Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Eosinophil levels: The cutoffs chosen for analysis were 100 cells/microliter and 300 cells/microliter based on the GOLD guidelines, which use these cutoffs to identify patients' likelihood of response to inhaled corticosteroids.[1,2] We excluded patients with a most recent eosinophil count > 5,000 cells/microliter in our primary analysis (the lower limit of severe eosinophilia) to avoid including patients with potential myeloproliferative hypereosinophilic disorders. On prespecified sensitivity analysis, we used different upper bounds of eosinophil levels, including the upper bound of 600 cells/microliter used in the FLAME trial,[3] an upper bound of 1,500 cells/microliter (the lower limit of moderate eosinophilia), and no upper bound.

Sensitivity analyses: We altered our primary analysis by shortening the grace period permitted between prescription fills to 30 days, lengthening it to 90 days, and performing an intention-to-treat analysis. On the intention-to-treat analysis, we followed patients for up to a year until death or the end of insurance coverage, regardless of whether they discontinued, switched, or added therapy during follow-up. We examined the effect of excluding outcomes of interest in the first 30 days and first 60 days after cohort entry to account for a potential lag in the effects of inhaler therapy, and we altered the follow-up time (shortened to 180 days and lengthened to 720 days) to account for potential attenuation or augmentation of effects over time. We also studied the effect of altering the definition of severe COPD exacerbation by requiring that patients have a specific exacerbation diagnosis code (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] 491.21 or 491.22 or *International Classification of Diseases, Tenth*

Revision, Clinical Modification [*ICD-10-CM*] J44.0 or J44.1) in any position. We altered the definition of moderate COPD exacerbations by requiring a 30-day gap (rather than 14-day gap) between a new prednisone fill and the last prednisone fill or COPD hospitalization and, in a separate sensitivity analysis, by requiring an emergency department visit or office visit for COPD within 5 days of the prednisone fill. In further post-hoc sensitivity analyses, we modified the definition of moderate exacerbation to include prescription fills of either prednisone or antibiotics; we also performed a sensitivity analysis in which moderate exacerbations were defined by fills of both prednisone and antibiotics on the same day. We altered the definition of pneumonia hospitalization by requiring that a pneumonia diagnosis appear in the primary position. We performed sensitivity analyses using 1:1 high-dimensional propensity score matching[4-6] and post-hoc sensitivity analyses adjusting for deciles of propensity score (both untrimmed and trimmed [2.5%, asymmetric method]).

High-dimensional propensity score matching: To perform high-dimensional propensity score matching, we used data for *ICD-9-CM* and *ICD-10-CM* diagnosis codes and procedure codes for inpatient confinements and medical services, Current Procedure Terminology codes for medical services, and prescription drug claims (based on National Drug Code generic name).

Outcome definitions: The outcome definitions used in our study had the following positive predictive values in previous validation studies: moderate COPD exacerbation, 0.73;[7] severe COPD exacerbation, 0.85;[8] and pneumonia hospitalization, 0.88.[9] Note that the validation study of moderate COPD exacerbations was conducted in the United Kingdom and was based on prescriptions in the electronic medical record rather than on prescriptions filled at the pharmacy.

The validation studies for severe COPD exacerbation and pneumonia hospitalization were conducted in the US based on claims with *ICD-9-CM codes*. To construct outcome definitions in our study, we converted *ICD-9-CM* codes to *ICD-10-CM* codes based on clinical review.

eTable 1. Key Randomized Controlled Trials Comparing LAMA-LABA to ICS-LABA Therapy in COPD

			Event rates	
Key trials	**Summary of findings**	**Key endpoints**	**ICS-LABA**	**LAMA-LABA**
FLAME[3]	LAMA-LABA therapy was associated with lower rates of COPD exacerbations and pneumonia hospitalizations compared to ICS-LABA therapy.	Annual rate of all COPD exacerbations (primary endpoint)	4.03	3.59
		Annual rate of moderate or severe COPD exacerbations[a]	1.19	0.98
		Time to first COPD exacerbation, days[a]	51	71
		Time to first moderate or severe COPD exacerbation, days[a]	87	127
		Incidence of pneumonia, %	4.8	3.2
IMPACT[10]	LAMA-LABA therapy was associated with higher rates of COPD exacerbations compared to ICS-LABA therapy but lower rates of pneumonia.	Annual rate of moderate or severe COPD exacerbations (primary endpoint)	1.07	1.21
		Annual rate of pneumonia episodes per 1,000 person-years	96.6	61.2
ETHOS[11]	LAMA-LABA therapy was associated with higher rates of COPD exacerbations compared to ICS-LABA therapy but lower rates of pneumonia.	Annual rate of moderate or severe COPD exacerbations (primary endpoint)	1.24	1.42
		Annual rate of pneumonia episodes per 1,000 person-years	63.8	37.3

FLAME: Effect of Indacaterol Glycopyrronium vs. Fluticasone Salmeterol on COPD Exacerbations; IMPACT: Informing the Pathway of COPD Treatment; ETHOS: Efficacy and Safety of Triple Therapy in Obstructive Lung Disease; ICS: inhaled corticosteroid; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; COPD: chronic obstructive pulmonary disease; CI: confidence interval

a. All secondary analyses in FLAME were reported in the modified intention to treat population.

eTable 2. Inhalers in the exposure and referent groups

LAMA-LABA (exposure)		ICS-LABA (referent)	
Generic name	*Brand-name*	*Generic name*	*Brand name*
aclidinium-formoterol	Duaklir Pressair	budesonide-formoterol	Symbicort
glyocpyrronium-formoterol	Bevespi Aerosphere	fluticasone-salmeterol	Advair Diskus
glycopyrronium-indacaterol	Utibron Neohaler	fluticasone-salmeterol	Advair HFA
tiotropium-olodaterol	Stiolto Respimat	fluticasone-salmeterol	AirDuo Respiclick[a]
umeclidinium-vilanterol	Anoro Ellipta	fluticasone-salmeterol	Wixela Inhub
		fluticasone-vilanterol	Breo Ellipta
		mometasone-formoterol	Dulera

LAMA: long-acting muscarinic antagonist; LABA: long-acting beta agonist; ICS: inhaled corticosteroid.
a. The AirDuo Respiclick also has an authorized generic that is included in the analysis.

eTable 3. Identification of Oral Antibiotics Used to Treat COPD Exacerbations[a]

Class	Antibiotics included
Aminopenicillin	amoxicillin, amoxicillin-clavulanate, ampicillin, ampicillin-sulbactam
Cephalosporins[b]	
Second generation	cefaclor, cefprozil, cefuroxime
Third generation	cefdinir, cefditoren, cefixime, cefpodoxime, ceftibuten
Fluoroquinolones	ciprofloxacin, delafloxacin, gemifloxacin, levofloxacin, moxifloxacin, ofloxacin
Ketolides	telithromycin
Macrolides	azithromycin, clarithromycin, erythromycin
Tetracyclines	demeclocycline, doxycycline, minocycline, omadacycline, oxytetracycline, tetracycline
Other	trimethoprim-sulfamethoxazole

a. Outpatient antibiotic treatment in COPD exacerbations is aimed at covering pathogens that are frequently isolated during exacerbations, including *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa*. To develop a list of antibiotics commonly used in COPD exacerbations, we first consulted guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[1] the American Thoracic Society/European Respiratory Society,[12] the American Family Physician,[13] *Annals of Internal Medicine* "In the Clinic,"[14] the United Kingdom National Institute for Health and Care Excellence guidelines,[15] the Johns Hopkins antibiotic guide,[16] and *UpToDate*.[17] We chose to include official guidelines (written for audiences in pulmonary medicine, family medicine, and internal medicine) and pocket/online guidelines to capture the gamut of choices that clinicians make when selecting antibiotics for COPD exacerbations. We identified all individual oral antibiotics explicitly mentioned in these guidelines. We then searched all clinical trials for outpatient COPD exacerbations that were referenced in each guideline for additional oral antibiotics that may not have been explicitly mentioned. The most recent Cochrane Review of antibiotics used to treat COPD exacerbations[18] and several other systematic reviews, meta-analyses, and pooled analyses[19-26] were included with this additional search. We grouped all drugs by class (using classes set out in the guidelines) and, for the sake of completeness, searched for other drugs in each class that were not explicitly mentioned in the guidelines or cited studies but still had an indication for respiratory conditions.[17,27] Oral antibiotics were excluded if they were not on the market during the study period, were not yet approved in the US, or were otherwise not available in the US. All intravenous agents were excluded.

b. No guidelines recommended 1st generation cephalosporins, and, while one 1st generation cephalosporin (cefalexin) was studied in a trial cited by the guidelines, we excluded 1st generation cephalosporins.

eTable 4. Reasons for Censoring in the Primary Effectiveness Analysis

Censoring reason	ICS-LABA, n (%) (n=30,216)[a]	LAMA-LABA, n (%) (n=30,216)[b]
Outcome	3,901 (12.9)	4,250 (14.1)
Death or end of patient enrollment	2,465 (8.2)	2,852 (9.4)
Start of exposure (LAMA-LABA or ICS-LABA) different from the index exposure	441 (1.5)	819 (2.7)
ICS or LAMA added or ICS-LAMA-LABA begun	4,264 (14.1)	2,166 (7.2)
End of index exposure	16,542 (54.8)	15,514 (51.3)
Maximum follow-up time	2,603 (8.6)	4,615 (15.3)

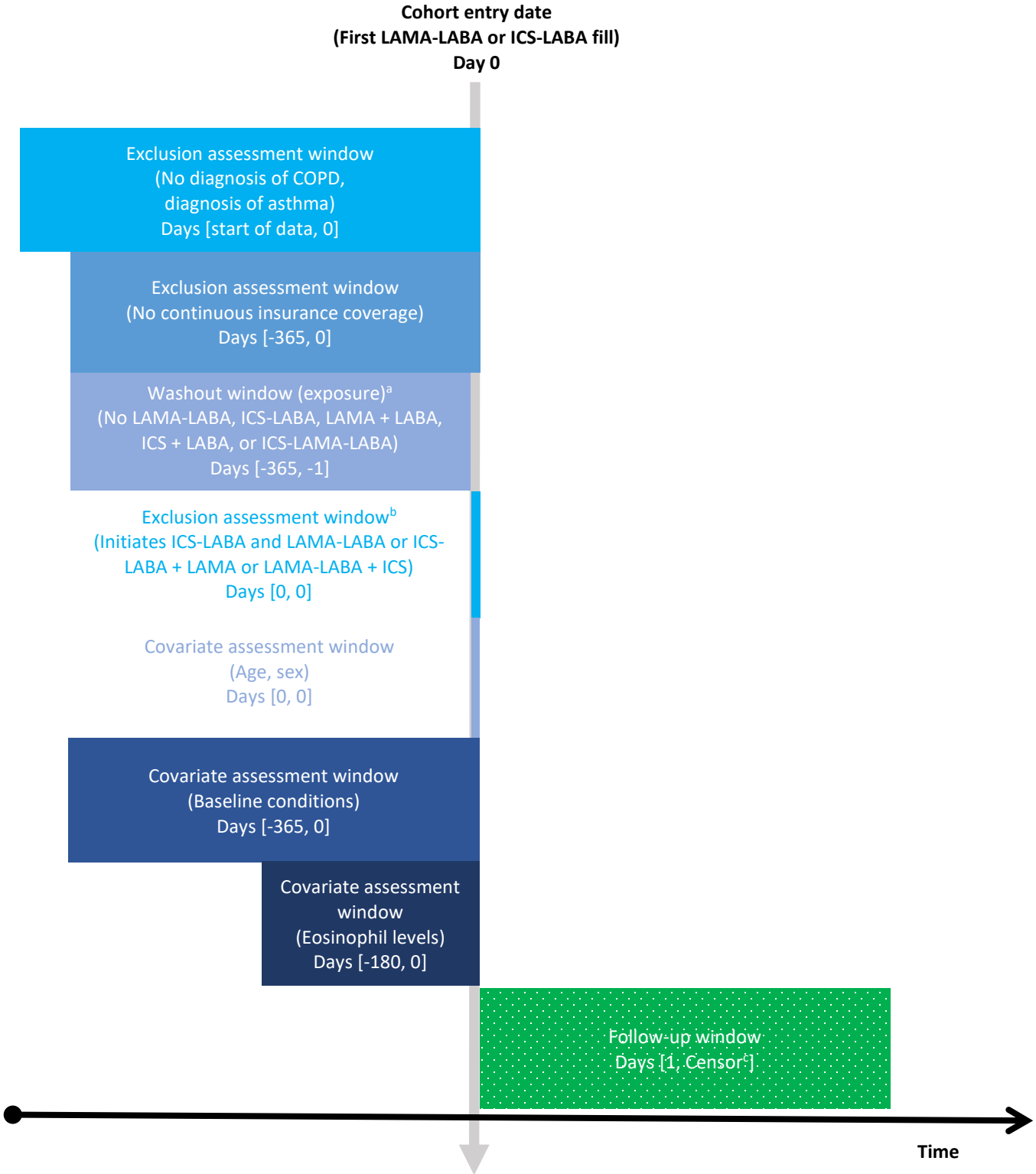
ICS: inhaled corticosteroid; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist.
a. Mean follow-up was 129.6 days in the ICS-LABA group.
b. Mean follow-up was 160.1 days in the LAMA-LABA group.

eTable 5. Reasons for Censoring in the Primary Safety Analysis

Censoring reason	ICS-LABA, n (%) (n=30,216)[a]	LAMA-LABA, n (%) (n=30,216)[b]
Outcome	1,201 (4.0)	1,177 (3.9)
Death or end of patient enrollment	2,574 (8.5)	2,996 (9.9)
Start of exposure (LAMA-LABA or ICS-LABA) different from the index exposure	494 (1.6)	940 (3.1)
ICS or LAMA added or ICS-LAMA-LABA begun	4,707 (15.6)	2,631 (8.7)
End of index exposure	17,988 (59.5)	16,835 (55.7)
Maximum follow-up time	3,252 (10.8)	5,637 (18.7)

ICS: inhaled corticosteroid; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist.
a. Mean follow-up was 139.5 days in the ICS-LABA group.
b. Mean-follow-up was 173.3 days in the LAMA-LABA group.

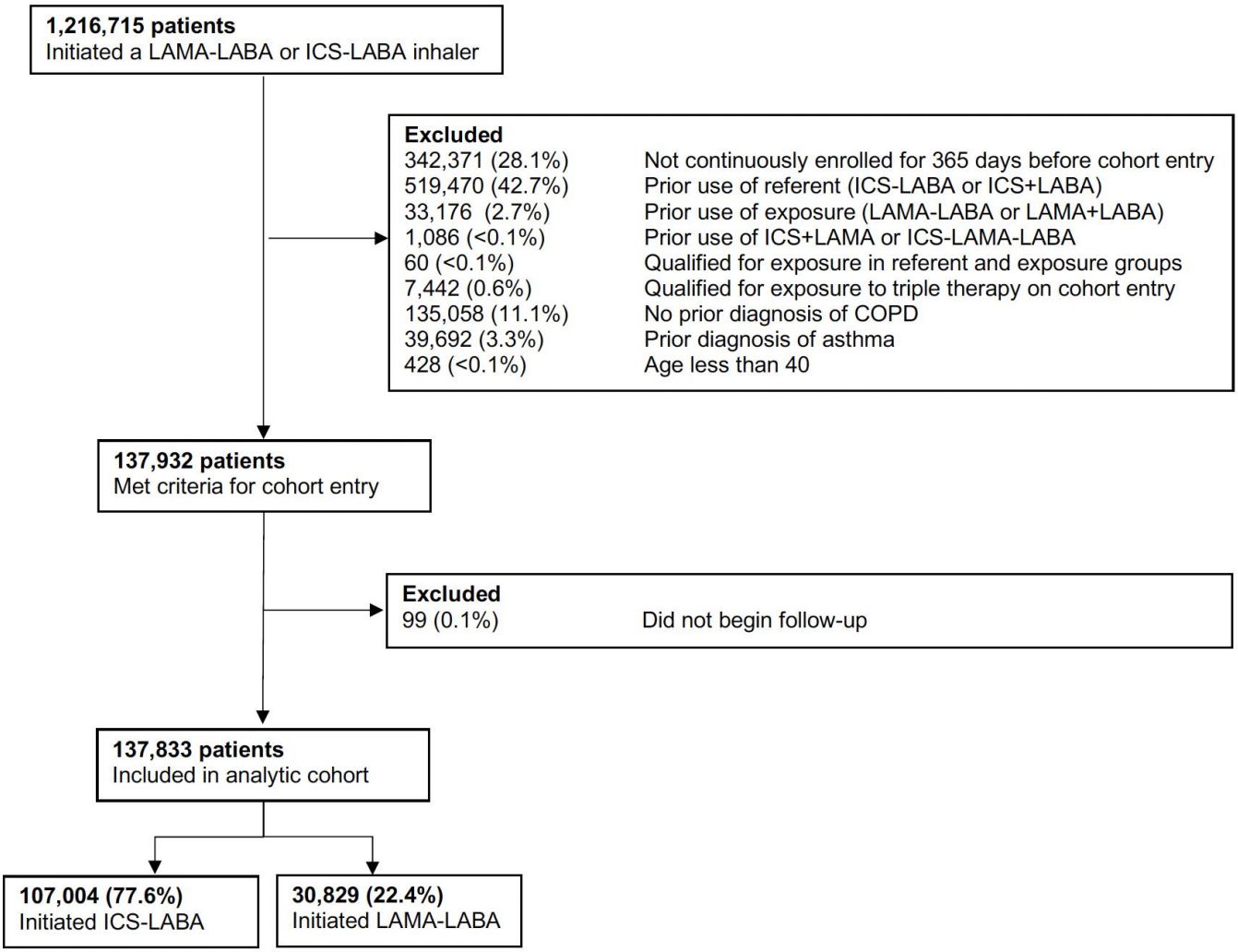
eFigure 1. Study Design Comparing New LAMA-LABA Users to ICS-LABA Users



ICS: inhaled corticosteroid; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist.
This graphical representation of study design shows how exclusion criteria were applied prior to cohort entry and how covariates were assessed.[28]

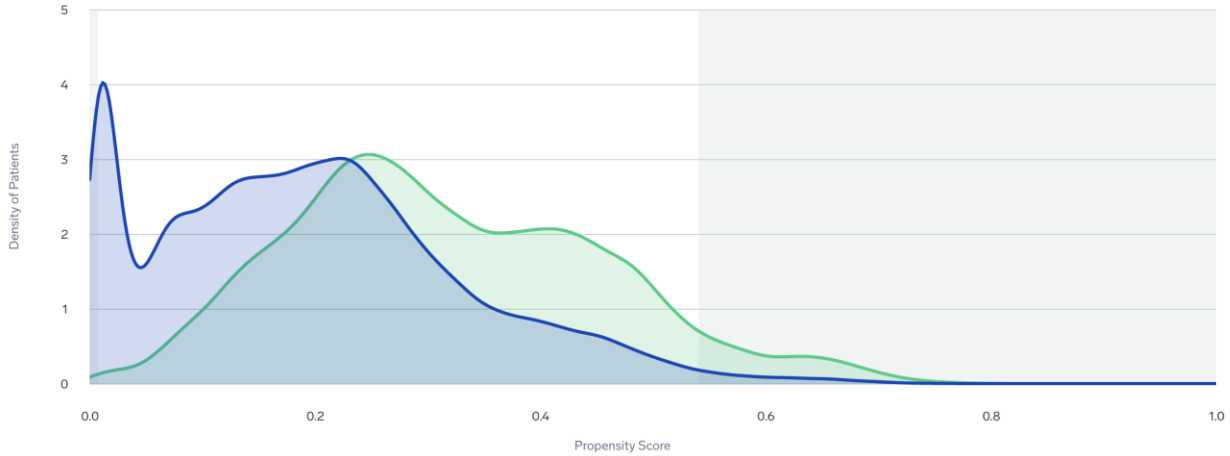
a. During the washout-period, patients could not receive the exposure in combination form (LAMA-LABA) or via separate inhalers (LAMA + LABA). Likewise, the patient could not receive the referent in combination form (ICS-LABA) or via separate inhalers (LAMA + LABA). The definition of receiving dual therapy via separate inhalers was receiving one single-agent inhaler (e.g. ICS inhaler) within 30 days of another single-agent inhaler (e.g. LABA inhaler). Any patient receiving triple therapy (ICS-LAMA-LABA) during the washout period was also excluded.
b. We excluded patients who initiated the exposure and referent on the same day and those who initiated triple therapy via separate inhalers on the cohort entry date (ICS-LABA + LAMA or LAMA-LABA + ICS).
c. Censoring occurred at the earliest event among the following: discontinuation of treatment (with a 60-day grace period between prescription fills), switch from exposure to referent or vise-versa, the addition of an ICS or LAMA, initiation of an ICS-LAMA-LABA, death, or the end of insurance coverage.

eFigure 2. Cohort Composition

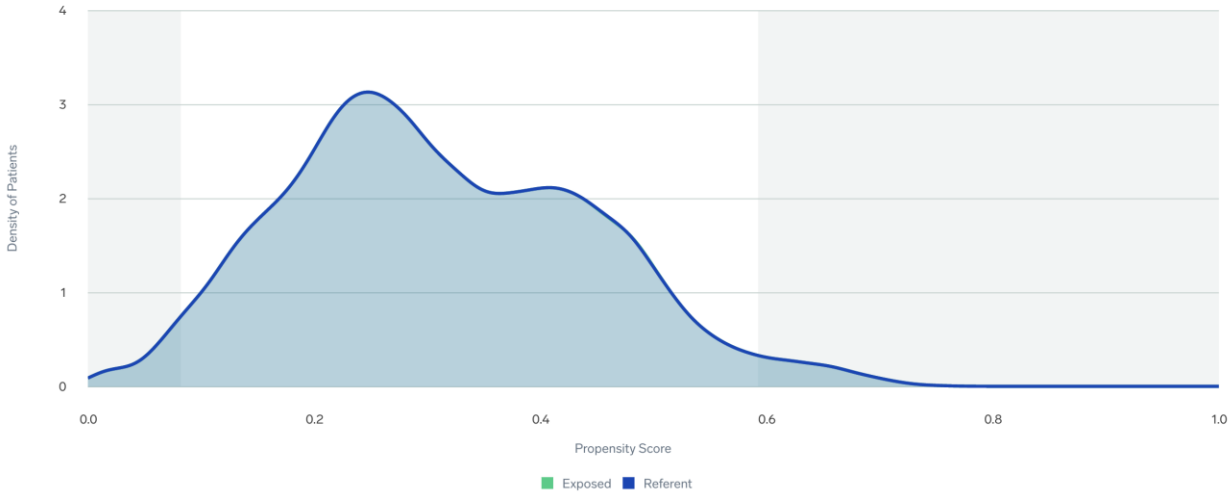


eFigure 3. Propensity Score Distributions Before and After Matching

A: Propensity score distributions before matching

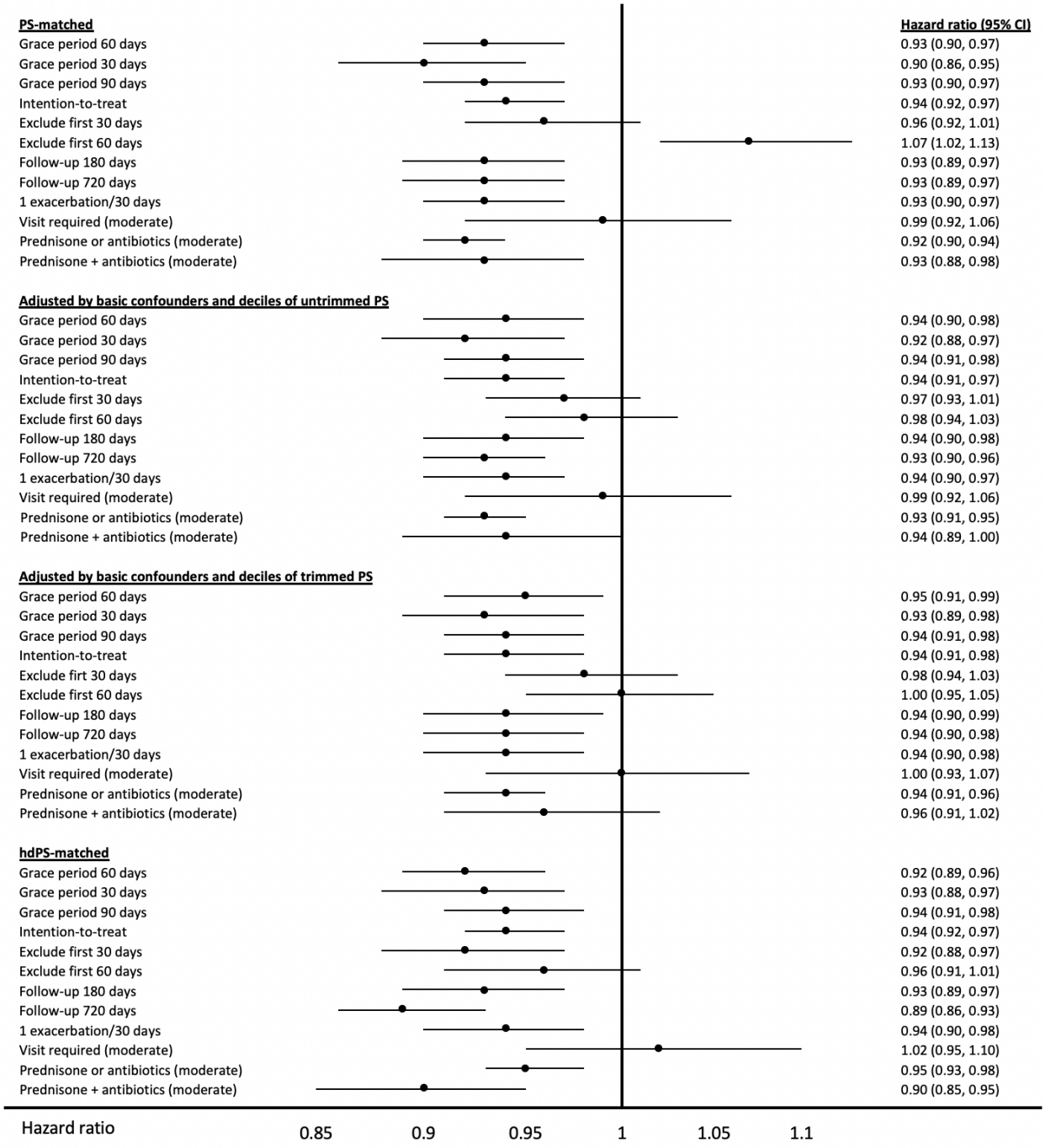


B: Propensity score distributions after matching



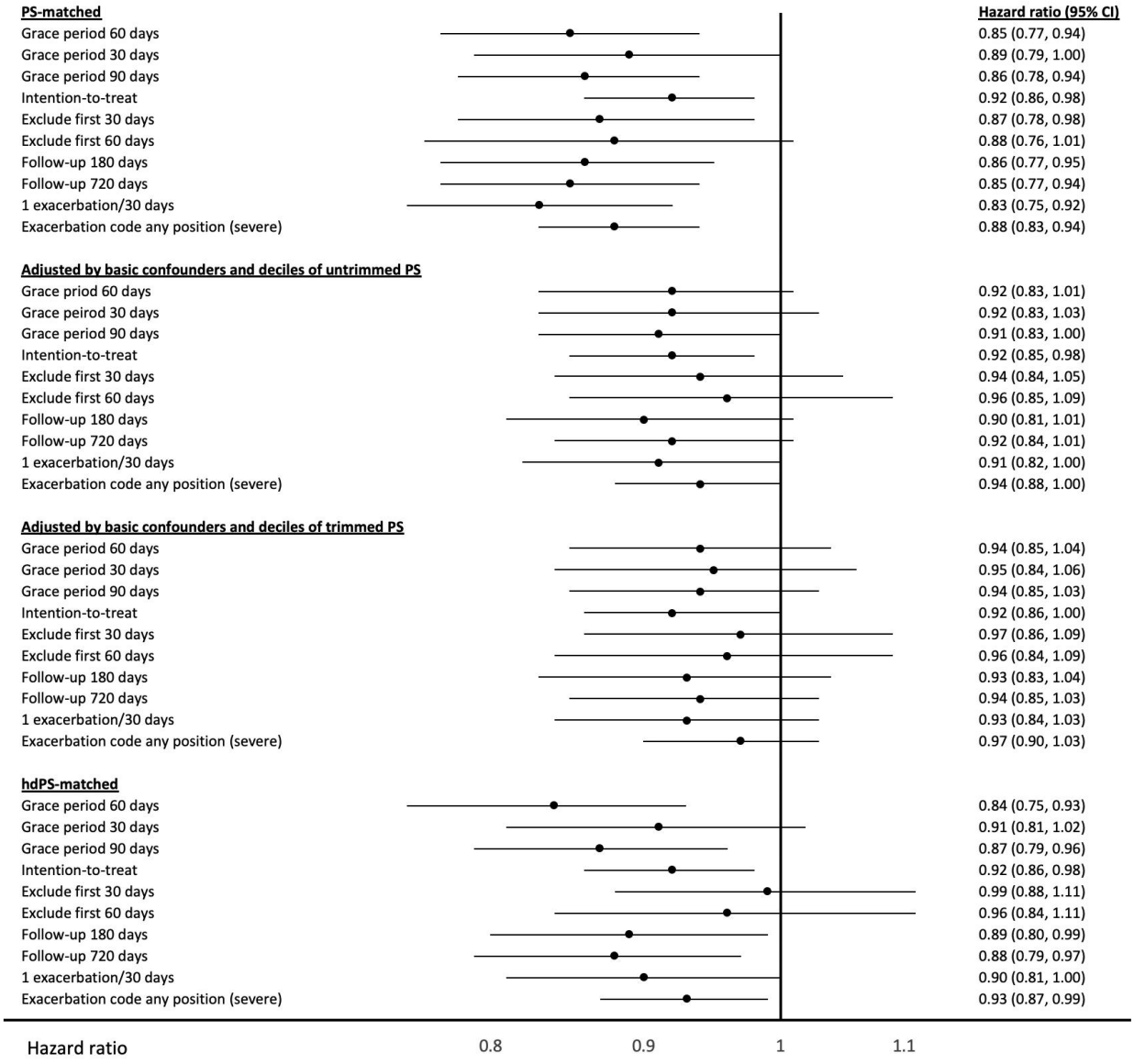
Panel A shows imbalance in the covariates in our propensity score model before matching, while Panel B shows balance in these covariates after matching.

eFigure 4. Sensitivity Analysis for the Incidence of First Moderate COPD Exacerbation



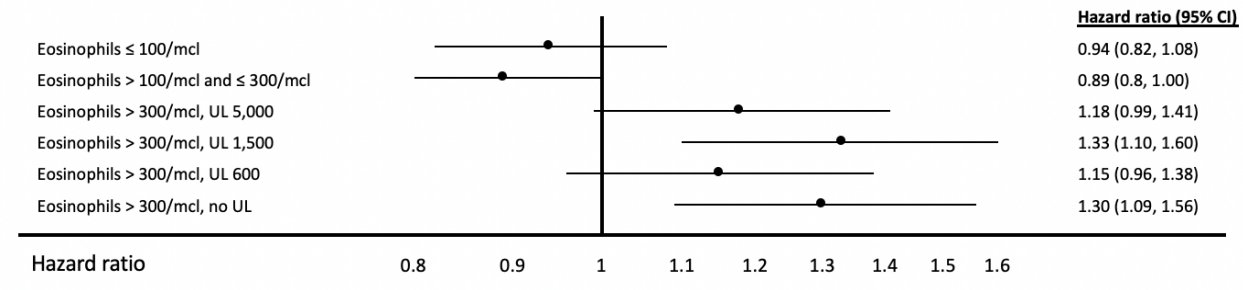
CI: confidence interval; PS: propensity score; hdPS: high-dimensional propensity score.

eFigure 5. Sensitivity Analysis for the Incidence of First Severe COPD Exacerbation



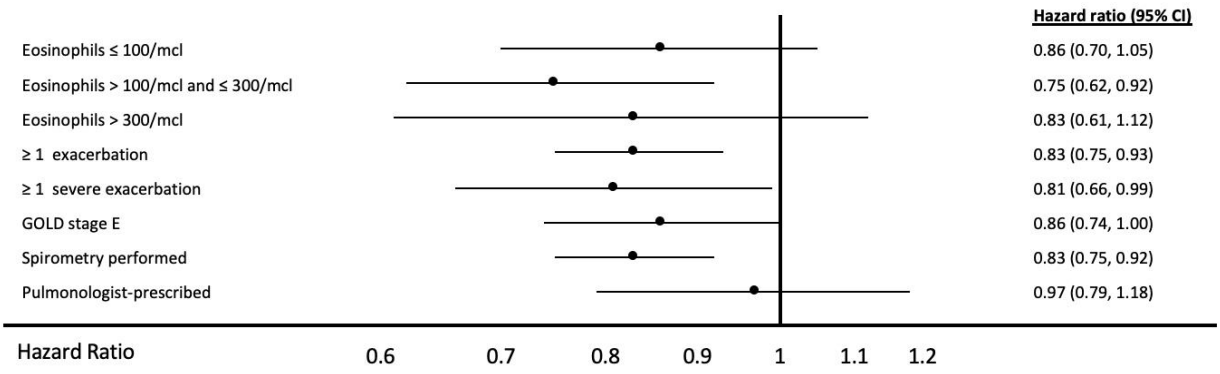
CI: confidence interval; PS: propensity score; hdPS: high-dimensional propensity score.

eFigure 6. Sensitivity Analysis for Subgroup Comparison of First Moderate or Severe COPD Exacerbation Based on Eosinophil Level



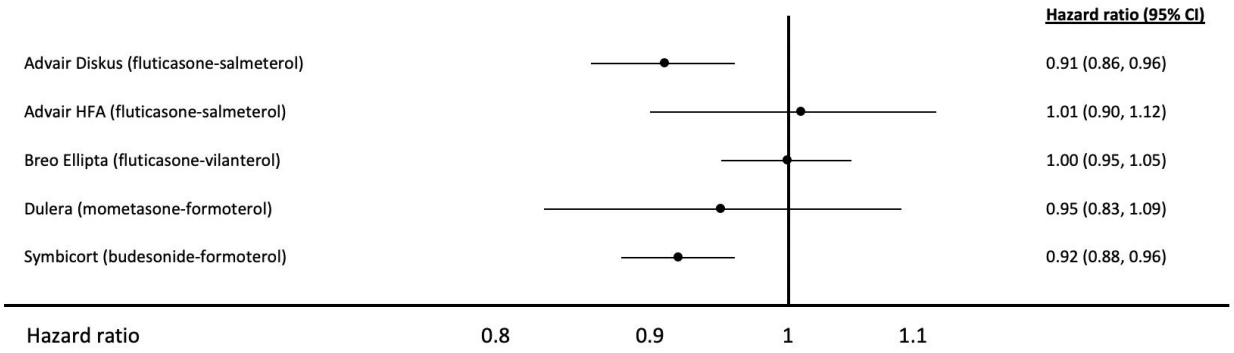
CI: confidence interval; mcl: microliter; UL: upper limit.

eFigure 7. Subgroup Analysis for the Incidence of First Pneumonia Hospitalization



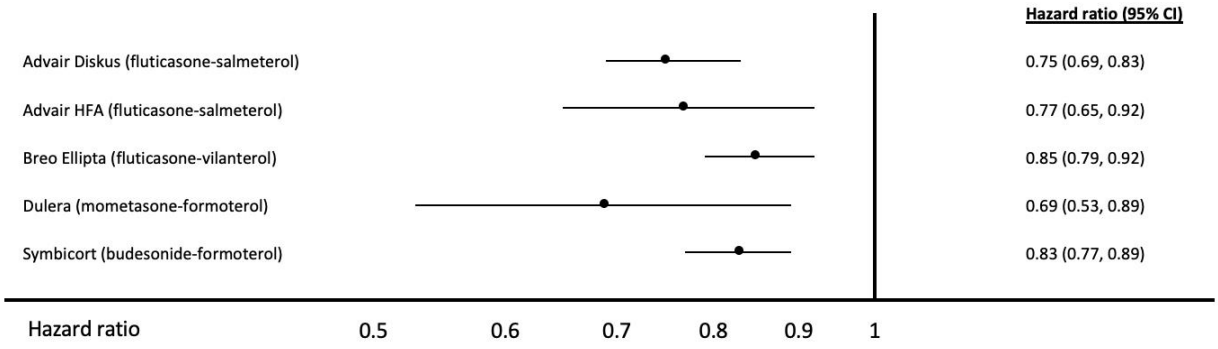
CI: confidence interval; mcl: microliter; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

eFigure 8. Incidence of first Moderate or Severe COPD Exacerbation by Type of ICS-LABA



CI: confidence interval.
Inhalers with low utilization, including AirDuo Respiclick (fluticasone-salmeterol) and Wixela Inhub (fluticasone-salmeterol), were excluded from our analysis.

eFigure 9. Incidence of First Pneumonia Hospitalization by Type of ICS-LABA



CI: confidence interval.
Inhalers with low utilization, including AirDuo Respiclick (fluticasone-salmeterol) and Wixela Inhub (fluticasone-salmeterol), were excluded from our analysis.

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