

CLINICAL COMMUNICATIONS

Vice President

Angelia Szwed, MS

Director, Scientific Services

Patty Taddej-Allen, PharmD, MBA

Director, Publications

Danielle Mroz, MA

Scientific Director

Daniel Winslow, PharmD

Associate Scientific Directors

Erin Potter, PharmD
Nicholas Nowotarski, MD

Senior Clinical Content

Manager

Ida Delmendo

Medical Writers

Dorothy Cooperson
Vieweg

Erin Garrow, PhD

Amanda Meyer, MS

Medical & Scientific Quality Review Editor

Jabir Bhuiyan, MS

Associate Editors

Amanda Thomas

Matthew Wynn

Assistant Editor

Thom LaPorte, MA

COPY & PRODUCTION

Vice President, Copy

Jennifer Potash

Copy Chief

Paul Silverman

Copy Supervisors

Angie DeRosa
Nicole Canfora Lupo

Senior Copy Editors

Cheney Baltz
Marie-Louise Best
Kelly King

Copy Editor

Kim Nir

Creative Director, Publishing

Melissa Feinen

Art Director

Julianne Costello

SALES & MARKETING

Vice President

Gil Hernandez

Associate Director, Business Development

Ben Baruch

Senior National Account Managers

Robert Foti
Kevin George

National Account

Manager

Shaye Zyskowski

National Account Associates

Michael Bachalis
Alessandra Santorelli

OPERATIONS & FINANCE

Circulation Director

Jon Severn
circulation@mjhassoc.com

Vice President, Finance

Leah Babitz, CPA

Controller

Katherine Wyckoff

CORPORATE

President & CEO

Mike Hennessy Jr

Chief Financial Officer

Neil Glasser, CPA/CFE

Chief Marketing Officer

Brett Melillo

Chief Data Officer

Terric Townsend

Executive Vice President, Global Medical Affairs & Corporate Development

Joe Petroziello

Senior Vice President, Content

Silas Inman

Senior Vice President, Human Resources & Administration

Shari Lundenberg

Senior Vice President, Mergers & Acquisitions, Strategic Innovation

Phil Talamo

Executive Creative Director

Jeff Brown

FOUNDER

Mike Hennessy Sr
1960-2021

© 2024 Clinical Care Targeted Communications Group, LLC

Opinions expressed by authors, contributors, and advertisers are their own and not necessarily those of Clinical Care Targeted Communications Group, LLC, the editorial staff, or any member of the editorial advisory board. Clinical Care Targeted Communications Group, LLC, is not responsible for accuracy of dosages given in articles printed herein. The appearance of advertisements in this publication is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality, or safety. Clinical Care Targeted Communications Group, LLC, disclaims responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements.

This publication was sponsored by Boehringer Ingelheim Pharmaceuticals, Inc.

Real-World Analysis of Clinical and Economic Outcomes Among Patients Initiating Dual or Triple Therapy for Maintenance of COPD: A Review

This *AJMC* Clinical Brief provides key information regarding a study by Sethi et al, which was published in the *Journal of Managed Care & Specialty Pharmacy* (doi:10.18553/jmcp.2023.22373) and the *International Journal of Chronic Obstructive Pulmonary Disease* (doi:10.2147/COPD.S386962).^{1,2} Please consult the full publications for complete study information and author affiliations.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogenous and often progressive lung condition in which respiratory abnormalities (eg, bronchitis, emphysema) cause persistent obstruction of airflow. Patients with COPD may experience exacerbations—acute events of increased respiratory symptoms—that adversely influence health status and disease prognosis. COPD exacerbations are the largest driver of COPD-related health care costs; further, greater disease severity is directly associated with higher costs.³

Use of pharmacologic therapy can both reduce symptoms of COPD, such as dyspnea and cough, and decrease the frequency and severity of exacerbations.³ Although guidelines exist for the management of COPD, there is a dearth of results from randomized clinical trials (RCTs) to

INDICATION for STIOLTO RESPIMAT

STIOLTO[®] RESPIMAT[®] (tiotropium bromide and olodaterol) Inhalation Spray is a combination of tiotropium, an anticholinergic, and olodaterol, a long-acting beta₂-adrenergic agonist (LABA), indicated for the long-term, once-daily maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

IMPORTANT LIMITATIONS OF USE

STIOLTO is NOT indicated to treat acute deterioration of COPD and is not indicated to treat asthma.

IMPORTANT SAFETY INFORMATION for STIOLTO RESPIMAT CONTRAINDICATION

Use of a LABA, including STIOLTO RESPIMAT, without an inhaled corticosteroid (ICS) is contraindicated in patients with asthma.

STIOLTO is contraindicated in patients with hypersensitivity to tiotropium, ipratropium (atropine derivatives), olodaterol, or any component of this product.

In clinical trials and postmarketing experience with tiotropium, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported. Hypersensitivity reactions were also reported in clinical trials with STIOLTO.

KEY TAKEAWAYS

- Chronic obstructive pulmonary disease (COPD) is a lung condition in which patients experience long-standing respiratory symptoms (eg, cough, shortness of breath). Acute exacerbations of these symptoms may negatively impact health status and disease prognosis and lead to increased use of health care resources.³
- Guidelines from the Global Initiative for Chronic Obstructive Lung Disease and the American Thoracic Society recommend that patients with COPD and low exacerbation risk start on dual therapy (long-acting beta₂-agonist [LABA]/long-acting muscarinic antagonist [LAMA]), whereas those at higher risk or who are experiencing more symptoms may start on triple therapy (TT) (LABA/LAMA plus an inhaled corticosteroid).^{3,4}
- In a retrospective observational study assessing outcomes associated with initiation of dual therapy or TT in patients with COPD, a significant lower risk of exacerbation was seen with TT in the overall population and in those who had more frequent/severe exacerbations previously; such a difference, however, was not noted in those naive to treatment or with fewer/less severe previous exacerbations. Further, TT was generally associated with higher COPD- and/or pneumonia-related costs than was dual therapy.^{1,2}
- Real-world clinical and economic evidence supports initiation of guideline-recommended treatment in patients with COPD.¹⁻⁷

support decision-making for pharmacologic maintenance treatment in patients newly diagnosed with COPD.³ In the absence of results from RCTs, data from retrospective studies that examine real-world evidence on treatment use can help inform treatment strategies. This article reviews a retrospective claims-based study (NCT05127304) in which Sethi et al analyzed differences in clinical and economic outcomes with initiation of 2 different treatments in patients with COPD, including among patients with different exacerbation histories and those naive to maintenance treatment.^{1,2}

BACKGROUND

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines provide evidence-based recommendations for the diagnosis, assessment, and treatment of patients with COPD. A diagnosis of COPD should be considered in any patient experiencing symptoms such as dyspnea (ie, difficulty breathing), chronic cough, or sputum production as well as those with a history of COPD risk factors (eg, tobacco smoking, air pollution exposure, asthma/airway hyperresponsiveness, abnormal lung development, certain genetic mutations). Diagnosis is confirmed through forced spirometry measure of airflow obstruction indicating a ratio of forced expiratory volume in the first second to forced vital capacity (FEV₁:FVC) of less than 0.7 postbronchodilation.³

The goals of therapy include reduction of symptoms and decrease in the frequency and severity of COPD exacerbations. To inform

initial treatment strategies, patients with COPD should be assessed for comorbidities and COPD-related symptom and exacerbation history and severity. Disease management for all patients should include education on inhaler technique, symptom monitoring, and lifestyle changes (eg, those to promote an active lifestyle and decrease exposure to modifiable risk factors). Following initial therapy, all patients should undergo assessment of clinical factors (eg, further symptoms and exacerbations, treatment efficacy, adverse effects) and patient-related factors (eg, inhaler technique, adherence to treatment, lifestyle changes) to inform maintenance treatment decisions.³

Pharmacologic Treatment Recommendations

The 2024 GOLD guidelines recommend initial COPD pharmacologic treatment according to an assessment scheme that divides patients into group A, B, or E based on clinical evaluation of symptoms and history of exacerbations (Figure 1).³ The two symptom measures used in this scheme are the mMRC scale, which measures breathlessness (ie, dyspnea; score, 0 to 4), and the CAT questionnaire, which assesses health status in patients with COPD (8 questions; total score, 0-40). Patients in group A and group B are classified as those who have experienced 0 or 1 moderate exacerbations (ie, treated with short-acting bronchodilators in combination with oral corticosteroids and/or antibiotics) that did not lead to hospital admission, with patients in group B assessed as having worse symptoms than those

**IMPORTANT SAFETY INFORMATION for STIOLTO RESPIMAT (Continued)
WARNINGS AND PRECAUTIONS**

LABA as monotherapy (without an ICS), for asthma increases the risk of asthma-related death, and in pediatric and adolescent patients, increases the risk of asthma-related hospitalizations.

Do not initiate STIOLTO in patients with acutely deteriorating COPD, which may be a life-threatening condition, or used as rescue therapy for acute symptoms. Acute symptoms should be treated with an inhaled short-acting beta₂-agonist.

STIOLTO should not be used more often or at higher doses than recommended, or with other LABAs as an overdose may result.

in group A. Patients who have experienced at least 2 moderate exacerbations or at least 1 exacerbation leading to hospitalization are categorized into group E, regardless of symptom measures.³

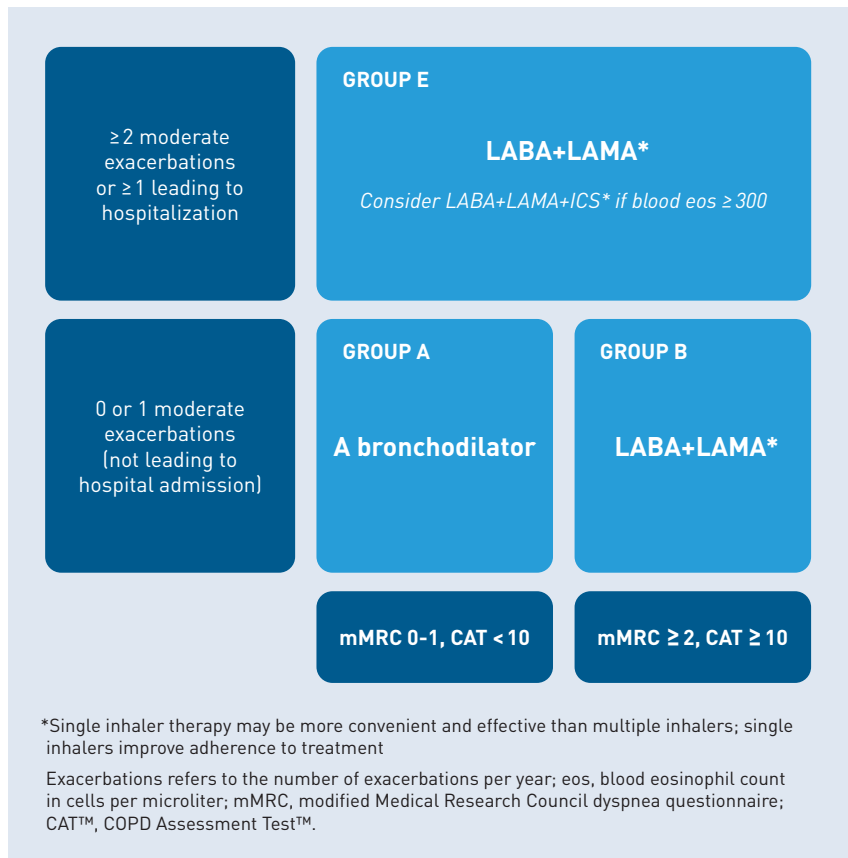
Appropriate initial therapy for each patient should be determined based on their GOLD grouping (Figure 1).³ Patients in group A should start on a bronchodilator, with long-acting agents preferred over short-acting bronchodilators for most patients. Treatment for those in groups B or E should consist of dual therapy with a long-acting beta₂-agonist (LABA) in combination with a long-acting muscarinic antagonist (LAMA). Addition of an inhaled corticosteroid (ICS) to the dual therapy (LABA/LAMA+ICS; triple therapy [TT]) may be appropriate for patients in group E who have an eosinophil count of 300 cells/μL or more. Addition of an ICS is mandatory in patients with concomitant asthma.³

After initial treatment, ongoing management for COPD involves reviewing response to current treatment. In patients with an appropriate response, the current treatment should be maintained. In patients without an appropriate treatment response, patient-related factors should be assessed, and a switch to use of an inhaler device or molecules within the same drug class should be considered. Based on symptom persistence and exacerbation risk, treatment escalation (eg, monotherapy to dual therapy, monotherapy to TT in those with blood eosinophil counts ≥300 cells/μL, dual therapy to TT in those with blood eosinophil counts ≥100 cells/μL) or de-escalation may be recommended, regardless of GOLD risk group.³

The American Thoracic Society (ATS) also provides guidelines on the management of COPD. ATS guidelines recommend escalation to LABA/LAMA dual therapy in patients still experiencing symptoms while on monotherapy. Further recommendations include escalation

of treatment to TT in those who, in the past year, experienced a COPD exacerbation requiring oral steroids, antibiotic treatment, or hospitalization and who continued to experience symptoms while on dual therapy. Removal of ICS (de-escalation) is suggested in patients using TT who had no exacerbations in the past year.⁴

Figure 1. 2024 GOLD Guideline-Recommended Initial COPD Pharmacologic Treatment³



Reprinted with permission from The Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2024 Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available at: <http://www.goldcopd.org>. 2023 © Global Initiative for Chronic Obstructive Lung Disease, All Rights Reserved.

**IMPORTANT SAFETY INFORMATION for STIOLTO RESPIMAT (Continued)
WARNINGS AND PRECAUTIONS (Continued)**

If immediate hypersensitivity reactions occur, such as urticaria, angioedema, rash, bronchospasm, anaphylaxis, or itching, discontinue STIOLTO at once and consider alternative treatment. Patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to STIOLTO.

If paradoxical bronchospasm occurs, discontinue STIOLTO immediately and institute alternative therapy.

STIOLTO can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, systolic or diastolic blood pressure, and/or symptoms. If such effects occur, STIOLTO may need to be discontinued.

Table 1. Characteristics of a Real-World Claims-Based Study on Clinical and Economic Outcomes Associated With TIO+OLO vs FF+UMEC+VI Among Patients With COPD^{1,2}

Study NCT	NCT05127304
Data source ^a (dates)	Optum Research Database (June 1, 2015 to November 30, 2019)
Patient population	Patients aged ≥ 40 years with a COPD diagnosis ^b who had continuous coverage during the baseline period ^c and for ≥ 30 days following index ^d
Study cohorts	Patients initiating FDC TIO+OLO were matched 1:1 with those initiating FDC FF+UMEC+VI based on baseline demographics
Study populations and subgroups	Total patient population (n=5658 in each treatment cohort) <ul style="list-style-type: none"> • Subgroup: Maintenance-naive^e (n=3025 in each cohort) And divided into groups ^f based on exacerbation history: <ul style="list-style-type: none"> • GOLD A/B (n=3884 in each cohort) <ul style="list-style-type: none"> » Subgroup: No exacerbation (n=2552 in each cohort) • GOLD C/D (n=1774 in each cohort)
Objective	To compare clinical and economic outcomes among patients newly treated with either TIO+OLO or FF+UMEC+VI in the overall population, in patients stratified by GOLD exacerbation risk, and in a subgroup of maintenance-naive patients
Follow-up	1-12 months from index
Outcomes analyzed	COPD exacerbations, pneumonia events, and COPD- and/or pneumonia-related and all-cause HCRU and costs

COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; FF+UMEC+VI, fluticasone furoate, umeclidinium, and vilanterol; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HCRU, health care resource utilization; TIO+OLO, tiotropium and olodaterol.

^aThe Optum Research Database provides deidentified medical and pharmacy claims data for patients with commercial and Medicare Advantage Part D health plan coverage.

^bCOPD was defined as having ≥ 1 facility claim with a COPD diagnosis in the primary position or ≥ 2 professional claims on unique dates of service with a COPD diagnosis code during the study period.

^cThe baseline period was defined as the 12 months prior to and including the index date.

^dThe index date was set to the first qualifying pharmacy fill date during the study period.

^eThe maintenance-naive population included the subgroup of patients with no COPD maintenance medication (long-acting muscarinic antagonist, long-acting beta₂-agonists, or inhaled corticosteroid) use for ≥ 12 months before initiating TIO+OLO or FF+UMEC+VI.

^fThe groups were defined as follows: GOLD A/B, patients with 0-1 baseline exacerbation not leading to hospitalization; No exacerbation, subgroup of GOLD A/B with 0 baseline exacerbations; GOLD C/D, patients with ≥ 2 baseline exacerbations not leading to hospitalization and/or ≥ 1 baseline exacerbation leading to hospitalization.

Guideline Discordance in TT Initiation

These COPD treatment guidelines advise using TT for certain patients with COPD; however, there is a suboptimal adherence to these recommendations in real-world practice, with a substantial number of patients in GOLD groups A and B still receiving TT.^{3,4,6,8,9}

(TIO) with the LABA olodaterol (OLO); this dual-therapy product is indicated for long-term, once-daily maintenance treatment of patients with COPD.¹⁰ Fluticasone furoate (FF), umeclidinium (UMEC), and vilanterol (VI) (Trelegy Ellipta; GlaxoSmithKline) inhalation powder for oral inhalation, is a combination of the ICS FF, the LAMA UMEC, and

According to the results of a retrospective analysis, only 25.6% of patients with COPD who initiated fixed-dose combination (FDC) TT in 2018 were prescribed this treatment in accordance with GOLD recommendations.⁹ Study authors investigated the proportions of patients (age, ≥ 40 years) who began TT by analyzing claims data from the 2013-2018 Optum Research Database (including both commercial and Medicare Advantage prescription drug [Part D] health plans) to identify those who were maintenance-naive (having no prior history of maintenance therapy) or those who exhibited exacerbation-discordance (falling into the GOLD A/B classification). Among 2311 patients who initiated FDC TT during 2018, 37.6% were maintenance-naive, and 64.4% were exacerbation-discordant; nearly 75% of those initiating TT were discordant on at least 1 GOLD TT-specific recommendation. Limitations of this claims-based analysis include the possibility of missing or miscoded claims and a lack of data on lung function measures, smoking status, and symptoms that may inform predictions of GOLD-discordant TT initiation.⁹

REAL-WORLD CLINICAL AND ECONOMIC OUTCOMES ASSOCIATED WITH COPD MAINTENANCE TREATMENT

STIOLTO[®] RESPIMAT[®] (tiotropium bromide and olodaterol inhalation spray; Boehringer Ingelheim), for oral inhalation use, contains the combination of the LAMA tiotropium

IMPORTANT SAFETY INFORMATION for STIOLTO RESPIMAT (Continued) WARNINGS AND PRECAUTIONS (Continued)

Use caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines.

Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.

Table 2. Risk of COPD Exacerbation and Pneumonia Diagnosis Associated With TIO+OLO vs FF+UMEC+VI by Subgroup^{1,2,a,b}

Subgroup	Risk of any COPD exacerbation FF+UMEC+VI [reference: TIO+OLO]		Risk of pneumonia diagnosis FF+UMEC+VI [reference: TIO+OLO]	
	aHR (95% CI)	P value	aHR (95% CI)	P value
Overall (N = 11,316)	0.93 (0.86-1.00)	.047	1.12 (0.98-1.27)	.103
Maintenance-naive (n = 6050)	0.99 (0.88-1.10)	.782	1.13 (0.95-1.36)	.171
GOLD A/B (n = 7768)	0.960	.458	1.189	.085
No exacerbation (n = 5104)	1.009	.898	1.295	.053
GOLD C/D (n = 3548)	0.872	.020	1.127	.198

aHR, adjusted HR; COPD, chronic obstructive pulmonary disease; FF+UMEC+VI, fluticasone furoate, umeclidinium, and vilanterol; GOLD, Global Initiative for Chronic Obstructive Lung Disease; TIO+OLO, tiotropium and olodaterol.

^aSignificant ($P < .05$) differences appear in **bold**.

^bMultivariable adjustment for key post-propensity score match differences observed between the cohorts.

the LABA VI; this TT product is indicated for maintenance treatment of patients with COPD.¹¹ TIO+OLO is delivered via a soft-mist inhaler, whereas FF+UMEC+VI is delivered via a dry powder inhaler.^{10,11}

Design

The goal of the retrospective observational study by Sethi et al was to assess differences in relevant clinical and economic outcomes associated with initiation of TIO+OLO or FF+UMEC+VI maintenance therapy in patients with COPD over up to 12 months of treatment (Table 1).^{1,2} Outcome differences between treatment groups were examined for the overall population, for subgroups broken down by differing exacerbation histories (GOLD risk groups), and for a separate subgroup of those naive to maintenance treatment (ie, maintenance-naive).^{1,2} To stratify the overall population by exacerbation history, all included patients were categorized into approximated GOLD risk groups: GOLD A/B (0-1 baseline exacerbation not leading to hospitalization in the previous year), No exacerbation (subgroup of GOLD A/B with 0 exacerbations in the prior year), and GOLD C/D (aligning with the 2024 GOLD E risk group; ≥ 2 baseline exacerbations not leading to hospitalization and/or ≥ 1 baseline exacerbation leading

to hospitalization in the previous year).¹⁻³ Patients in the 2 treatment groups were matched 1:1 using propensity score matching on baseline characteristics.^{1,2} After matching, there were 5658 patients in each treatment cohort.^{1,2} Overall, at baseline, the mean age of included patients was approximately 72 years, with around half being female; further, over 90% of patients had Medicare Advantage Part D insurance.¹

Results

This article reviews results on the following clinical and economic outcomes in Sethi et al: adjusted risk of COPD exacerbation and of pneumonia diagnosis and both COPD- and/or pneumonia-related population annualized health care resource use (HCRU) and health care costs (authors adjusted to 2020 US\$) (for more information on additional outcomes, please see the published studies).^{1,2}

After multivariable adjustment to account for any remaining imbalance in patient baseline characteristics, the adjusted risk of COPD exacerbation between treatment groups was not significantly different among maintenance-naive patients or among the GOLD A/B or No exacerbation risk groups (Table 2).^{1,2} Compared with that seen for TIO+OLO initiators, the adjusted risk of COPD exacerbation

IMPORTANT SAFETY INFORMATION for STIOLTO RESPIMAT (Continued) WARNINGS AND PRECAUTIONS (Continued)

Use with caution in patients with urinary retention especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Patients with moderate to severe renal impairment (creatinine clearance of < 60 mL/min) should be monitored closely for anticholinergic side effects.

Be alert to hypokalemia and hyperglycemia.

Table 3. Significant Differences in COPD- and/or Pneumonia-Related Population Annualized HCRU Associated With TIO+OLO vs FF+UMEC+VI by Subgroup^{1,2,a}

HCRU outcome	Overall population (N = 11,316)			Maintenance-naive (n = 6050)		
	COPD- and/or pneumonia-related HCRU, population annualized average [95% CI]					
	TIO+OLO	FF+ UMEC+VI	P value	TIO+OLO	FF+ UMEC+VI	P value
Inpatient visits	0.40 (0.37-0.43)	0.45 (0.42-0.49)	.036	0.42 (0.37-0.47)	0.50 (0.44-0.55)	.029
Ambulatory visits	9.01 (8.54-9.48)	9.85 (9.33-10.37)	.017	9.24 (8.51-9.96)	9.57 (8.83-10.31)	.528
Outpatient visits	4.98 (4.55-5.42)	5.67 (5.19-6.15)	.036	5.34 (4.66-6.02)	5.63 (4.94-6.31)	.559
Other medical visits	4.36 (4.11-4.61)	4.94 (4.68-5.20)	.001	3.69 (3.38-4.00)	4.23 (3.88-4.57)	.021
Pharmacy fills	15.48 (15.20-15.77)	15.08 (14.82-15.35)	.037	14.83 (14.45-15.21)	14.52 (14.17-14.88)	.238

(Continued on next page >>)

for FF+UMEC+VI initiators was 7% lower in the overall population (adjusted HR [aHR], 0.93; 95% CI, 0.86-1.00; $P = .047$) and 13% lower in the GOLD C/D risk group (aHR, 0.87; 95% CI, 0.78-0.98; $P = .020$).^{1,2} There were no significant differences in adjusted risk of pneumonia diagnosis between treatment groups, regardless of subgroup examined.

The majority of population annualized COPD- and/or pneumonia-related HCRU outcomes were similar between the treatment groups; however, several outcomes were significantly different within the overall population and across subgroups (Table 3).^{1,2} In the overall study population, HCRU was significantly greater for inpatient, ambulatory, outpatient, and other medical visits among FF+UMEC+VI initiators as compared with TIO+OLO initiators, whereas pharmacy fills were significantly lower for FF+UMEC+VI initiators.¹ Among maintenance-naive patients, FF+UMEC+VI initiators had significantly more inpatient and other medical visits. In addition, those in the GOLD A/B risk group who initiated FF+UMEC+VI had significantly more hospitalizations, ambulatory visits, outpatient visits, and other medical visits.² In the No exacerbation group, the only significant HCRU difference was a greater number of other medical visits among

those initiating FF+UMEC+VI. However, in the GOLD C/D risk group, those initiating FF+UMEC+VI had significantly fewer pharmacy fills.

Across most subgroups, initiation of TIO+OLO was associated with significantly lower population annualized COPD- and/or pneumonia-related total costs as compared with initiation of FF+UMEC+VI (Figure 2).^{1,2} Significantly lower total costs were seen with TIO+OLO initiation in the overall population, maintenance-naive patients, and those in the GOLD A/B and No exacerbation subgroups (all $P < .001$), although there were no significant differences in total cost between treatment cohorts in the GOLD C/D risk group. Furthermore, across all populations and subgroups, COPD- and/or pneumonia-related pharmacy costs were lower for TIO+OLO initiators than for FF+UMEC+VI initiators.^{1,2}

Limitations of this study include those inherent to claims-based studies, such as the potential for missing or misclassified data, nonrandom allocation of treatment, and lack of clinically relevant data (ie, lung function, symptom burden). Additional limitations include a relatively short follow-up period and a lack of generalizability to patients who do not remain on a study treatment or who do not have commercial or Medicare Advantage Part D health insurance.^{1,2}

IMPORTANT SAFETY INFORMATION for STIOLTO RESPIMAT (Continued) ADVERSE REACTIONS

The most common adverse reactions with STIOLTO (>3% incidence and higher than an active control) were: nasopharyngitis, 12.4% (11.7%/12.6%), cough, 3.9% (4.4%/3.0%), and back pain, 3.6% (1.8%/3.4%).

» HCRU outcome	GOLD A/B (n = 7768)			No exacerbation (n = 5104)			GOLD C/D (n = 3548)		
	COPD- and/or pneumonia-related HCRU, population annualized average (95% CI)								
	TIO+OLO	FF+ UMEC+VI	P value	TIO+OLO	FF+ UMEC+VI	P value	TIO+OLO	FF+ UMEC+VI	P value
Inpatient visits	0.27 (0.24-0.30)	0.33 (0.29-0.36)	.022	0.26 (0.23-0.30)	0.30 (0.26-0.34)	.212	0.73 (0.65-0.81)	0.74 (0.65-0.82)	.927
Ambulatory visits	7.02 (6.59-7.46)	7.72 (7.23-8.22)	.036	6.51 (6.01-7.00)	6.95 (6.43-7.46)	.222	14.09 (12.89-15.29)	14.64 (13.41-15.88)	.530
Outpatient visits	3.51 (3.11-3.91)	4.12 (3.66-4.59)	.048	3.30 (2.84-3.75)	3.59 (3.12-4.05)	.379	8.74 (7.60-9.89)	9.15 (8.00-10.29)	.625
Other medical visits	3.10 (2.85-3.35)	3.62 (3.35-3.89)	.004	2.71 (2.43-2.99)	3.39 (3.07-3.71)	.001	7.58 (7.01-8.16)	7.90 (7.34-8.46)	.441
Pharmacy fills	13.81 (13.54-14.09)	13.70 (13.44-13.97)	.577	13.21 (12.89-13.53)	13.21 (12.89-13.54)	.995	19.74 (19.08-20.40)	18.18 (17.62-18.74)	<.001

COPD, chronic obstructive pulmonary disease; FF+UMEC+VI, fluticasone furoate, umeclidinium, and vilanterol; GOLD, Global Initiative for Chronic Obstructive Lung Disease; TIO+OLO, tiotropium and olodaterol.

*Significant ($P < .05$) differences appear in **bold**.

DISCUSSION

Clinical and economic results from this study reinforce use of guideline-recommended treatments, and align with findings from several other real-world analyses.¹⁻⁷ Results of a subgroup analysis of the study by Sethi et al, presented at the ATS 2023 International Conference in May 2023, showed that patients with an index blood eosinophil count of 300 cells/ μ L or less experienced similar rates of COPD exacerbations regardless of treatment with TIO+OLO or FF+UMEC+VI (n = 1098 in each group).⁵ According to GOLD recommendations, individuals with a blood eosinophil count of 300 cells/ μ L or more are likely to derive the greatest benefit when an ICS is added to their treatment regimen.³ Most COPD- and/or pneumonia-related HCRU and costs were similar between cohorts; however, pharmacy costs were significantly lower in patients initiating TIO+OLO than in those initiating FF+UMEC+VI (\$4692 vs \$6573; $P < .001$).⁵

Results of a Medicare Advantage Part D claims-based study also showed lower health care costs and improved COPD- and pneumonia-related outcomes in patients with COPD initiating dual therapy

(including TIO+OLO) than in those initiating TT. Further, most of those who initiated TT had no baseline LAMA or LABA exposure, indicating potential noncompliance with GOLD treatment recommendations.⁷

In a separate commercial and Medicare Advantage claims-based analysis that examined clinical and economic outcomes among patients categorized into GOLD risk groups, fewer than one-third of patients in the GOLD A/B group and fewer than two-thirds of patients in the GOLD C/D group were prescribed COPD treatment according to GOLD guideline recommendations. Results showed that treatment aligning with GOLD recommendations was associated with fewer exacerbations and lower COPD-related HCRU and costs.⁶

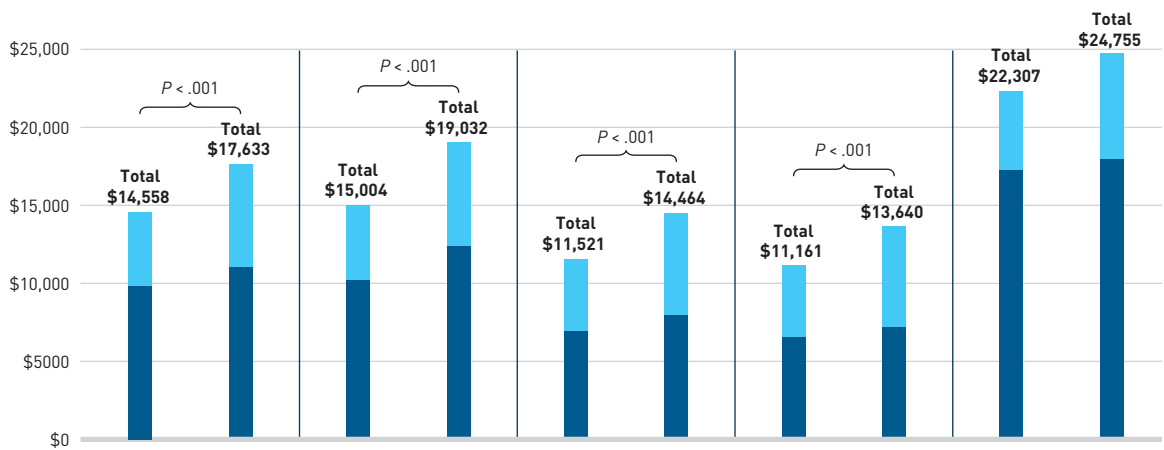
CONCLUSIONS

Clinical results of the study by Sethi et al support ATS and GOLD guidelines, which recommend using LABA/LAMA therapy in patients with COPD and low exacerbation risk and TT in those at higher risk. Economic results support the lower health care costs associated with following these recommendations. •

IMPORTANT SAFETY INFORMATION for STIOLTO RESPIMAT (Continued) DRUG INTERACTIONS (Continued)

- Use caution if administering adrenergic drugs because sympathetic effects of olodaterol may be potentiated.
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of olodaterol.
- Use with caution in patients taking non-potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant beta-agonists.

Figure 2. Post-Matching Population Annualized Average COPD- and/or Pneumonia-Related Costs During Follow-Up With TIO+OLO vs FF+UMEC+VI^{1,2,a}



	Overall population (N = 11316)		Maintenance-naive (n = 6050)		GOLD A/B (n = 7768)		No exacerbation (n = 5104)		GOLD C/D (n = 3548)	
	TIO+OLO	FF+UMEC+VI	TIO+OLO	FF+UMEC+VI	TIO+OLO	FF+UMEC+VI	TIO+OLO	FF+UMEC+VI	TIO+OLO	FF+UMEC+VI
Pharmacy costs	\$4729	\$6567	\$4750	\$6642	\$4612	\$6484	\$4605	\$6451	\$5027	\$6754
Medical costs (combined)	\$9829	\$11,066	\$10,254	\$12,390	\$6909	\$7980	\$6556	\$7189	\$17,280	\$18,001
Total	\$14,558	\$17,633	\$15,004	\$19,032	\$11,521	\$14,464	\$11,161	\$13,640	\$22,307	\$24,755

COPD, chronic obstructive pulmonary disease; FF+UMEC+VI, fluticasone furoate, umeclidinium, and vilanterol; GOLD, Global Initiative for Chronic Obstructive Lung Disease; TIO+OLO, tiotropium and olodaterol.

^aSignificant (P < .05) differences appear in **bold**.

REFERENCES

- Sethi S, Palli SR, Bengtson LGS, et al. Clinical and economic outcomes in patients with chronic obstructive pulmonary disease initiating maintenance therapy with tiotropium bromide/olodaterol or fluticasone furoate/umeclidinium/vilanterol. *J Manag Care Spec Pharm.* 2023;29(7):791-806. doi:10.18553/jmcp.2023.22373
- Sethi S, Clark B, Bengtson LGS, et al. Healthcare resource utilization, cost and clinical outcomes in patients diagnosed with COPD initiating tiotropium bromide/olodaterol versus fluticasone furoate/umeclidinium/vilanterol based on exacerbation history. *Int J Chron Obstruct Pulmon Dis.* 2023;18:625-641. doi:10.2147/COPD.S386962
- Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2024 report. Global Initiative for Chronic Obstructive Lung Disease. November 2023. Accessed November 13, 2023. https://goldcopd.org/wp-content/uploads/2023/11/GOLD-2024_v1.0-30oct23_WMV.pdf
- Nici L, Mammen MJ, Charbek E, et al. Pharmacologic management of chronic obstructive pulmonary disease. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med.* 2020;201(9):e56-e69. doi:10.1164/rccm.202003-0625ST
- Clark B, Sethi S, Bengtson L, et al. COPD exacerbations, resource use, and costs among COPD patients with eosinophil count ≤300 cells/μl who initiate therapy with tiotropium/olodaterol or fluticasone furoate/umeclidinium/vilanterol. Presented at: ATS 2023 International Conference; May 23, 2023; Washington, DC. *Am J Respir Crit Care Med.* 2023;207:A5921 doi:10.1164/ajrccm-conference.2023.207.1-MeetingAbstracts.A5921

IMPORTANT SAFETY INFORMATION for STIOLTO RESPIMAT (Continued) DRUG INTERACTIONS (Continued)

- The action of adrenergic agents on the cardiovascular system may be potentiated by monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval. Therefore, STIOLTO should be used with extreme caution in patients being treated with these drugs. Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD.
- Avoid co-administration of STIOLTO with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

6. Palli SR, Zhou S, Shaikh A, Willey VJ. Effect of compliance with GOLD treatment recommendations on COPD health care resource utilization, cost, and exacerbations among patients with COPD on maintenance therapy. *J Manag Care Spec Pharm.* 2021;27:625-637. doi:10.18553/jmcp.2021.20390
7. Palli SR, Frazer M, DuCharme M, Buikema AR, Anderson AJ, Franchino-Elder J. Differences in real-world health and economic outcomes among patients with COPD treated with combination tiotropium/olodaterol versus triple therapy. *J Manag Care Spec Pharm.* 2020;26(10):1363-1374. doi:10.18553/jmcp.2020.20159
8. Li Y, Lim J, Stenkowski S, Kaila S, Renda A, Shaikh A. Initiation of triple therapy maintenance treatment among patients with COPD. *Am J Manag Care.* 2020;26(4):e106-e112. doi:10.37765/ajmc.2020.42837
9. Bhatt SP, Blauer-Peterson C, Buysman EK, Bengtson LGS, Palli SR. Trends and characteristics of Global Initiative for Chronic Obstructive Lung Disease guidelines-discordant prescribing of triple therapy among patients with COPD. *Chronic Obstr Pulm Dis.* 2022;9(2):135-153. doi:10.15326/jcopdf.2021.0256
10. Stiolto® Respimat®. Prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc; 2021. Accessed October 25, 2023. <https://content.boehringer-ingelheim.com/DAM/7fe8a4a7-9ed3-41ef-a565-af1e0120af14/stiolto%20respimat-us-pi.pdf>
11. Trelegy Ellipta. Prescribing information. GlaxoSmithKline; 2023. Accessed October 25, 2023. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Trelegy_Ellipta/pdf/TRELEGY-ELLIPTA-PI-PIL-IFU.PDF

IMPORTANT SAFETY INFORMATION for STIOLTO RESPIMAT (Continued)

STIOLTO is for oral inhalation only.

The STIOLTO cartridge is only intended for use with the STIOLTO RESPIMAT inhaler.

Inform patients not to spray STIOLTO into the eyes as this may cause blurring of vision and pupil dilation.

CL-STO-100021 6.5.2019

