year Baseline Period. For the purposes of general co-morbidity assessment and vaccination for pneumonia, a longer history will be examined. Although patients may have varying periods of history, this is not expected to be differentially recorded by treatment (which could result in information bias). A longer look back period is needed to identify co-morbidities given they may not be recorded in the Baseline Period.

Confounders that are based on "counts" of healthcare encounters and exacerbation will be categorized during analysis (e.g., tabular summaries, propensity score creation, Cox modeling).

Variable	**Parameterization**
Age at Cohort Entry	Age will be treated either as a continuous variable, or as a categorical one (see Table shells for intervals)
Gender	Male=1 or Female=0
Body Mass Index (BMI) during Ever in Patient History	Weight in kilograms divided by height in meters squared, will be utilised as a categorical variable using the following categories widely referenced as WHO classification: Underweight (Below 18.5), Normal (18.5 - 24.9), Overweight (25.0 - 29.9), and Obese (30.0 and greater). For modelling, the following cutoff values will also be examined: BMI<21, BMI 21-24.9, BMI ≥25.
Smoking status during Ever in Patient History	Four categories will be created: ex-smoker, current smoker, non-smoker, and unknown smoking status containing patients with missing entries or other types of tobacco exposure (e.g. passive smoking). Non-smoker will be the referent group in modelling.
Overall Social Deprivation Scores for England	The deprivation quintile is derived the 32,482 areas of social deprivation, with 1 being most deprived and 32,482 being least deprived. quintiles will be identified as follows (with least deprived the referent in modelling). Quintiles are provided by CPRD:

Variable	Parameterization
Townsend Scores	Quintile. Townsend scores will be described by quintile, as provided by CPRD-GOLD.
Charlson Co-morbidity index and individual chapters Ever in Patient History (prior to Cohort Entry Date)	Charlson's comorbidity index chapter indicator measures will be created using a recently published algorithm by Khan and colleagues [Khan, 2010] after removing COPD and AIDS from the disease list. Some patients may have COPD and some may not (incident diagnosis). AIDS will be excluded due to very low prevalence in the general population. In addition, individual indicator variables will be retained for conditions that contribute to the overall Charlson index, including indicators for the following (1=Yes, 0=No): • AIDS (excluded) • Cerebrovascular disease • Chronic pulmonary disease (excluded) • Congestive heart disease • Dementia • Diabetes • Diabetes with complications • Hemiplegia and paraplegia • Mild liver disease • Moderate or severe liver disease • Myocardial infarction • Peptic ulcer disease • Peripheral vascular disease • Renal disease • Rheumatological disease • Cancer • Metastatic tumour
Additional Co-morbidities Ever in patient history (prior to Cohort entry Date): Depression, Anxiety, Asthma, GERD	1=Yes, 0=No for each condition (ever in the patient's history) • Anxiety diagnosis or anxiety medications (since diagnosis is underrecorded) • Depression diagnosis or anti-depressants (since diagnosed underrecorded) • Asthma diagnosis • GERD diagnosis or GERD treatments
Co-Medications of Interest associated previously with CAP in Baseline Period	• Statins • ACE-inhibitors • Immunosuppressive treatment including antiretroviral medications

Variable	Parameterization
COPD severity during Baseline Period (1-Year Prior to and 3 Mo Following Cohort Entry Date)	will be defined according to GOLD-defined lung obstruction based classification with Gold Stage II as the referent in modeling. • COPD diagnosis and spirometry mismatch: COPD diagnosis but not according to spirometry • GOLD 0: FEV_1/FVC≥70% and FEV1% predicted <80% • GOLD 1: FEV_1/FVC<70% and FEV1% predicted ≥80% • GOLD 2: FEV_1/FVC<70% and FEV1 % predicted ≥50 - <80% • GOLD 3: FEV_1/FVC<70% and FEV1% predicted ≥30 - <50% • GOLD 4: FEV_1/FVC<70% and FEV_1 % predicted <30% • Unknown (if missing spirometry during the one-year baseline period to 3 months following Cohort Entry Date)
Number of GP visits in One-Year Baseline Period	One encounter will be allowed per day to avoid counting several records referring to a single healthcare visit.
Number of Moderate and Number of Severe COPD Exacerbations in One-Year Baseline Period	COPD exacerbations are characterized as 'episodes' and consist of two sub-types (1) **'severe' episode** characterized with hospitalization for COPD, and (2) **'moderate' episode also called as 'community-treated'** characterized with management with COPD-specific antibiotics, oral corticosteroids and/or COPD exacerbation medical diagnosis. Each episode can consist of one or more events, i.e. hospitalization for COPD, management with COPD-specific antibiotics, oral corticosteroids and/or COPD exacerbation medical diagnosis, which occur within a pre-defined time interval. All these events will be flagged in order to allow for tabulation and determination of severity and start/end dates. If a hospitalization for COPD occurs then the exacerbation episode is called 'severe' episode. Episodes will be counted for each person in the baseline period: Each event will have a set of indicator variables • Moderate Exacerbation (yes/no) • Severe Exacerbation (yes/no)

Variable	Parameterization
	Each person will have a summary measure for the count of exacerbations in the Baseline Period (for subsequent propensity score adjustment rather than the yes/no dichotomous variable). • Number of moderate exacerbations • Number of severe exacerbations Algorithms for exacerbation will be based on prior work within GSK.
Number of Emergency Hospitalizations in One-Year Baseline Period	Spells whose first episode is an emergency admission on the first episode within a spell. Emergency admissions are based on one of the following categories in HES for ADMIMETH: • 21 = Emergency: via Accident and Emergency (A&E) services, including the casualty department of the provider • 22 = Emergency: via general practitioner (GP) • 23 = Emergency: via Bed Bureau, including the Central Bureau • 24 = Emergency: via consultant outpatient clinic • 28 = Emergency: other means, including patients who arrive via the A&E department of another healthcare provider
Number of Non-Emergency Hospitalizations in One-Year Baseline Period	Spells whose first episode is a non-emergency admission within a spell. This includes all categories other than those in the emergency section including unknown reasons. Admissions due to delivery of a baby, etc. are included for completeness but not expected with the exception of data anomaly. • 11 = Elective: from waiting list • 12 = Elective: booked • 13 = Elective: planned • 31 = Maternity: where the baby was delivered after the mother's admission • 32 = Maternity: where the baby was delivered before the mother's admission • 81 = Transfer of any admitted patient from another hospital provider other than in an emergency; this does not include admissions to high security psychiatric hospitals (HSPH) • 82 = Other: babies born in health care provider • 83 = Other: babies born outside the health care

Variable	Parameterization
	provider, except when born at home as intended • 84 = Admission by the admission panel of an HSPH; patient not entered on the HSPH admissions waiting list (not valid for admissions after 31 March 2002) • 89 = From the admissions waiting list of an HSPH (not valid for admissions after 31 March 2002) • 98 = Not applicable (e.g. other maternity event) • 99 = Not known
Number of non-severe CAP Baseline Period (no hospitalization or death)	Number of non-Severe CAP and Dichotomous variable (1=yes, 0=No)
Number of severe CAP in Baseline Period	Number of Severe CAP and dichotomous variable (1=Yes, 0=No)
Number of HAP in Baseline period	Number of HAP and dichotomous variable (1=Yes, 0=No)
Prior vaccination for influenza in Baseline Period	Influenza vaccination in the year prior to cohort entry (1=Yes, 0=No)
Prior vaccination for pneumonia in past 5-years	Pneumococcal vaccination in the 5-year prior to cohort entry based on recommended frequency of vaccination in the UK (1=Yes, 0=No)
Medical Research Council (MRC) dyspnea scale.	MRC value if recorded in the year prior to 3 months following Cohort Entry Date will be included in modeling. If unknown, "unknown" would be the assigned value. • Grade 1: No Dyspnea except on strenuous Exercise • Grade 2: Short of breath when walking up a short hill • Grade 3: Dyspnea limits walking pace (slower than others) and stops to catch breath • Grade 4: Stops to catch breath after walking 100 meters (328 feet) on level ground • Grade 5: Dyspnea prevents leaving house and performing Activities of Daily Living • Unknown / Unavailable • Collapsing of responses into fewer categories will be considered during the analysis
Calendar year of Cohort Entry	Indicator variable for all years (2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010. During modeling, 2002 will be the reference year.

Additional parameterization of the data, including grouping of the count data into categories, will be considered during the creation of PS or modeling based on the distribution of the data. Details of the analysis and modeling strategy will be described in a statistical analysis plan.

5.7. Analysis

5.7.1. New User Cohort

Patients in the cohort will be described according to their COPD disease severity, treatment patterns, demographic characteristics, and co-morbidities. Treatment guidelines for COPD consider long-acting bronchodilators as monotherapy as being prescribed for patients that have less severe COPD than those who would be given an ICS as add-on to a long-acting bronchodilator.

For the primary objective, patients were required to be new users of ICS-containing medications or LABD after a one-year period of non-use. ICS are add-on therapy for LABD; therefore, new users of ICS could have ICS monotherapy or ICS/LABA as fixed dose inhaler in the one year prior to **Cohort Entry Date**.

The primary pneumonia outcomes are severe pneumonias, which are severe CAP and HAP. As there was only one patient with HAP according to the database algorithm, severe CAP and HAP were combined. The secondary outcome is all pneumonias, including HAP, severe CAP, and CAP combined. Patients can have only one pneumonia outcome (e.g., severe CAP, HAP, or non-severe HAP) in the analysis based on the first pneumonia event.

Confounders will be were selected for inclusion in the analysis based on clinical importance and are described in Section 5.7 and respiratory medications in Section 5.6. Additional information about the modeling strategy will be addressed in a statistical analysis plan.

5.7.2. Patient Follow-up Time from Cohort Entry

Patients will be followed from the date of their first eligible prescription (New User entry date) until the earliest of the following:

- date of treatment end (up to 90-day gap allowed for each inhaler),
- date of study end point (first pneumonia event of interest)
- date of transfer to a new practice / practice stops participating or CPRD ends,
- date of ICS initiation (among LABD new users)
- death or
- HES data ends (last available HES data)

As part of the primary analysis, patients will be examined for their first pneumonia (severe CAP, HAP, or non-severe CAP). For example, a patient who has HAP and then

another year has a severe CAP would be considered only for his first event, the HAP. For the analysis of severe CAP, this same patient would be censored on the start date of their HAP episode.

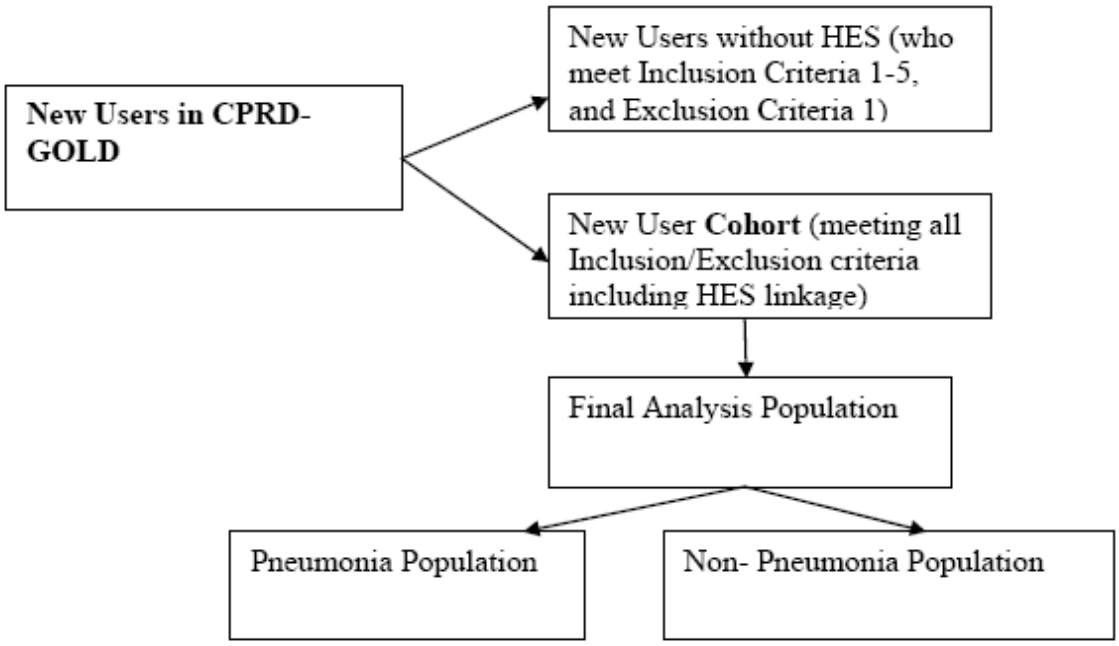
Each patient will have a time and "censoring" variable, which is an indicator variable (yes/no) that indicates 1 if they have had the event of interest or 0 if they are censored. Time will be calculated as the date of the event or censoring minus the cohort entry date plus 1.

Incidence rates of the pneumonia outcomes will be calculated as the number of patients experiencing an event divided by the person-years at risk. Incidence rate ratios were calculated as the incidence rate in the ICS-containing group divided by the incidence rate in the LABD group. Precision of effect estimates will be evaluated from the width of the 95% CIs.

5.7.3. Analysis Populations

There are a few analysis populations of interest in this study for tabular summaries and/or modeling. Patient populations are described below and presented graphically in Figure 3 to illustrate subsets.

Figure 3 Summary of Populations



New User Cohort: These patients meet the inclusion/exclusion criteria in the protocol regarding being classified as new users of ICS-containing medications or LABD with HES linkage.

New Users without HES Linkage: These patients meet the inclusion criteria 1-5 and Exclusion criteria 1 except for the fact that they are missing the HES linkage (e.g., they

fail inclusion criteria 6, 7). These individuals will be described to compare to the New User Cohort group in the study who have the HES linkage.

New User Cohort Free of Pneumonia at Index Date: These patients are a subset of new users that are at risk of pneumonia at the time of their new use. Patients in the new user cohort who are experiencing an episode of pneumonia that is on-going or has not been resolved for at least 14 days prior to their index date will be excluded from this cohort.

New Users with HES Linkage Excluded from Final Analysis: These patients meet all inclusion/exclusion criteria except are excluded for having an influential propensity score weight or on-going pneumonia or at the time of entry into the New User Cohort.

Final Analysis Population: These patients are a subset of the New User cohort who have PS within an acceptable range, were not experiencing a pneumonia episode at the time of their Cohort Entry Date, and had HES and CPRD data during the period following the Cohort Entry Date.

Pneumonia Population: These patients are a subset of the New User Cohort free of pneumonia at index date and have experience at least one pneumonia event in the year following Cohort Entry, regardless of censoring status in the Cox modeling. The first pneumonia event will be tabulated as either HAP (most severe), severe HAP (less severe), or non-severe CAP (least severe) to count patients in one category. . These patients will be compared to those new users free of pneumonia at the Cohort Entry Date who do not develop pneumonia in the year following Cohort Entry.

5.7.4. Multivariable Modeling

Multivariable analysis will be performed using Cox proportional hazard model with adjustment for confounders and exposures in Section 5.6 and Section 5.7.

The following outcomes will be examined:

- Severe pneumonia events (HAP and Severe CAP combined)
- All pneumonia events

Severe pneumonia events will be examined as the primary outcome. As a secondary outcome, all pneumonia events will be analyzed. The number of confounders can be supported in the modeling will be based on the total number of severe pneumonia and all pneumonia events and their distribution by treatment..

To adjust for differences confounding by severity due to differences in prescribing between ICS-containing medications and LABD, propensity scores (PS) will be utilized. The propensity score will be estimated to model the probability that a chance of a patient receiving ICS-containing medications compared with receiving LABD given a patient's observed set of baseline covariates. The logistic models used to calculate the propensity scores, all available variables in Section 5.5 (exposures) and in Section 5.6 (confounders) will be entered into the model. Propensity scores will be produced.

The PS in both groups would be evaluated for overlap, and patients with scores in the tails of the distribution that were not represented in both groups would be eliminated from the analysis. Patients with extreme PS weights (values >10) will be examined and may be removed from the analysis as their contribution would be influential and affect the model. Patients eliminated from the analysis would be described.

Multivariable analysis will be performed using Cox proportional hazard model with adjustment for the propensity score using inverse probability of treatment weighting (IPTW). This approach is more appropriate then propensity score matching when there may be effect measure modification [Stürmer, 2006]. Because of the cohort design, it is possible to adjust for confounders in the PS approach as well as include them as main effects in the model; however, it has been demonstrated that the addition of confounders with propensity scores does not contribute appreciably to the model [Rubin, 2000; Stürmer, 2006

Parameterization of the explanatory variables in the propensity score generation and subsequent modeling will be based on determining the most appropriate measure (e.g., number of moderate exacerbations may be collapsed into ordinal categories or yes/no if there are few patients with more than 1 in the Baseline Period.) Imputation, removal of outliers, and parameterization of variables for the model will be described in the analysis plan and determined prior to fitting final outcome models.

For the primary analyses (severe CAP and HAP combined), patients will be followed using a Cox proportional hazards model until they experience the first of the following events or censoring: (1) pneumonia event of interest (based on their first pneumonia episode following Cohort Entry), or censoring for (2) death (competing cause), (3) other pneumonia event of interest prior to severe event (competing cause), (4) cohort exit / transfer, practice stopped participating, or end of CPRD follow-up, (5) new user treatment ends, (6) LABD new user is prescribed an ICS, or (7) end of HES follow-up (). Each patient will have a time and "censoring" variable, which is an indicator variable (yes/no) that indicates 1 if they have had the event of interest or 0 if they are censored.

For the analysis of all pneumonia patients will be followed using a Cox proportional hazards model until they experience any pneumonia event (as their first pneumonia episode) or censoring.

To test proportionality of the hazard functions, model diagnostics will be evaluated by including time-dependent covariates in the Cox model. The primary outcomes will be severe pneumonia, (defined as severe CAP and HAP). As a secondary analysis, all pneumonia will be examined.

If one of the explanatory variables is not proportional, we will consider alternatives (time-dependent variable for the non-proportional predictors or stratification on the non-proportional predictors).

If the number of confounders requires reduction to be supported in the Cox model (based on feasibility), a variable selection strategy may be employed as described in the analysis plan.

Interactions between explanatory variables will be determined based on available theory and include ICS/LABD medication use by known risk factors for pneumonia (BMI, age, GOLD stage III/IV, MRC ≥4, history of pneumonia, current smoking status, deprivation quintiles). Additional interactions may be evaluated with ICS and other patient characteristics.

Additional analysis or adjustments to the analytic or modeling strategy will be performed if the data warrants. A more detailed modeling strategy, including generation of the propensity scores and Cox modeling, will be provided in the analysis plan.

5.7.5. Additional Multivariable Analyses

All pneumonia events will be combined as a secondary pneumonia outcome. Multivariable modeling will be employed on this outcome (all pneumonia) in the same manner as applied to the primary severe pneumonia outcome.

To examine a potential dose-response relationship with ICS-containing medications, the strength of the prescribed ICS medication on the Cohort Entry Date will be categorized into equipotent doses of low, medium, and high-dose ICS based on classification according to Figure 3-1 presented in the Global Initiative for Asthma (GINA) guidelines [GINA, 2011]. The strength of the new user prescription would be entered into the Cox model primary outcome models as low, medium, and high relative to LABD (e.g. dummy variables). Cumulative dose may be considered.

To identify more persistent users, the primary endpoint (severe pneumonia) will be evaluated restricting to patients who are prescribed treatment for greater than 6 months (allowing for 90-day gaps between treatments). Each inhaler can last up to 90 days.

As there may be differential drop out over time, ICS-Containing vs. LABD new users who continue taking medications for at least 6 months may not be clinically similar. Therefore, additional confounders will be identified in the 6-mo period to account for any events that would affect censoring or outcomes (e.g., COPD exacerbations, emergency and non-emergency hospitalization, primary care visits). The PS will be regenerated among the more persistent group to include updated confounders measured in the 6-mo period of persistent use as the new analysis "start". Patients who have an unresolved episode of pneumonia after 6 months of persistent use would be excluded from the persistent analysis. Patients would be required to have at least 14 days between their last pneumonia episode and the persistent analysis "start" date.

All analyses will be performed using SAS [Cary, NC].

If there is sufficient sample size, MRC dyspnea score will be included as a confounder in the primary model (collected 2009 onwards) as part of secondary analyses. Otherwise, it will not be included.

To examine potential differences in patient groups, demographic characteristics of patients with HES linkage vs. those without HES linkage will be compared. It is not expected that there will be clinically significant differences between these groups.

The number of deaths in each treatment group will be described. If available, the cause of death will be summarized for each treatment group.

5.7.6. Comparisons of Patient Characteristics by Pneumonia Status

To evaluate the third objective comparing patients developing severe pneumonia vs. non-severe pneumonia, a Pneumonia Population will be identified. The first pneumonia (or no pneumonia) within one year following the Cohort Entry Date will be included regardless of censoring in the proportional hazards model. Patients who do not experience pneumonia within the first year will be included in this analysis and counted as having no pneumonia.

As it is also of interest to compare patients who get pneumonia versus those who do not get pneumonia during this period, descriptive summaries will include all three categories: severe pneumonia (severe CAP and HAP combined), non-severe pneumonia, and no pneumonia. To assess differences between pneumonia groups, clinical and patient characteristics will be compared using the chi-square test or chi-square test using the row mean scores differ option in SAS to account for ordered response categories. For continuous measures, nonparametric tests including Wilcoxon rank sum test will be used as they do not require assumptions about normality or equal variance.

Characteristics of patients experiencing pneumonia within the year following Cohort may be compared to those individuals that did not develop and episode of pneumonia using multiple logistic regression modeling in an exploratory fashion in the new user cohort, irrespective of treatment and censoring. Based on the number of events, the number of confounders included in the model will be reduced using a variable reduction strategy to be described in the analysis plan. Treatment will not be included in the logistic regression modeling, as the model will focus on patient characteristics and does not account for treatment discontinuation.

5.7.7. Severe Pneumonia Descriptive Statistics

Further characterization of the severe pneumonias may be performed using descriptive statistics. Each severe CAP or HAP will be described using ICD-10 codes, primary vs. secondary cause, and length of stay in hospital. Reasons for primary admission will be described when pneumonia is a secondary cause. Pneumonia that did not result in hospitalization will be described according to medical codes.

If sample size allows, additional descriptive analysis or modeling among patients who are hospitalized for pneumonia will be performed to better understand if there are patient characteristics that could explain who may have more severe within-hospital pneumonia in terms of longer length of stay, fatality, etc.

5.7.8. Estimates of Precision

Estimates of precision were calculated on the expanded cohort including new users from the 2002-2010 study period, which included 12,000 ICS-containing medication users and 6,600 LABD users who experienced 283 first pneumonia events, including 106 severe

pneumonia events. Based on the number of pneumonia events prior to censoring, fixed sample size of new users, and rates of pneumonia in the combined population, this study should be able to exclude a margin of 2.0 for severe pneumonia and 1.5 for overall pneumonia.

Rates of pneumonia for the pooled new user cohort were: 15.8 per 1000 PY for CAP, 5.3 per 1000 person years for severe CAP. This was lower than the 22.4 per 1000 person years observed in a prevalent COPD cohort [Müllerova, 2012], but this is plausible as new users would not include as high a proportion of patients with more severe COPD

As part of the additional feasibility analysis, sample size calculations were tabulated to determine the differences that could be detected assuming the rates of CAP in the LABD control arm as 11 per 1000 PY, an odds ratio of 1.5 could be detected assuming a two-sided significance test at the 0.05 level with 85% power: (This would require a rate of 16.4 per 1000 PY and 270 pneumonia events.)

Assuming 5.3 per 1000 PY for severe CAP in the overall new user cohort, if the rate of severe pneumonia is 4 per 1000 PY in the LABD control arm, an odds ratio of 1.85 could be detected assuming a two-sided test at the 0.05 significance level with 82% power. (This would require a rate of 7.4 per 1000 PY in the ICS-containing group for a total of 115 pneumonia events.)

Although ruling out a 20 to 40% margin is desirable for most events, ruling out a margin between approximately 1.5 to 2.0 for overall CAP and severe CAP is still clinically relevant for rare but severe adverse events.

5.7.9. Statistical Analysis Plan

A more detailed statistical analysis plan will be written prior to analysis to clarify analyses required for the protocol. The analysis will primarily address the planned modeling and creating of propensity scores; however, additional programming or operational details may be provided. As data may have anomalies or issues that were not anticipated during the writing of the protocol, some refinements to the analysis are expected as the data warrant. Any differences from the planned analysis (e.g., differences in definitions, covariates, etc) and their rationale will be described in the study report.

6. DISCUSSION

Evidence generated from this observational study is complementary to analyses from the FF/VI clinical development program. An advantage of the primary care database (CPRD-GOLD) is the ability to examine and adjust for risk factors for pneumonia (e.g., BMI, lung function, smoking history, MRC dyspnea score) included in the UK Quality Outcomes Framework (QOF) for COPD that are not collected routinely in most other observational data sources (e.g. healthcare insurance claims). A further advantage of the design is the increased specificity of COPD diagnosis relative to other healthcare databases enabled by the routinely collected lung function and QOF protocol. Another advantage of this study is the new-user design, which minimizes biases that can be caused by comparing events between prevalent user groups (e.g., survivor bias, covariates altered by exposure which cannot be resolved through statistical adjustment). However, a disadvantage of the new-user approach is a smaller sample size relative to alternative designs that include prevalent users and potentially a loss in generalizability of the results.

As a result of the subsequent feasibility prior to the conduct of the study, this protocol was amended to improve precision. The study period was expanded to include more patients and pneumonia events. In addition, the pneumonia endpoints were grouped as severe events (1 HAP and all severe CAP combined). In addition, an overall pneumonia outcome was included rather than severe CAP and non-severe CAP in order to improve on precision and to inform on pneumonia overall. There are also known limitations of database analyses, including the potential for confounding by severity. ICS-containing medications may be dispensed to patients who have more severe COPD or those at higher risk for exacerbation than patients who are receiving long-acting bronchodilators alone. In this study, we will adjust for disease severity in the year prior to initiation using propensity scores, including lung function, exacerbation history, pneumonia history, smoking status, and treatment. Only diagnosed diseases are recorded in CPRD-GOLD. Medication use in CPRD-GOLD is based on prescribed medications recorded by the GP, which might not have been dispensed at the pharmacy or ultimately utilized by the patient. Diagnostic practices for pneumonia may be different in the UK compared with other countries limiting the generalizability. A final disadvantage is that this study does not include the investigational combination inhaled medication FF/VI, but rather can only examine approved ICS-containing medications in this retrospective cohort design.

When identifying pneumonia in databases, definitions are based upon existing information collected in routine healthcare which may not include all details measured in clinical trials. In addition, there is lack of agreement between pneumonia classification in the absence of chest x-rays, sputum, etc. Our definitions were based on using HES for hospitalization and built upon prior work (including validation of severe CAP). There may be some confusion between diagnoses of pneumonia versus influenza-related morbidity.

Despite the limitations, this study will provide insights into risk factors for all pneumonias and severe pneumonia, including whether ICS modify the effect of risk factors for severe pneumonia. The results may identify more specific patient groups that are at greatest risk of severe pneumonia and may identify where risk minimization and/or medical recommendations may be appropriate.

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8. TABLE SHELLS

New User Feasibility to be Completed Prior to Analysis Study Tables

Table 5 New User Feasibility: Estimates of New Users by Year Meeting Inclusion/Exclusion – New User Cohort

	Year of Cohort Entry						
Number of New Users	**2002..**	**2006**	**2007**	**2008**	**2009**	**2010**	**Total Number of Patients***
LABD							
LABD new users							
LABA							
LAMA							
Persistent LABD new users (≥6 mo treatment)							
LABA							
LAMA							
ICS							
ICS new users							
ICS-Containing fixed dose combination							
ICS Monotherapy							
ICS/SABA							
Persistent ICS-Containing new users (≥6 mo treatment)							
ICS/LABA fixed dose inhaler							
ICS Monotherapy							
ICS/SABA							
Average Follow-Up Time (Censoring/Event-Cohort entry+1)							
Mean (SD)	-	-	-	-	-	-	
Median	-	-	-	-	-	-	
Min, Max	-	-	-	-	-	-	

*Patients are counted exactly once and will be selected into the group of their first new use in the period. In the case of more than one type of new use or more than one new use for the same medication, the first instance of new use is selected. All inclusion/exclusion criteria will be applied from the protocol minus the information relating to censoring and pneumonia endpoints.

Table 6 New User Feasibility: First Pneumonia Events Prior to Censoring by Type- New User Cohort

	Cohort Entry Date						
Pneumonia Events	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**Total Number of Patients**
All Pneumonia							
Non-severe CAP							
Severe CAP							
HAP							

Patients can have only **one** pneumonia in this table if they have non-severe CAP, severe CAP, and HAP following their Cohort Entry Date. The first pneumonia only is retained.

Table 7 Descriptive characteristics for the new user COPD cohort from Baseline Period / Patient History- New User Cohort Free of Pneumonia at Index Date

Variable		ICS -Containing-	LABD	p-value
N				
Gender	Male, %			
Age in years (%)	45 to 64			
	65 to 79			
	80 and older			
Smoking history (%)	Current			
	Former			
	Non-Smoker			
	Unknown/Missing			
COPD severity (%)	COPD Dx but spirometry conflicts			
	Gold 0			
	I			
	II			
	III			
	IV			
	Unknown			
Asthma history (%)	Yes			
Any Pneumonia episode history within baseline period (%) Yes				
Number of non-severe pneumonia episodes (within the baseline period) (N, %) 0				
	1			
	2			
	3			
	4+			
Number of severe CAP episodes (within the baseline period) (N, %) 0				
	1			
	2			
	3			
	4+			
Number of HAP episodes (within the baseline period) (N, %) 0				
	1			

Variable		ICS -Containing-	LABD	p-value
	2			
	3			
	4+			
Deprivation Quintile	1			
	2			
	3			
	45			

Treatment groups will be compared on baseline characteristics using chi-square test and if appropriate, the row mean scores differ option in SAS for ordered categorical variables to take advantage of the ordering for ordinal categories. Unknown or missing would be excluded.

Note: This table is to be repeated for the New User Cohort free of pneumonia at index date, New Users without HES (complete the table through asthma history) , New Users with HES Excluded from Final Analysis(for information on patients influential values / on-going pneumonia) and Final Analysis Population.

Table 8 Patient Co-morbidities and Medications used in the Baseline Period / Patient History- New User Cohort Free of Pneumonia at Index Date

Variable	ICS-Containing	LABD	p-value
N			
Vaccination (%)			
Influenza in the past 12 mo			
Pneumococcal in the past 5 years			
BMI mean (SD)			
Underweight (<18.5),			
Low Normal (18.5-≤20.9)			
High Normal (21 - ≤24.9)			
Overweight (25.0 - ≤29.9)			
Obese (>30.0)			
Comorbid conditions (%)			
Asthma			
Myocardial Infarction			
Congestive Heart Failure			
CerebroVascular Disease			
Dementia			
GERD			
Peptic Ulcer			
Peripheral Vascular Disease			
Mild Liver Disease			
Moderate Liver Disease			
Connective Tissue Disorder			
Hemiplegia/Paraplegia			
Diabetes			
Diabetes (with complications)			
Anxiety			
Depression			
Cancer (non-metastatic solid tumours, leukemias/lymphomas)			
Cancer (metastatic solid tumours)			
Lung cancer			
Renal diseases			
COPD Therapy			
COPD therapy in prior 12 months associated with severity (%)			
Oral Corticosteroids (>4 Rx in 12 months)			
Home Oxygen therapy			
Nebulized therapy			
Other COPD therapy in prior 12 (%)			
SABD			

Variable	ICS-Containing	LABD	p-value
Theophylline			
Other Medications			
ACE-inhibitors			
Statins			
Immunosuppresants			
Cancer treatment			
All GP visits within past 12 mo			
Mean (SD)			
Median			
Min, Max			
0			
1-5			
6-10			
11-15, 16-20, >20			
All Emergency Hospitalizations within past 12 mo			
Mean (SD)			
Median			
Min, Max			
0			
1-2			
3+			
All Non-Emergency Hospitalizations within past 12 mo			
Mean (SD)			
Median			
Min, Max			
0			
1-2			
3+			
COPD exacerbations within prior 12 mo			
COPD hospitalisations			
0			
1			
2+			
Moderate exacerbations			
0			
1			
2+			

1. *Tables maybe updated if needed to reflect final modelling strategy as outlined in the statistical analysis plan
2. Note: This table is to be repeated for the **New User Cohort without HES and Final Analysis Cohort.**

Table 9 The incidence density, rates per 1,000 person-years, of first pneumonia episodes in a new user COPD cohort, GPRD, stratified by covariates: Severe CAP, All CAP –Final Analysis Population

		ICS-containing new users			LABD new users		
Stratum	**Value**	**N**	**Person Years**	**Rate per 1000 PY**	**N**	**Person Years**	**Rate per 1000 PY**
Overall							
Gender	Female						
	Male						
Age	45 to 64						
	65 to 79						
	>= 80						
Smoking	Current						
	Past						
	Never						
	Unknown						
Asthma history	Yes						
	No						
Prior pneumonia	Yes						
	No						
COPD severity	Dx but spirometry conflicts						
	Gold 0						
	1						
	II						
	III						
	IV						
	Unknown						

1. Note: Table will be repeated for each pneumonia outcome separately (non-severe CAP, Severe CAP, HAP).

Table 10 First Pneumonia Events and Censoring Information –Final Analysis Population

Event or Censoring	**All pneumonia events N=XXX**
Pneumonia Event	
Censored	
Death	
Cohort Exit/transfer, practice stopped participating, or end of CPRD	
HES Study Period Ended	
New User Treatment discontinued	
LABD new user is prescribed an ICS	
Time until event or censoring (days)	
Mean (SD)	
Median	
Min, Max	

Table 11 Factors Associated with time to first severe pneumonia event(HAP, or non-severe CAP combined) occurrence from Multivariable Cox model with propensity score adjustment –Final Analysis Population

		Hazard Rates		
Stratum	**Value**	**Adjusted HR**	**Lower 95% CI**	**Upper 95% CI**
Overall				
Treatment	ICS-Containing Medication=1			
Gender	Female (reference)			
Age	45 to 64			
	65 to 79			
	>= 80			
Smoking	Current			
	Past			
	Never / Non-smoker (reference)			
	Unknown			
Asthma history	Yes			
Prior pneumonia	Yes			
COPD severity	Dx but spirometry conflicts (no COPD)			
	Gold 0 (reference)			
	I			
	II			
	III			
	IV			
	Unknown			

		Hazard Rates		
Stratum	**Value**	**Adjusted HR**	**Lower 95% CI**	**Upper 95% CI**
Influenza Vaccination (past 12 mo) Yes				
Pneumococcal vaccination (past 5 years.) Yes				
BMI	Underweight (<18.5),			
	Low Normal (18.5 - ≤21)			
	High Normal (21-≤24.9)			
	Overweight (25.0 - ≤29.9)			
	Obese (≥30.0)			
	Underweight (<18.5),			
Comorbid conditions prior to new use **No is reference for each condition**				
	Asthma			
	Myocardial Infarction			
	Congestive Heart Failure			
	CerebroVascular Disease			
	Dementia			
	GERD			
	Peptic Ulcer			
	Peripheral Vascular Disease			
	Mild Liver Disease			
	Moderate Liver Disease			
	Connective Tissue Disorder			
	Hemiplegia/Paraplegia			
	Diabetes			

		Hazard Rates		
Stratum	**Value**	**Adjusted HR**	**Lower 95% CI**	**Upper 95% CI**
	Diabetes (with complications)			
	Anxiety			
	Depression			
	Cancer (non-metastatic solid tumours, leukemias/lymphomas)			
	Cancer (metastatic solid tumours)			
	Lung cancer			
	Renal diseases			
COPD therapy, past 12 mos associated with severity / frailty (%)				
	Frequent Oral Corticosteroids			
	Home Oxygen therapy			
	Nebulized therapy			
Other COPD therapy in prior 12 (%)				
	SABD			
	Theophylline			
Other Medications	ACE-inhibitors			
	Statins			
	Immunosuppresants			
	Cancer treatment			
All GP visits within past 12 mo				
	0			
	1-5			

		Hazard Rates		
Stratum	**Value**	**Adjusted HR**	**Lower 95% CI**	**Upper 95% CI**
	6-10			
	11-15, 16-20, >20			
All Emergency Hospitalizations, past 12 mo				
	0			
	1-2			
	3+			
All Non-Emergency Hospitalizations, past 12 mo				
	0			
	1-2			
	3+			
COPD exacerbations, past 12 mo				
	COPD hospitalisations			
	0			
	1			
	2+			
	Moderate exacerbations			
	0			
	1			
	2+			

1. *Adjustments to these confounders, including re-parameterization of the confounders, may be performed during the analyses as outlined in the analysis plan.
2. Note: This table will be repeated on Final Analysis Population examining All pneumonia events, dose (Low, Medium, High), among persistent users (at least 6 months), and by dose among persistent users.

Table 12 Patient characteristics of Patients with COPD who experience Severe Pneumonia, Non-Severe Pneumonia, or No Pneumonia within first year

Variable		Severe Events	Non- Severe CAP	No Pneumonia	p-value
N					
Gender	Male, %				
Age in years (%)	45 to 64				
	65 to 79				
	80 and older				
Smoking history (%)	Current				
	Former				
	Non-Smoker				
	Unknown/Missing				
COPD severity (%)	COPD Dx but spirometry conflicts				
	Gold 0				
	I				
	II				
	III				
	IV				
	Unknown				
Asthma history (%)	Yes				
Any Pneumonia episode history (%)	Yes				

Variable		Severe Events	Non- Severe CAP	No Pneumonia	p-value
Number of severe pneumonia episodes (within the baseline period) (N, %)	0				
	1				
	2				
	3				
	4+				
Number of severe pneumonia episodes (within the baseline period) (N, %)	0				
	1				
	2				
	3				
	4+				
Deprivation Quintile	1				
	2				
	3				
	4				
	5				

a. Treatment groups will be compared on baseline characteristics using chi-square test row mean scores differ for categorical variables to take advantage of the ordering for ordinal categories.

Table 13 Patient Co-morbidities and Medications used in the period prior to Severe vs. Non-Severe Pneumonia Diagnosis – Pneumonia Population

Variable	Severe Events	Non-Severe CAP	No Pneumonia	p-value
N				
Vaccination (%)				
Influenza in the past 12 mo				
Pneumococcal in the past 5 years				
BMI mean (SD)				
Underweight (<18.5),				
Low Normal (18.5-≤20.9)				
High Normal (21 - ≤24.9)				
Overweight (25.0 - ≤29.9)				
Obese (>30.0)				
Comorbid conditions (%)				
Asthma				
Myocardial Infarction				
Congestive Heart Failure				
CerebroVascular Disease				
Dementia				
Peptic Ulcer				
Peripheral Vascular Disease				
Mild Liver Disease				
Moderate Liver Disease				
Connective Tissue Disorder				

Variable	Severe Events	Non-Severe CAP	No Pneumonia	p-value
Hemiplegia/Paraplegia				
Diabetes				
Diabetes (with complications)				
Anxiety				
Depression				
Cancer (non-metastatic solid tumours, leukemias/lymphomas)				
Cancer (metastatic solid tumours)				
Lung cancer				
Renal diseases				
COPD therapy in prior 12 months associated with severity (%)				
Oral Corticosteroids				
Home Oxygen therapy				
Nebulised therapy forms				
Other medicines in prior 12 months (%)				
ACE-inhibitors				
Statins				
Immunosuppresants				
Cancer treatment				

Variable	Severe Events	Non-Severe CAP	No Pneumonia	p-value
All GP visits within past 12 mo				
0				
1-5				
6-10				
11+				
All Emergency Hospitalizations within past 12 mo				
0				
1-2				
3+				
All Non-Emergency Hospitalizations within past 12 mo				
0				
1-2				
3+				
COPD exacerbations within prior 12 mo				
COPD hospitalisations				
0				
1				
2+				

Variable	Severe Events	Non-Severe CAP	No Pneumonia	p-value
Moderate exacerbations				
0				
1				
2+				

1. *Tables will be updated to match protocol any adjustments to the analysis based on the analysis plan.

Table 14 Exploratory Analysis: Factors Associated with Severe Pneumonia vs. No Pneumonia during multivariable logistic regression-within the first year

		Odds Ratio		
Stratum	**Value**	**Adjusted OR**	**Lower 95% CI**	**Upper 95% CI**
Overall				
Gender	Female (reference)			
Age	45 to 64			
	65 to 79			
	>= 80			
Smoking	Current			
	Past			
	Never / Non-smoker (reference)			
	Unknown			
Asthma history	Yes			
Prior pneumonia	Yes			
COPD severity	Dx but spirometry conflicts (no COPD)			
	Gold 0 (reference)			
	I			
	II			
	III			
	IV			
	Unknown			
Influenza Vaccination (past 12 mo) Yes				
Pneumococcal vaccination (past 5 years.) Yes				
BMI	Underweight (<18.5),			
	Low Normal (18.5 - ≤20.9)			
	High Normal (21-≤24.9)			
	Overweight (25.0 - ≤29.9)			
	Obese (>30.0)			
	Underweight (<18.5),			
Comorbid conditions prior to new use No is reference for each condition				
	Asthma			
	Myocardial Infarction			
	Congestive Heart Failure			
	CerebroVascular Disease			
	Dementia			
	GERD			
	Peptic Ulcer			
	Peripheral Vascular Disease			
	Mild Liver Disease			

		Odds Ratio		
Stratum	**Value**	**Adjusted OR**	**Lower 95% CI**	**Upper 95% CI**
	Moderate Liver Disease			
	Connective Tissue Disorder			
	Hemiplegia/Paraplegia			
	Diabetes			
	Diabetes (with complications)			
	Anxiety			
	Depression			
	Cancer (non-metastatic solid tumours, leukemias/lymphomas)			
	Cancer (metastatic solid tumours)			
	Lung cancer			
	Renal diseases			
COPD therapy, past 12 mo associated with severity / frailty (%)				
	Frequent Oral Corticosteroids			
	Home Oxygen therapy			
	Nebulized therapy			
Other COPD therapy in prior 12 (%)				
	SABD			
	Theophylline			
Other Medications	ACE-inhibitors			
	Statins			
	Immunosuppresants			
	Cancer treatment			
All GP visits within past 12 mo				
	0			
	1-5			
	6-10			
	11-15, 16-20, >20			
All Emergency Hospitalizations, past 12 mo				
	0			
	1-2			
	3+			
All Non-Emergency Hospitalizations, past 12 mo				
	0			
	1-2			
	3+			

		Odds Ratio		
Stratum	**Value**	**Adjusted OR**	**Lower 95% CI**	**Upper 95% CI**
COPD exacerbations, past 12 mo				
	COPD hospitalisations			
	0			
	1			
	2+			
	Moderate exacerbations			
	0			
	1			
	2+			

1. Note: This table may be repeated for All pneumonia vs. No pneumonia.
2. The number of covariates will be adjusted based on the number that can be supported by the number of events.

Figures

1. Consort Diagram for new user cohort to final analysis population (how many are lost/retained with each inclusion/exclusion including additional requirements for final analysis population
2. Time to severe pneumonia (by ICS-containing vs. LABD)
3. Time to all pneumonia (by ICS containing vs. LABD)
4. Length of Stay boxplots for hospitalized pneumonia (Severe CAP and HAP combined)