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ORIGINAL RESEARCH

Ipratropium/Salbutamol Comparator Versus Originator for Chronic Obstructive Pulmonary Disease Exacerbations: USA Observational Cohort Study Using the Clinformatics™ Health Claims Database

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ABSTRACT

Introduction: Affordable treatment alternatives are needed to prevent and treat chronic obstructive pulmonary disease (COPD) exacerbations and reduce the economic burden of COPD. This study evaluated whether the effectiveness of Steri-Neb™ (Teva Pharmaceuticals, Inc.), the comparator ipratropium/salbutamol (I/S) nebulizer solution, is non-inferior to Duo-Neb® (Mylan Specialty L.P.), the originator with the same chemical composition, the first FDA-approved product of this kind, for the prevention of COPD exacerbations. I/S comparator versus originator safety also was examined. Both the I/S comparator and the originator are indicated (EU/USA) for bronchospasm management in patients with COPD.

Methods: This matched, historical USA cohort study used Clinformatics™ claims data and included a 1-year baseline, starting 1 year before the index prescription date, and 1-year outcome period. Patients received either I/S comparator or originator treatment. The primary outcome was rate of moderate and severe COPD exacerbations. Non-inferiority for I/S comparator versus originator was satisfied if the 95% confidence interval (CI) upper limit for mean difference in proportions between treatments was <15%. The secondary outcome examined safety through rate of adverse events (AEs).

Results: After matching, 550 I/S comparator and 1535 originator patients were included. Adjusted upper 95% CI for the difference in proportion of patients experiencing moderate and severe exacerbations between I/S comparator and originator cohorts was 0.092 (9.2%), and for severe exacerbations was 0.040 (4.0%), demonstrating non-inferiority. No significant differences were found in rates of moderate and severe exacerbations (rate ratio [RR] 0.96; 95% CI 0.89, 1.04), severe exacerbations (RR 1.00; 95% CI 0.81, 1.24), or any AE (RR 1.06; 95% CI 0.92, 1.22) after adjusting for baseline confounders.

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Conclusion: The real-world clinical outcomes of this matched cohort study support the I/S comparator as non-inferior to the originator, providing an effective and safe treatment alternative for COPD exacerbations.
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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, progressive, inflammatory disease characterized by persistent airflow limitation [1]. COPD is predicted to be the 3rd leading cause of death worldwide by the year 2030 [2], the 7th leading cause of disability-adjusted life years lost worldwide by 2030 [3], and is currently a principal cause of morbidity and mortality worldwide [1]. Exacerbations, the acute worsening of respiratory symptoms that may require a change in medication, often occur in patients with COPD. Exacerbations are known to accelerate lung function decline and are associated with significant mortality [1, 4]. Of the total economic burden of COPD on the health care system, the greatest proportion is due to COPD exacerbations [1]. Notably, hospitalizations are the primary component of COPD-related medical costs and prevention of exacerbations can reduce this economic burden [5–7].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend the use of short-acting β_2-agonists (SABAs) with or without short-acting muscarinic antagonists (SAMAs) as the preferred bronchodilators for the treatment of exacerbations [1, 4]. In line with effective treatment of an exacerbation serving to minimize its impact and prevent hospitalizations and subsequent exacerbation relapse [4, 8], the American College of Chest Physicians and Canadian Thoracic Society Guidelines advises combination treatment with SAMA/SABA to prevent moderate COPD exacerbations [9]. A nebulized combination inhalation solution of ipratropium bromide (a SAMA) and salbutamol sulfate (a SABA) for the treatment and prevention of COPD exacerbations was first licensed in the USA as the originator (DuoNeb®, Mylan Specialty L.P., formerly Dey Pharma, L.P.). Ipratropium/salbutamol comparator (I/S Steri-Neb™, Teva Pharmaceuticals, Inc.) is a generic version of the originator with the same chemical composition as the originator, and both are indicated for bronchospasm in patients with COPD [10, 11]. The nebulized solutions simultaneously deliver ipratropium bromide and salbutamol sulfate, and effects are produced on both muscarinic and β_2-adrenergic receptors in the lung [10]. The anticholinergic effects of inhaled ipratropium bromide inhibit vagally mediated reflexes by antagonizing the muscarinic action of acetylcholine and result in bronchodilation that is primarily local, selective to the lung, and not systemic [12, 13]. Salbutamol, a β_2-adrenoceptor agonist, results in relaxation of the airway smooth muscle from the trachea to the terminal bronchioles and protects against bronchoconstrictor challenges [12, 13]. This combination has been shown to produce enhanced bronchodilation compared with that provided by each drug alone [14, 15].

Pharmacologic management that can prevent and treat COPD exacerbations reduces overall costs; however, these medications can be expensive, creating the need for affordable treatment alternatives. The present analysis examined real-life clinical management of a broad population of USA COPD patients using a historic cohort study of patients enrolled in a healthcare claims database. The aim of the current study was to evaluate whether the I/S comparator is non-inferior in effectiveness to the originator in patients with COPD. I/S comparator versus originator safety also was examined.

METHODS

Study Design and Population

The study protocol was registered with the European Network of Centres for

Pharmacoepidemiology and Pharmacovigilance (ENCePP; ENCePP/SDPP/7753). The analyses and the dissemination of the results were approved by the advisory group and were conducted in accordance with the Respiratory Effectiveness Group (REG) standards [16] and the ENCePP Code of Conduct. The study was a matched, historical cohort study, using anonymous data from the Clinformatics™ Data Mart (CDM) database. The CDM is a patient longitudinal database containing retrospective claims data (2000–2012) from an employed, commercially insured USA population. The database contains primary and secondary care medical claims, pharmacy claims, laboratory results, and pricing information.

The study period comprised a 1-year baseline period preceding and including the index prescription date, followed by a 1-year outcome period after the index prescription date. The index prescription date was defined as the date at which COPD patients who were not on SAMA/SABA nebulisers in baseline received their first prescription for I/S comparator or originator. The analysis included CDM data entered from January 2007 until the last available data included in the CDM (September 2012). The January 2007 study onset was determined by the FDA approval date of the I/S comparator in the USA (January 2008 versus the originator March 2001) to ensure the patient cohorts received treatment within a similar timeframe. The outcome period was used to compare drug effectiveness and safety between cohorts.

Study Drugs

The comparator drug was I/S solution for inhalation via nebulizer, containing ipratropium bromide (0.5 mg) and salbutamol sulfate (3.0 mg) in a sterile single-dose, 3-mL ampule. Inactive ingredients include sodium chloride and 1 N hydrochloric acid for pH adjustment. The originator drug contained ipratropium bromide (0.5 mg) and salbutamol sulfate (3.0 mg) solution for inhalation via nebulizer. Patients received the originator as a single-dose, 3-mL sterile solution for nebulization in low-density polyethylene unit-dose vials. Inactive ingredients include sodium chloride, hydrochloric acid for pH adjustment, and edetate disodium USP (a chelating agent). The prescribing information for both the I/S comparator and originator indicates administration of the inhalation solution via jet nebulizer connected to an air compressor with an adequate air flow using a face mask or mouthpiece [10, 11]. Specifically noted in the prescribing information for both products is the Pari-LC-Plus™ nebulizer connected to a PRONEB™ compressor system.

Inclusion and Exclusion Criteria

Patients aged ≥35 years with 2 years of continuous practice data and medical insurance coverage, including 12 months prior to and 12 months following the index prescription date for either I/S comparator or originator, and ≥1 prescription for either I/S comparator or originator within the outcome period were included in the study. Patients who had ≥1 prescription for a SAMA/SABA nebulizer during baseline were excluded.

Prior and Maintenance Therapies

Baseline respiratory drugs included SABA inhalers/nebulizers, SAMA inhalers/nebulizers, long-acting β_2-agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and inhaled corticosteroids (ICS). Additional information about baseline respiratory drugs is provided in Table 2.

Study Outcomes

The primary outcome was the rate of moderate and severe exacerbations and rate of severe exacerbations during the outcome period. A moderate-to-severe exacerbation was defined as an event in which the patient had any of the following: COPD-related emergency department (ED) visit, COPD-related inpatient admission, acute course of oral corticosteroids for lower respiratory event(s), or antibiotic

prescription for lower respiratory event(s). Any hospitalizations, oral corticosteroids, or antibiotic prescriptions occurring within 2 weeks of each other were considered to be the result of the same exacerbation and were counted only once. A severe COPD exacerbation was defined as any event that resulted in COPD-related ED visits or inpatient hospital admissions.

The secondary outcome included the rate of any adverse events (AEs) and the rate of AEs by system organ class (SOC) between the I/S comparator versus originator cohorts during the outcome period. Potential AEs to search within the CDM database were identified using the I/S comparator and originator Summary of Product Characteristics (SPC)/Prescribing Information list of possible AEs [10, 11]. The SPC-listed AEs identified in the database are proxies for possible AEs rather than actual known AEs in response to treatment. Their occurrence indicates the patient had a consultation associated with the AE. The list of potential AEs derived from the SPC was identified in the CDM database using International Classification of Diseases, Ninth Revision (ICD-9-CM) codes. For comparison between the I/S comparator and originator cohorts, the AEs were classified by MedDRA (available at http://www.meddra.org/) SOC.

Statistical Analyses

Exploratory analysis of baseline variables for the I/S comparator and originator cohorts was conducted for data validation and to establish whether the analysis would benefit from matching. For variables measured on the interval/ratio scale, a *t* test (normal distribution) or Mann–Whitney U test (skewed data) was used; for categorical variables, a Chi squared test was used. Statistical significance was set at $P < 0.05$. Patients were characterized according to age, gender, year of receipt of index prescription for I/S comparator or originator, evidence of comorbidities (including comorbidity score calculated via the Charlson Comorbidity Index [CCI] [17]), baseline use of prescriptions for non-steroidal anti-inflammatory drugs and beta blockers, prior respiratory maintenance therapies, acute oral corticosteroids, antibiotic prescriptions for lower respiratory events, baseline COPD exacerbations, and occurrence of AEs.

Based on differences identified through exploratory analysis of baseline variables, individual patients from each cohort were matched to ensure comparison of similar patients. Exact matching for categorical variables and coarsened exact matching for numeric variables were used to match patients using 1:1, 2:1, and 3:1 (originator: I/S comparator) nearest-neighbor matching, without replacement. Mixed matching (1:1, 2:1, 3:1) was used to maintain overall statistical power due to low patient numbers after applying inclusion/exclusion criteria. Matching variables, such as demographic data, disease comorbidity, and indicators of disease severity, were considered for selection using a combination of baseline data analysis and predictive modeling of baseline data in relation to the primary outcome variable (independently of treatment group). Final matching criteria were age at receipt of index prescription for I/S comparator or originator, subcohort, gender, baseline number of moderate and severe exacerbations, baseline SABA prescribed daily dose, and baseline ICS, LAMA, and LABA use.

In the power analysis, 40.8% of COPD patients on SABA inhalers were expected to have an exacerbation within a 1-year period following treatment initiation [18]. Assuming a 40.8% proportion in the standard group and an expected difference between the proportions of 0.000, the sample sizes required for adequate statistical power in a two-group, large-sample normal approximation, with a one-sided 0.05 significance level, are 536 and 1606 patients for the I/S comparator and originator cohorts, respectively. Previous randomized clinical studies evaluating efficacy and safety in COPD patients have reported that a 20% difference between treatment groups is clinically significant [19, 20]; therefore, a more stringent 15% limit was used in the current study. Taken together, this enabled an 80% power to show that there was no statistical difference between groups when the 95% CI upper limit of mean difference in proportions between treatments was <15%.

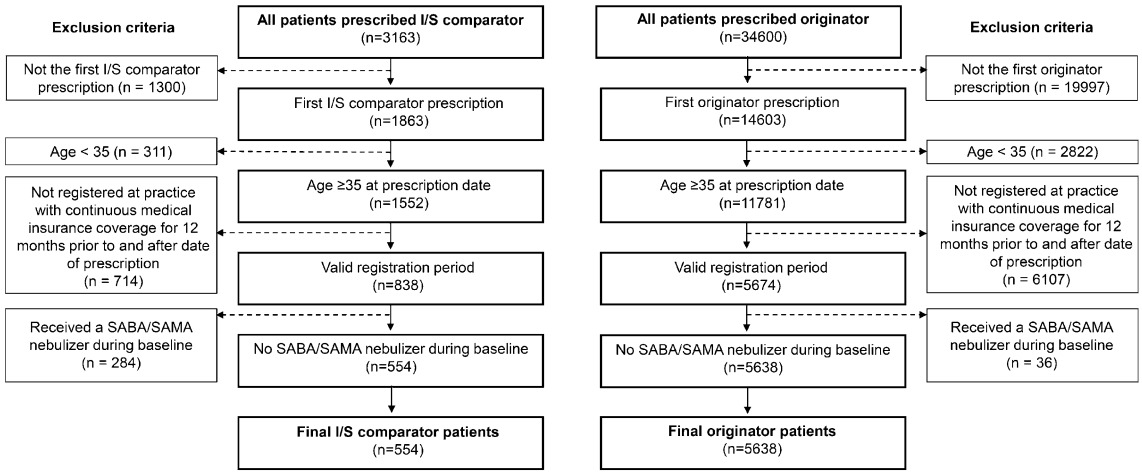

Fig. 1 Flow diagram of patient population. *I/S* ipratropium/salbutamol, *SABA* short-acting β_2-agonist, *SAMA* short-acting muscarinic antagonist

For the primary outcome, non-inferiority for I/S comparator versus originator was established if the 95% CI upper limit of mean difference in proportions between treatments of the rate of moderate and severe exacerbations was <15%. Conditional Poisson regression models used empirical standard errors for more conservative CI estimations and adjusted for potential baseline confounders. Rates of exacerbations and rates of AEs were compared between cohorts using conditional logistic regression models adjusted for potential baseline confounders and presented as rate ratios (RR) with 95% CI. Whereas the main analyses included all matched patients, a subgroup analysis also was conducted using only the 3:1 matched patient cohorts to ensure that I/S comparator patients were not overrepresented in the main analysis. The 3:1 matched subgroup analysis was powered at 73%. All study analyses were intent-to-treat based on the ≥1 prescription for either I/S comparator or originator that determined the patient cohort assignment. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Marlow, Buckinghamshire, UK).

RESULTS

A total of 6192 valid patient records were identified, including 5638 patients in the originator cohort and 554 patients in the I/S comparator cohort (Fig. 1). Following patient matching, a total of 1535 and 550 patients were selected for the originator and I/S comparator cohorts, respectively (Fig. 2). The 3:1 matched subgroup included a total of 1326 patients in the originator cohort and 442 patients in the I/S comparator cohort. Baseline characteristics, use of respiratory therapies, and AEs are summarized in Tables 1, 2, and 3 (baseline comparisons in unmatched patients are shown in Tables S1–S3). The mean age of patients when they received their first prescription for I/S comparator or originator was 59 for the I/S comparator cohort and 58 for the originator cohort. Approximately 39% of patients in both cohorts were male.

Following matching, some differences in baseline characteristics remained between cohorts, including year of index prescription, age at index prescription, comorbidities, comedications, use of respiratory-related drugs, and AE prevalence (Tables 1, 2, 3). The percentage of patients was greater in the I/S comparator versus originator cohort across these clinical characteristics, indicating poorer health and more prevalent AEs in the I/S comparator cohort at baseline.

COPD Exacerbations

The I/S comparator was non-inferior to the originator for the primary outcome of rate of moderate and severe COPD exacerbations and

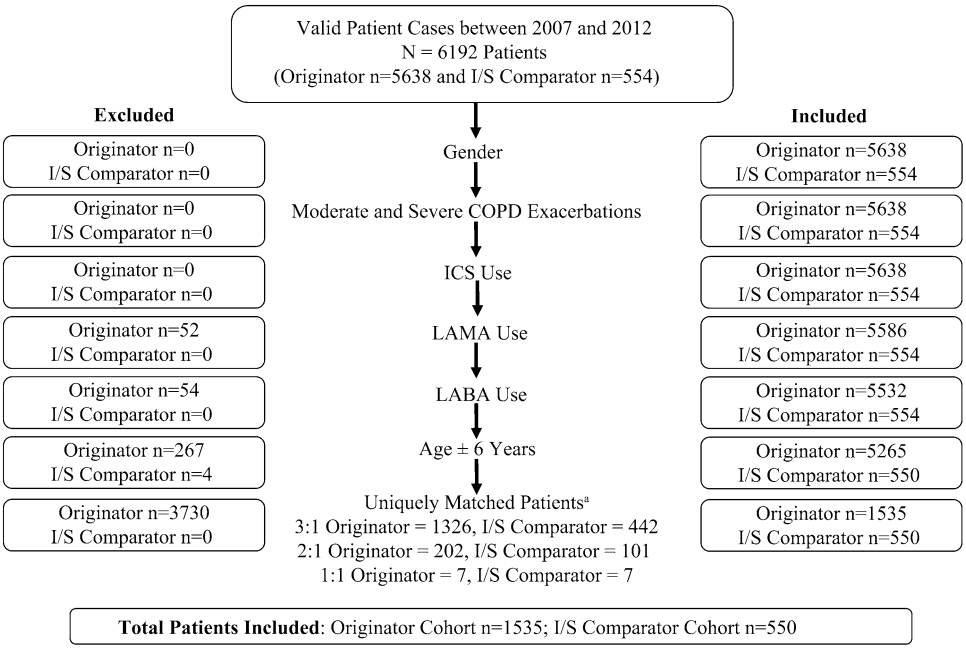

Fig. 2 Flow diagram of study inclusion criteria for matched patients. *ICS* inhaled corticosteroid, *I/S* ipratropium/salbutamol, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist. [a]Software was used to randomly select unique matched patients

rate of severe COPD exacerbations, with an adjusted upper 95% CI for the difference in proportions for the I/S comparator versus the originator of 0.092 (9.2%) and 0.040 (4.0%), respectively, which were below the non-inferiority criterion of <15%. In the 3:1 matched subgroup analysis, the adjusted upper 95% CI for the difference in proportions for I/S comparator versus originator for moderate and severe exacerbations was 0.082 (8.2%) and for severe exacerbations was 0.028 (2.8%).

Additionally, there was no significant difference in the rate of moderate and severe exacerbations (adjusted RR 0.96; 95% CI 0.89, 1.04) or severe exacerbations (adjusted RR: 1.00; 95% CI: 0.81, 1.24) between the I/S comparator and originator cohorts (Table 4; Fig. 3). The 3:1 matched subgroup analysis was consistent with the main analysis and showed no significant difference between cohorts (Table 4).

Safety

The rate of any AEs did not significantly differ between the I/S comparator and originator cohorts during the 1-year outcome period (adjusted RR 1.06; 95% CI 0.92, 1.22; Table 4; Fig. 4). For the majority of AEs by system organ class (SOC), no significant differences were observed between cohorts (Table 5). Significant differences were found between I/S comparator and originator cohorts for metabolic and nutritional disorders (8% versus 5.5%, respectively), psychiatric disorders (26.9% versus 20.5%), and nervous system disorders (9.5% versus 6.2%).

DISCUSSION

Within this historical, matched study population of patients with COPD, the I/S comparator was non-inferior to the originator in effectiveness for the prevention of moderate and severe exacerbations of COPD. The upper limit of the 95% CI for the difference in proportions of the I/S comparator versus originator cohorts was <12%, thus meeting the non-inferiority threshold of <15%. The 3:1 subgroup analyses were consistent with the outcomes of the main analyses.

Table 1 Baseline demographics and clinical characteristics of matched patients

	I/S comparator $n = 550$	Originator $n = 1535$	P value[a]
Year index prescription was received, mean ± SD	2011 ± 0.8	2006 ± 0.7	<0.001
Age when index prescription was received, mean ± SD	*58.8 ± 12.0*	*58.3 ± 11.3*	*0.020*
Age, categories, *n* (%)			<0.001
35–60 years	321 (58.4)	933 (60.8)	
60–80 years	191 (34.7)	601 (39.2)	
>80 years	38 (6.9)	1 (0.1)	
Gender, n (%) Males	*214 (38.9)*	*591 (38.5)*	*N/A*
Asthma diagnosis, *n* (%)	258 (46.9)	757 (49.3)	0.239
Rhinitis diagnosis, *n* (%)	134 (24.4)	345 (22.5)	0.435
GERD[b], *n* (%)	214 (38.9)	506 (33.0)	0.011
Ischemic heart disease diagnosis, *n* (%)	154 (28.0)	360 (23.5)	0.030
Prescribed NSAIDs, *n* (%)	201 (36.5)	533 (34.7)	0.456
Prescribed beta blockers, *n* (%)	164 (29.8)	377 (24.6)	0.019
Charlson Comorbidity Index score[c], *n* (%)			<0.001
0	70 (12.8)	256 (16.7)	
1–4	225 (41.1)	689 (44.9)	
≥5	253 (46.2)	588 (38.4)	
Moderate and severe COPD exacerbations in the year before and including the date the index prescription was received, n (%)			*NA*
0	164 (29.8)	470 (30.6)	
1	148 (26.9)	418 (27.2)	
2	100 (18.2)	273 (17.8)	
≥3	138 (25.1)	374 (24.4)	
Severe COPD exacerbations in the year before and including the date the index prescription was received, *n* (%)			0.488
0	363 (66.0)	1049 (68.3)	
1	127 (23.1)	332 (21.6)	
2	39 (7.1)	81 (5.3)	
≥3	21 (3.8)	73 (4.8)	

Patients were matched on the basis of gender, moderate and severe COPD exacerbations in baseline (categorized), ICS use in baseline (yes/no), LABA use in baseline (yes/no), LAMA use in baseline (yes/no), and age (± 6 years). Data for unmatched cohorts are provided in Table S1

Items italicized were among the final matching criteria

COPD chronic obstructive pulmonary disease, *GERD* gastroesophageal reflux disease, *I/S* ipratropium/salbutamol, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SD* standard deviation

[a] *P* value based on conditional logistic regression

[b] Includes diagnosis and/or therapy

[c] Charlson Comorbidity Index [17] is a method of predicting 1-year mortality for a patient who may have a range of comorbid conditions that are each assigned a "weight" corresponding to risk of death associated with the condition; scores are then summed to give a total score predicting mortality

Table 2 Baseline use of respiratory therapies in matched patients

	I/S comparator $n = 550$	Originator $n = 1535$	P value[a]
≥1 Prescription for respiratory therapies in the year before patients received the index prescription, *n* (%)			
ICS	*251 (45.6)*	*686 (44.7)*	*N/A*
LABA	*215 (39.1)*	*588 (38.3)*	*N/A*
LAMA	*70 (12.7)*	*174 (11.3)*	*N/A*
SAMA nebulizer	36 (6.5)	82 (5.3)	0.365
SAMA inhaler	7 (1.3)	24 (1.6)	0.634
SABA nebulizer	81 (14.7)	213 (13.9)	0.742
SABA inhaler	244 (44.4)	600 (39.1)	0.018
Prescribed daily dose of SABA inhalers (μg)[b] in the year before patients received the index prescription, categorized, *n* (%)			0.674
0	306 (55.6)	935 (60.9)	
1–200	140 (25.5)	258 (16.8)	
>200	104 (18.9)	342 (22.3)	
Prescriptions of acute oral corticosteroids[c] for lower respiratory events[d] in the year before patients received the index prescription, *n* (%)			0.362
0	261 (47.5)	745 (48.5)	
1	130 (23.6)	380 (24.8)	
2	60 (10.9)	168 (10.9)	
≥3	99 (18.0)	242 (15.8)	
Prescriptions for antibiotics for lower respiratory events[d] in the year before patients received the index prescription, *n* (%)			<0.001
0	233 (42.4)	685 (44.6)	
1	141 (25.6)	399 (26.0)	
2–3	117 (21.3)	345 (22.5)	
≥4	59 (10.7)	106 (6.9)	

Patients were matched on the basis of gender, moderate and severe COPD exacerbations in baseline (categorized), ICS use in baseline (yes/no), LABA use in baseline (yes/no), LAMA use in baseline (yes/no), and age (±6 years). Data for unmatched cohorts are provided in Table S2

Items italicized were among the final matching criteria

ICS inhaled corticosteroid, *I/S* ipratropium/salbutamol, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *SABA* short-acting β_2-agonist, *SAMA* short-acting muscarinic antagonist

[a] *P* value based on conditional logistic regression

[b] Daily dose was calculated as [(count of inhalers × doses in pack)/365] × μg strength

[c] Defined as all courses where dosing instructions suggest exacerbation treatment and/or unlikely to be maintenance treatment

[d] Defined as a COPD-related emergency department visit/hospital admission/ambulatory visit or a respiratory investigation recorded within a ± 5-day window from the prescription

Table 3 Baseline prevalence of adverse events in matched patients

	I/S comparator $n = 550$	Originator $n = 1535$	P value[a]
Any AE, *n* (%)			<0.001
0	115 (20.9)	510 (33.2)	
1	72 (13.1)	241 (15.7)	
≥2	363 (66.0)	784 (51.1)	
Immune system disorders, *n* (%)			0.264
0	546 (99.3)	1530 (99.7)	
1	2 (0.4)	4 (0.3)	
≥2	2 (0.4)	1 (0.1)	
Metabolism and nutrition disorders, *n* (%)			0.005
0	517 (94.0)	1480 (96.4)	
1	14 (2.5)	33 (2.1)	
≥2	19 (3.5)	22 (1.4)	
Psychiatric disorders, *n* (%)			<0.001
0	432 (78.5)	1316 (85.7)	
1	42 (7.6)	66 (4.3)	
≥2	76 (13.8)	153 (10.0)	
Nervous system disorders, *n* (%)			0.676
0	510 (92.7)	1439 (93.7)	
1	28 (5.1)	59 (3.8)	
≥2	12 (2.2)	37 (2.4)	
Eye disorders, *n* (%)			0.038
0	511 (92.9)	1463 (95.3)	
1	19 (3.5)	38 (2.5)	
≥2	20 (3.6)	34 (2.2)	
Skin and subcutaneous tissue disorders, *n* (%)			0.852
0	543 (98.7)	1514 (98.6)	
1	5 (0.9)	15 (1.0)	
≥2	2 (0.4)	6 (0.4)	
Cardiovascular disorders, *n* (%)			0.043
0	380 (69.1)	1128 (73.5)	
1	41 (7.5)	102 (6.6)	
≥2	129 (23.5)	305 (19.9)	

Table 3 continued

	I/S comparator $n = 550$	Originator $n = 1535$	P value[a]
Respiratory, thoracic and mediastinal disorders, *n* (%)			<0.001
0	282 (51.3)	964 (62.8)	
1	120 (21.8)	286 (18.6)	
≥2	148 (26.9)	285 (18.6)	
Musculoskeletal and connective tissue disorders, *n* (%)			0.025
0	495 (90.0)	1423 (92.7)	
1	25 (4.5)	57 (3.7)	
≥2	30 (5.5)	55 (3.6)	
Gastrointestinal disorders, *n* (%)			<0.001
0	413 (75.1)	1255 (81.8)	
1	49 (8.9)	99 (6.4)	
2	88 (16.0)	181 (11.8)	

Patients were matched on the basis of gender, moderate and severe COPD exacerbations in baseline (categorized), ICS use in baseline (yes/no), LABA use in baseline (yes/no), LAMA use in baseline (yes/no), and age (±6 years). Data for unmatched cohorts are provided in Table S3

AE adverse event, *I/S* ipratropium/salbutamol

[a] *P* value based on conditional logistic regression

Differences between the cohorts at baseline showed that the I/S comparator cohort was older, experienced greater comorbid illness (as assessed by the CCI score) [17], and used SABA inhaler respiratory therapy and antibiotics for lower respiratory events more frequently. Baseline differences in AEs were also noted, with the I/S comparator cohort reporting a greater frequency of AEs for the outcome of any AE and for the AEs by SOC of metabolic and nutritional disorders, psychiatric disorders, eye disorders, cardiovascular disorders, respiratory, thoracic, and mediastinal disorders, musculoskeletal and connective tissue disorders, and gastrointestinal disorders during the baseline period. At the 1-year timepoint, greater frequency of metabolic and nutritional disorders (i.e., hypokalemia, urinary retention), psychiatric disorders (i.e., restlessness, memory disorders, anxiety), and nervous system disorders (i.e., headache, tremor, dizziness) was shown for patients in the I/S comparator cohort compared with the originator cohort. Although the I/S comparator cohort showed statistically significant differences compared with the originator cohort, this was likely due to the large sample sizes as the percentage differences between cohorts were small. Additionally, the differences in AEs at the 1-year timepoint were consistent with the differences between cohorts at baseline. Altogether, this suggests the differences between cohorts in AEs are unlikely related to treatment.

The current analyses help to address a critical need for improved understanding of real-life clinical outcomes and treatment use in patients with COPD. While randomized clinical trials examining COPD treatment provide essential outcome data with high internal validity, the study population typically includes highly selected patients which limits generalizability to the real-life clinical practice COPD population [21]. Alternatively, analyses of real-world clinical practice databases that include the broad population of patients receiving treatment, such as in the current study, address the generalizability of treatment outcomes in real-life clinical management of diverse patients [22]. Strengths of the

current study include the large patient population available within the database of commercially insured USA patients that allowed the matching of patients on potential baseline confounders. The statistical analysis plan, study population, and outcomes were conceived prior to any analyses to ensure all potentially relevant variables for characterizing patients were included, and that the key outcomes could be assessed. The 1-year baseline and outcome periods allowed recording of measurable changes in outcomes and seasonal changes in respiratory disease and its related conditions. The study was conducted in accordance with the ENCePP Code of Conduct and REG standards [16]. Nevertheless, given the inherent limitations of database studies, such as potential confounding factors with internal validity, results from this study should ideally be considered in conjunction with those of randomized controlled trials. Ideally, a direct comparison of our observational database study findings with a randomized controlled trial examining a highly similar COPD patient population with a similar rate of exacerbations would be conducted to confirm the reliability and validity of our observational database outcomes [23]; however, for the I/S comparator versus originator, such a randomized controlled trial is not yet available. Thus, the current study findings should be interpreted with appropriate caution.

COPD exacerbations are clinically meaningful events [4] with significant healthcare costs [24–26]. Considered the "stroke of the lungs," COPD exacerbations initiate a catastrophic cascade of increased symptoms, decline in lung function, reduced exercise/physical function, increased hospitalization risk, lower quality of life, and accelerated disease progression [27]. Rapid health decline has been demonstrated following a second severe exacerbation, with progressively increased risk of more frequent subsequent severe exacerbations and increased mortality rate [28]. Patients with severe COPD exacerbation that required hospitalization showed physical and functional impairment during hospitalization with continued worsening in upper and lower limb muscle strength and postural steadiness through 1 month following hospital discharge, and significant decline in physical function (as assessed by the 2-min step-in-place test) from discharge to 1-month follow-up [29]. In addition to physical decline and increased mortality risk, the critical need for effective prevention of acute exacerbations is indicated by the persistence of decreased quality of life and social and emotional impairments that follow exacerbations, including patients with moderate disease [30].

Given the high prevalence and burden of COPD, the prevention and effective treatment of COPD exacerbations are key clinical goals [1]. To minimize the impact of a current exacerbation and prevent the development of subsequent exacerbations, short-acting inhaled β_2-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators [4]. In the outpatient setting, SABA and SAMA bronchodilators are essential in the treatment of COPD exacerbations, with the goal to disrupt decompensation in lung function, prevent hospitalization, and prevent relapse [8]. The GOLD guidelines recommend a combination of bronchodilators of different pharmacological classes as it may improve efficacy and decrease AE risk versus increasing the dose of single agents [1]. Similarly, in patients with moderate-to-severe COPD, the American College of Chest Physicians and Canadian Thoracic Society Guidelines suggests combination treatment with SAMA/SABA to prevent moderate COPD exacerbations [9].

The clinical benefit of a combined SAMA/SABA bronchodilator with the components ipratropium-salbutamol compared with each individual component on outcomes such as forced expiratory volume in 1 s (FEV_1) has previously been demonstrated [15, 31]. Additionally, using a healthcare claims database for a retrospective pharmacoeconomic analysis of COPD exacerbations and patient healthcare use, it was found that a combined ipratropium-salbutamol bronchodilator significantly decreased morbidity and financial burden as assessed through ED or hospital use compared with treatment using the separate components [32]. One hypothesized mechanism for improved outcomes with combined SAMA/SABA treatment is decreased daily variability in patient bronchodilator response; i.e., reduced response to one bronchodilator on a given treatment day is moderated by the second bronchodilator with a differing mechanism of action [33]. Consistent with this hypothesized

Table 4 Percentage of patients with COPD exacerbation and any AE by number of events during the outcome period in matched patients

	All matched patients			3:1 Matched patient subgroup		
	I/S comparator $n = 550$	Originator $n = 1535$	*P* value[a]	I/S comparator $n = 442$	Originator $n = 1326$	*P* value[a]
Primary outcome						
COPD moderate and severe exacerbations, *n* (%)			0.382			0.312
0	88 (16.0)	311 (20.3)		72 (16.3)	272 (20.5)	
1	155 (28.2)	386 (25.1)		125 (28.3)	344 (25.9)	
2	114 (20.7)	299 (19.5)		94 (21.3)	252 (19.0)	
≥3	193 (35.1)	539 (35.1)		151 (34.2)	458 (34.5)	
RR (95% CI)	0.96 (0.89, 1.04)[b]	1.00		0.95 (0.87, 1.04)[c]	1.00	
COPD severe exacerbations, *n* (%)			0.929			0.669
0	394 (71.6)	1082 (70.5)		318 (71.9)	925 (69.8)	
1	93 (16.9)	274 (17.9)		75 (17.0)	241 (18.2)	
2	31 (5.6)	108 (7.0)		22 (5.0)	96 (7.2)	
≥3	32 (5.8)	71 (4.6)		27 (6.1)	64 (4.8)	
RR (95% CI)	1.00 (0.81, 1.24)[d]	1.00		0.94 (0.76, 1.19)[e]	1.00	
Secondary outcome						
Any AE[f], *n* (%)			0.107			0.118
0	123 (22.4)	380 (24.8)		99 (22.4)	334 (25.2)	
1	66 (12.0)	216 (14.1)		53 (12.0)	181 (13.7)	
≥2	361 (65.6)	939 (61.2)		290 (65.6)	811 (61.2)	
RR (95% CI)	1.06 (0.92, 1.22)[g]	1.00		1.07 (0.92, 1.24)[g]	1.00	

Patients were matched on the basis of gender, moderate and severe COPD exacerbations in baseline (categorized), ICS use in baseline (yes/no), LABA use in baseline (yes/no), LAMA use in baseline (yes/no), and age (±6 years)

AE adverse event, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *I/S* ipratropium/salbutamol, *RR* rate ratio

[a] *P* value represents conditional logistic regression results

[b] Adjusted for baseline COPD exacerbations (categorized) and consultations

[c] Adjusted for baseline COPD exacerbations (categorized)

[d] Adjusted for baseline asthma diagnosis, baseline GERD and/or drugs, and baseline hospitalizations (categorized)

[e] Adjusted for baseline asthma diagnosis, beta blocker prescriptions, baseline GERD and/or drugs, and baseline hospitalizations (categorized)

[f] Any AE included the AEs reported in the I/S Comparator Summary of Product Characteristics

[g] Adjusted for year when patients received index prescription and baseline total AEs (categorized)

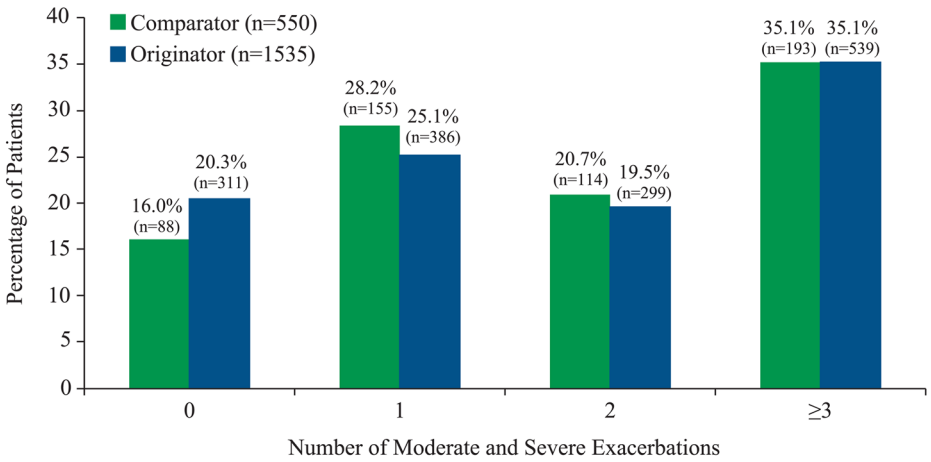

Fig. 3 Percentage distribution of patients by number of moderate to severe exacerbations in the outcome period. *CI* confidence interval, *I/S* ipratropium/salbutamol, *RR* rate ratio. Adjusted for baseline COPD exacerbations (categorized) and consultations

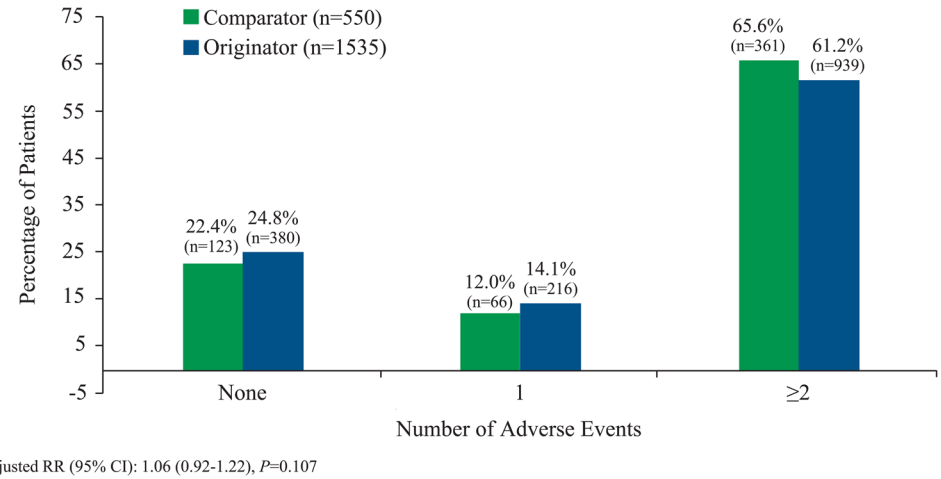

Fig. 4 Percentage distribution of patients by number of any adverse events (AEs) in the outcome period. *CI* confidence interval, *I/S* ipratropium/salbutamol, *RR* rate ratio. Adjusted for year when patients received the index prescription and baseline total AEs (categorized)

mechanism, combined ipratropium-salbutamol produced lower daily variability in FEV_1 compared with monotherapy with either agent, resulting in increased stability of airway tone that may improve symptom control [33]. The current analysis showing non-inferiority in effectiveness for the I/S comparator versus the originator supports the availability of another treatment alternative for combination SAMA/SABA treatment in patients with COPD who experience exacerbations.

A limitation associated with the use of a database is the possibility of coding errors or inconsistencies, although these are not expected to differentially affect the studied cohorts. The inclusion criteria of respiratory medication and age 35 or older was used to identify patients with COPD as the database does not specifically contain "COPD diagnosis" as a variable. As SAMA/SABA medication is more commonly prescribed for patients with COPD than asthma, it is likely that most, if not all, patients had

Table 5 AE categories during the outcome period in matched patients

	I/S comparator $n = 550$	Originator $n = 1535$	P value[a]
Immune system disorders (hypersensitivity reactions with angioedema, anaphylactic reactions), n (%)			0.525
0	546 (99.3)	1526 (99.4)	
1	2 (0.4)	7 (0.5)	
≥2	2 (0.4)	2 (0.1)	
RR (95% CI)[b]	1.52 (0.43, 5.28)	1.00	
Metabolic and nutritional disorders (hypokalemia, urinary retention), n (%)			0.011
0	506 (92.0)	1451 (94.5)	
1	22 (4.0)	52 (3.4)	
≥2	22 (4.0)	32 (2.1)	
RR (95% CI)[c]	1.01 (0.40, 2.54)	1.00	
Psychiatric disorders (restlessness, memory disorders, anxiety), n (%)			0.004
0	402 (73.1)	1221 (79.5)	
1	43 (7.8)	89 (5.8)	
≥2	105 (19.1)	225 (14.7)	
RR (95% CI)[c,d]	1.15 (0.61, 2.15)	1.00	
Nervous system disorders (headache, tremor, dizziness), n (%)			0.032
0	498 (90.5)	1439 (93.7)	
1	35 (6.4)	59 (3.8)	
≥2	17 (3.1)	37 (2.4)	
RR (95% CI)[c,e]	1.48 (0.97, 2.26)	1.00	
Eye disorders (cataract, glaucoma, accommodation disorders, mydriasis), n (%)			0.457
0	510 (92.7)	1415 (92.2)	
1	22 (4.0)	58 (3.8)	
≥2	18 (3.3)	62 (4.0)	
RR (95% CI)[c,f]	0.72 (0.47, 1.12)	1.00	
Skin and subcutaneous tissue disorders (rash, urticaria, pruritus, hyperhidrosis), n (%)			0.983
0	538 (97.8)	1503 (97.9)	
1	9 (1.6)	22 (1.4)	
≥2	3 (0.5)	10 (0.7)	
RR (95% CI)[b]	0.82 (0.36, 1.87)	1.00	
Cardiovascular disorders (palpitations, tachycardia, cardiac arrhythmias, atrial fibrillation, myocardial ischemia, peripheral vasodilation, coronary ischemic disease), n (%)			0.817
0	371 (67.5)	1032 (67.2)	

Table 5 continued

	I/S comparator $n = 550$	Originator $n = 1535$	P value[a]
1	35 (6.4)	123 (8.0)	
≥2	144 (26.2)	380 (24.8)	
RR (95% CI)[c]	1.25 (0.55, 2.83)	1.00	
Respiratory, thoracic, and mediastinal disorders (laryngospasm, pharyngeal edema, throat irritation, hoarseness/dysphonia, sinusitis, dyspnea, bronchospasm/paradoxical bronchospasm), *n* (%)			0.927
0	339 (61.6)	941 (61.3)	
1	97 (17.6)	275 (17.9)	
≥2	114 (20.7)	319 (20.8)	
RR (95% CI)[c]	0.66 (0.61, 1.01)	1.00	
Musculoskeletal and connective tissue disorders (muscle cramps, myalgia), *n* (%)			0.625
0	495 (90.0)	1399 (91.1)	
1	30 (5.5)	66 (4.3)	
≥2	25 (4.5)	70 (4.6)	
RR (95% CI)[c]	0.74 (0.45, 1.20)	1.00	
Gastrointestinal disorders (dry mouth, nausea, motility disorders [diarrhea, constipation, vomiting], mouth edema, stomatitis), *n* (%)			0.274
0	415 (75.5)	1204 (78.4)	
1	48 (8.7)	100 (6.5)	
≥2	87 (15.8)	231 (15.0)	
RR (95% CI)[c]	1.03 (0.73, 1.44)	1.00	

CI confidence interval, *I/S* ipratropium/salbutamol, *RR* rate ratio

Patients were matched on the basis of gender, moderate and severe COPD exacerbations in baseline (categorized), ICS use in baseline (yes/no), LABA use in baseline (yes/no), LAMA use in baseline (yes/no), and age (±6 years). Data for unmatched cohorts are provided in Table S3

[a] *P* value represents conditional logistic regression

[b] No adjustments were made due to low numbers of AEs

[c] Adjusted for baseline level of corresponding AE

[d] Adjusted for age, year when patients received index prescription

[e] Adjusted for cardiac diagnosis and beta blockers

[f] Adjusted for age

COPD. Additionally, due to the complexities of the database, the SPC-listed AEs used to indicate AEs during treatment are proxies for potential AEs rather than known actual AEs in response to treatment. Although their occurrence indicates that the patient had a consultation associated with the AE, it is not known whether another pre-existing condition was the cause of the AE. As a result, the rate of AEs is likely to be over-reported. The frequency of use of the I/S comparator and originator, the nebulizer delivery system(s) used by patients, and mortality rates could not be examined as these data were not available in the database. The determination of the patient cohorts from ≥1 prescription for either I/S comparator or originator and an

intent-to-treat analysis approach, though appropriate for our safety analysis and real-life varied respiratory cohort, may have attenuated differences between cohorts in the examined outcomes. Although the patient cohorts were matched for baseline respiratory medication use, the current study outcomes related to I/S comparator and originator treatment should be interpreted within the context of treatment with multiple respiratory medications. Additionally, it is possible that the I/S comparator and originator were used to treat rather than prevent COPD exacerbations and this possibility could not be examined within the database. Finally, the current study evaluated the treatment effect in patient cohorts with first initiation of the I/S comparator or originator. The treatment effect of the I/S comparator among patients who switched from prior use of the originator could not be examined due to the small sample size (n = 40) of this patient group; this may be of interest for a future study.

CONCLUSIONS

In this matched cohort study of patients with COPD, the I/S comparator demonstrated non-inferiority versus the originator for the prevention of moderate and severe exacerbations. The real-world clinical outcomes of this matched cohort study support the I/S comparator as a treatment alternative for the prevention of COPD exacerbations. The availability of the I/S comparator lower-cost generic treatment alternative with equivalent effectiveness may help reduce the cost of COPD exacerbation prevention and provide potential economic benefit in COPD care.

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Compliance with Ethics Guidelines. The study protocol was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; ENCePP/SDPP/7753). The analyses and the dissemination of the results were approved by the advisory group and were conducted in accordance with the Respiratory Effectiveness Group (REG) standards and the ENCePP Code of Conduct. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Data Availability. The dataset is not available as it had to be accessed and analyzed remotely.

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