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Benefit of Prompt Versus Delayed Initiation of Single-Inhaler Triple Therapy on Exacerbations and Healthcare Costs Among Patients With Chronic Obstructive Pulmonary Disease in the US

This *AJMC*® Clinical Brief provides key information regarding a poster presented by lead investigator Michael Bogart, PharmD, director of U.S. Value, Evidence, and Outcomes at GSK at the 2021 American Thoracic Society Annual Congress on May 14, 2021. The authors of the study are Michael Bogart, PharmD; Guillaume Germain, MA; Shirley Huang, PharmD; Afisi Ismaila, PhD; Young Jung, PhD; Francois Laliberté, MA; Sean D. MacKnight, MScPH; and Mei Sheng Duh, MPH, ScD. This study was funded and developed by GSK (GSK ID: 209575).

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STATEMENT OF MATERIAL DIFFERENCES

In TRELEGE COPD clinical trials, prompt versus delayed initiation of TRELEGE was not evaluated. In this study, 21.4% of the prompt cohort and 23.1% of the delayed cohort had comorbid asthma.¹ Patients with asthma were not included in TRELEGE COPD clinical trials.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality, with a substantial economic impact.^{2,3} Episodes of acute worsening of respiratory symptoms, known as COPD exacerbations, are a driver of clinical and economic burden.⁴⁻⁸ Hospitalizations due to COPD exacerbations are associated with higher costs and higher hospital readmission rates.

In 2012, the US Centers for Medicare & Medicaid Services implemented the Hospital Readmissions Reduction Program, supporting the national goal of improving healthcare and reducing avoidable readmissions by linking reimbursement payment to the quality of hospital care.⁹ There are 6 conditions, or measures, participating in this program, including COPD.

INDICATION

TRELEGE 100/62.5/25 is for maintenance treatment of patients with COPD. TRELEGE is NOT indicated for the relief of acute bronchospasm.

IMPORTANT SAFETY INFORMATION FOR TRELEGE ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol)

CONTRAINDICATIONS

TRELEGE is contraindicated in the following:

- Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required.
- Patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate (FF), umeclidinium (UMEC), vilanterol (VI), or any of the excipients.

Please see additional Important Safety Information for TRELEGE throughout.
Please see full **Prescribing Information**, including **Patient Information**, for TRELEGE.

The predominant classes of inhaled medications used for the maintenance treatment of COPD are long-acting muscarinic antagonists (LAMA), long-acting β_2 agonists (LABA), and inhaled corticosteroids (ICS; usually in combination with a LABA).^{4,10} These medications help relieve symptoms by improving lung function and reducing the frequency of exacerbations. The 2021 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report supports escalation to triple therapy (ICS/LABA/LAMA) for patients with COPD who continue to experience persistent breathlessness or exacerbations on ICS/LABA therapies.⁴

The dispensing of a bronchodilator within 30 days of hospital discharge after admission for a COPD exacerbation has been identified by the National Committee for Quality Assurance (NCQA) as a quality-of-care measure in the United States.¹¹ There is limited real-world evidence to inform the impact of prompt versus delayed timing of therapy initiation. This article highlights the results of a retrospective study that were presented at the American Thoracic Society 2021 International Conference, which aimed to evaluate how the timing of initiation of TRELEGY ELLIPTA (fluticasone furoate 100 mcg [an ICS], umeclidinium 62.5 mcg [a LAMA], and vilanterol 25 mcg [a LABA] inhalation powder)—once-daily in a single inhaler—following a first exacerbation can affect rates of subsequent exacerbations and hospital readmission, as well as healthcare costs in a large commercially insured population of patients with COPD in the United States.^{1,12} TRELEGY is indicated for the maintenance treatment of patients with COPD. TRELEGY is NOT indicated for the relief of acute bronchospasm.

METHODS

This retrospective claims analysis included a commercially insured US population from the IQVIA Real-World Data Adjudicated Claims database.^{1,12}

This study evaluated outcomes between prompt and delayed TRELEGY initiation in patients following their first COPD exacerbation.^{1,12} Prompt TRELEGY initiation was defined as within 30 days of the index date and delayed treatment was defined as within 31 to 180 days following the index date. The index date was the last day of the first COPD-related moderate or severe exacerbation (ie, discharge date for a hospitalization and the day of the visit for an emergency department [ED] or outpatient visit) on or after the TRELEGY approval date of September 18, 2017. The baseline period was 1 year prior to the index date. The follow-up period spanned from the index date to the end of continuous enrollment or end of data (September 30, 2019).

COPD-Related Exacerbation Definitions

In this study, a moderate COPD-related exacerbation was defined as an outpatient or ED visit with a COPD exacerbation diagnosis code in the primary position and at least 1 dispensing or administration of a systemic corticosteroid or antibiotic within 5 days following, or prior to, the visit.¹ A severe COPD-related exacerbation was defined as an inpatient hospitalization with a diagnosis code for COPD exacerbation in the primary position. Overall exacerbations included both moderate and severe exacerbations. Exacerbations that occurred within 14 days of each other were considered a single exacerbation episode and were classified according to the highest severity.

Inclusion and Exclusion Criteria

To be eligible for participation in this study, patients were required to have at least 12 months of continuous enrollment with medical and pharmacy coverage in the pre-index period and at least 6 months of coverage in the post-index period.^{1,12} Participants were required to be at least 40 years of age who experienced at least 1 COPD-related moderate or severe exacerbation and had at least 1 pharmacy claim for TRELEGY within 6 months after the index date. Patients with at

IMPORTANT SAFETY INFORMATION FOR TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol) (cont'd)

WARNINGS AND PRECAUTIONS

- Long-acting beta₂-adrenergic agonist (LABA) monotherapy for asthma increases the risk of asthma-related death, and in pediatric and adolescent patients, available data also suggest an increased risk of asthma-related hospitalization. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with inhaled corticosteroids (ICS), data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.
- TRELEGY should NOT be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- TRELEGY is NOT a rescue medication and should NOT be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist.
- TRELEGY should not be used more often or at higher doses than recommended or with another LABA for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.

least 1 pharmacy claim for TRELEGY prior to the index date or at least 1 COPD-related moderate or severe exacerbation during the 12-month baseline period were excluded from study participation.¹

Study Population

A total of 1904 patients were eligible for the study and divided into 2 cohorts: prompt initiators (n = 529) and delayed initiators (n = 1375).^{1,12} After weighting, the baseline characteristics were balanced between cohorts. The mean age of prompt initiators was 59.8 years and the mean age of delayed initiators was 59.9 years. More than half of all study participants were women. Index exacerbation type (moderate or severe) was similar between cohorts; most patients experienced moderate exacerbation in both the prompt (81.2%) and delayed (82.6%) cohorts. Medication use was also similar between the 2 groups.

Primary and Secondary Objectives

The primary objective of the study was the rate of COPD-related overall, moderate, and severe exacerbations among prompt (0-30 days) initiators and delayed (31-180 days) initiators of TRELEGY.¹ The secondary objectives were the time to first COPD-related exacerbations among prompt initiators versus delayed initiators of TRELEGY, time to first all-cause and COPD-related hospital readmissions (ie, 30-day, 60-day, and 90-day rates) among prompt versus delayed initiators of TRELEGY following a COPD-related hospitalization, and all-cause and COPD-related medical costs among prompt versus delayed initiators of TRELEGY.

RESULTS

Rates of COPD-Related Exacerbations

Prompt initiation of TRELEGY significantly lowered rates of COPD-related exacerbations versus delayed initiation.^{1,12} Prompt TRELEGY

initiators had a 21% lower rate of overall exacerbations (0.98 vs 1.23 per person-year [PPY]; rate ratio [RR], 0.79; 95% confidence interval [CI], 0.65-0.94; $P = 0.004$), 16% lower rate of moderate exacerbations (0.86 vs 1.03 PPY; RR, 0.84; 95% CI, 0.69-0.99; $P = 0.038$), and 43% lower rate of severe exacerbations (0.11 vs 0.20 PPY; RR, 0.57; 95% CI, 0.37-0.79; $P = 0.002$) than delayed initiators. Also, patients who initiated TRELEGY promptly had a longer median time to next overall exacerbation (367 days) than patients who had delayed initiation of TRELEGY (200 days). A weighted analysis of Kaplan-Meier rates of overall COPD exacerbation is presented in **Figure 1**.

Hospital Readmission Rates

Prompt initiation of TRELEGY numerically reduced rates of hospital readmissions versus delayed initiation; however, statistical significance was not reached.^{1,12}

Prompt TRELEGY initiators had a 60% lower risk of 30-day all-cause readmission (hazard ratio [HR], 0.40; 95% CI, 0.08-1.92; $P = 0.252$), a 23% lower risk of 60-day all-cause readmission (HR, 0.77; 95% CI, 0.30-2.00; $P = 0.590$), and a 26% lower risk of 90-day all-cause readmission (HR, 0.74; 95% CI, 0.36-1.54; $P = 0.425$) than delayed TRELEGY initiators.^{1,12}

As for COPD-related readmissions, defined as hospitalizations with a primary or secondary diagnosis of COPD, prompt TRELEGY initiators had an 82% lower risk of 30-day readmission (HR, 0.18; 95% CI, 0.02-1.68; $P = 0.133$), a 30% lower risk of 60-day readmission (HR, 0.70; 95% CI, 0.25-1.97; $P = 0.498$), and a 30% lower risk of 90-day readmission (HR, 0.70; 95% CI, 0.33-1.51; $P = 0.365$) than delayed TRELEGY initiators.^{1,12}

Healthcare Costs

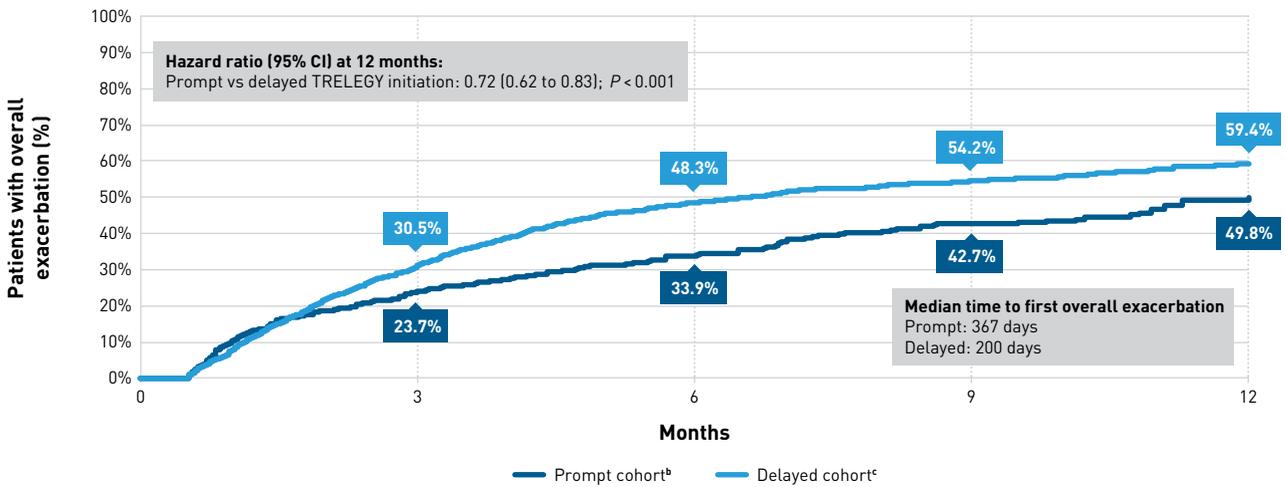
Prompt initiation of TRELEGY resulted in lower all-cause and COPD-related annual healthcare costs than delayed initiation of TRELEGY (**Figure 2**).^{1,12} These costs include pharmacy and direct medical costs.

IMPORTANT SAFETY INFORMATION FOR TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol) (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing fluticasone furoate. Advise patients to rinse their mouths with water without swallowing after inhalation.
- Lower respiratory tract infections, including pneumonia, have been reported following use of ICS, like fluticasone furoate. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as clinical features of pneumonia and exacerbations frequently overlap.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients.
- Particular care is needed for patients transferred from systemic corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to TRELEGY.
- Hypercorticism and adrenal suppression may occur with higher than the recommended dosage or at the regular dosage of ICS in susceptible individuals. If such changes occur, reduce the dose of TRELEGY slowly, and consider other treatments for management of COPD or asthma symptoms.

Figure 1. Kaplan-Meier Rates of Overall COPD Exacerbation (Weighted Analysis)^{1,12,a}



^aOverall exacerbation was defined as having at least 1 of a moderate or severe exacerbation during the post-index period, not including the index date.

^bPrompt cohort started TRELEGY within 30 days following the index date.

^cDelayed cohort started TRELEGY between 31 and 180 days following the index date.

Prompt initiation of TRELEGY significantly reduced mean total all-cause healthcare costs by \$6293 per patient per year (PPY) ($P = 0.014$).^{1,12} Total medical costs were lower for prompt initiators of TRELEGY versus delayed initiators of TRELEGY, which included hospitalization costs (\$6201 [prompt] vs \$9346 [delayed]; $P < 0.05$), outpatient visit costs (\$12,250 [prompt] vs \$14,517 [delayed]), and ED visit costs (\$419 [prompt] vs \$496 [delayed]).

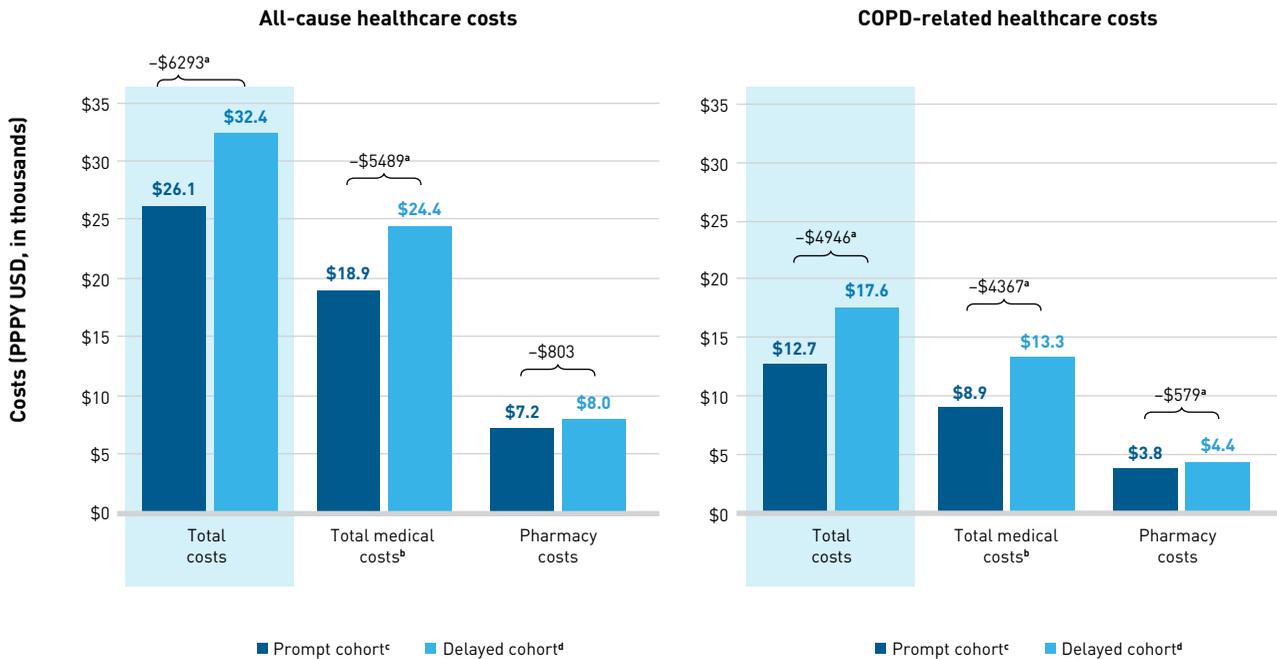
Prompt initiation of TRELEGY significantly reduced mean total COPD-related healthcare costs by \$4946 PPY ($P = 0.002$).^{1,12} Total medical costs were lower for prompt initiators of TRELEGY versus delayed initiators of TRELEGY, which included hospitalization costs (\$5499 [prompt] vs \$8075 [delayed]; $P < 0.05$); outpatient visit costs (\$3223 [prompt] vs \$4909 [delayed]; $P < 0.05$); ED visit costs (\$197 [prompt] vs \$303 [delayed]).

IMPORTANT SAFETY INFORMATION FOR TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol) (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Caution should be exercised when considering the coadministration of TRELEGY with ketoconazole and other known strong CYP3A4 inhibitors (including, but not limited to, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue TRELEGY and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, TRELEGY may need to be discontinued. TRELEGY should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Figure 2. All-Cause and COPD-Related Healthcare Costs: Differences for Prompt Versus Delayed Initiation of TRELEGY^{1,12}



USD = United States dollar.

^aP < 0.05.

^bTotal medical costs include hospitalization, outpatient visit, and emergency department visit costs.

^cPrompt cohort started TRELEGY within 30 days following the index date.

^dDelayed cohort started TRELEGY between 31 and 180 days following the index date.

IMPORTANT SAFETY INFORMATION FOR TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol) (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Decreases in bone mineral density have been observed with long-term administration of products containing ICS. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (eg, anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care prior to initiating TRELEGY and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the long-term administration of ICS or inhaled anticholinergics. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use TRELEGY long term.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develop.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.

LIMITATIONS

Although propensity score weighting was used on baseline characteristics to account for potential differences between the prompt and delayed treatment cohorts, the possibility of unmeasured confounding cannot be excluded.¹ Missing data in the claims database can yield biased results if the data are not missing at random. Medications not recorded in the claims data were not accounted for in the analysis. The analysis was vulnerable to coding inaccuracies and may have led to misclassification bias. A claim for a filled prescription does not indicate that the medication was consumed or taken as prescribed. Results and conclusions are limited to the patient populations in this

study and may not be generalizable to uninsured or other insured US populations.

SUMMARY

Results from this retrospective, real-world study demonstrated that prompt initiation of TRELEGY after a COPD exacerbation, compared with delayed initiation of TRELEGY, significantly reduced the annual rate of overall, moderate, and severe exacerbations; increased the time to next overall exacerbation; numerically reduced all-cause and COPD-related 30-, 60-, and 90-day readmissions; and significantly reduced all-cause and COPD-related mean total healthcare costs.^{1,2}

IMPORTANT SAFETY INFORMATION FOR TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol) (*cont'd*)

ADVERSE REACTIONS

- In subjects with COPD, the most common adverse reactions ($\geq 1\%$ and more common than placebo + FF/VI 100/25) reported in two 12-week clinical trials with UMEC + FF/VI 100/25, the components of TRELEGY 100/62.5/25, (and placebo + FF/VI 100/25) were: headache, 4% (3%); back pain, 4% (2%); dysgeusia, 2% ($< 1\%$); diarrhea, 2% ($< 1\%$); cough, 1% ($< 1\%$); oropharyngeal pain, 1% (0%); and gastroenteritis, 1% (0%).
- Additional adverse reactions ($\geq 1\%$ incidence) reported in subjects with COPD taking TRELEGY 100/62.5/25 in a 52-week trial included upper respiratory tract infection, pneumonia, bronchitis, oral candidiasis, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, constipation, urinary tract infection, and dysphonia.

DRUG INTERACTIONS

- TRELEGY should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because they may potentiate the effect of vilanterol on the cardiovascular system.
- Use beta-blockers with caution, as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD or asthma.
- Use with caution in patients taking non-potassium-sparing diuretics, as ECG changes and/or hypokalemia associated with these diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of TRELEGY with other anticholinergic-containing drugs, as this may lead to an increase in anticholinergic adverse effects.

USE IN SPECIFIC POPULATIONS

- Use TRELEGY with caution in patients with moderate or severe hepatic impairment, as fluticasone furoate systemic exposure may increase by up to 3-fold. Monitor for corticosteroid-related side effects.

Q&A WITH LEAD INVESTIGATOR, MICHAEL BOGART, PHARM.D, DIRECTOR, U.S. VALUE, EVIDENCE, AND OUTCOMES, GSK

In your study, “prompt” initiation of TRELEGY ELLIPTA (fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder), a once-daily, single-inhaler triple therapy (SITT), was defined as within 30 days of a COPD exacerbation and “delayed” was defined as 31 to 180 days after COPD exacerbation. What is the clinical significance of this time to initiation following the exacerbation?

In clinical trials, all patients are expected to use medications per protocol. In the real world, this may not be the case and the timing of initiation of treatment in the real world is not well understood. The 30-day window was chosen because NCQA has defined the dispensing of a bronchodilator within 30 days of hospital discharge after admission for a COPD exacerbation as a quality-of-care measure in the United States.

What are common barriers in healthcare delivery systems that could delay SITT initiation in patients who experience moderate or severe COPD exacerbations?

Typically, COPD maintenance medication is prescribed by a patient’s primary care provider or pulmonologist. They are not typically prescribed acutely in an inpatient setting. Therefore, gaps in care can exist when a patient transitions from an inpatient to outpatient setting, including challenges with medication management. In patients with a COPD exacerbation, time, access, and distance to provider could impact getting the proper treatment at the right time.

In what ways can you foresee the results from this study affecting formulary decision-making?

Results such as these reinforce the importance of proper access to medication. Once a patient experiences a worsening event as part of their COPD, providers should assess how well a patient is controlled on therapy and, if necessary, make timely adjustments to the patient’s medication regimen. If the patient is unable to fill their medication in a timely manner due to an access issue, this study suggests that they may experience future events and worsening.

How can payers and decision-makers alleviate barriers that potentially delay the start of COPD therapies?

The most important barrier that can be lifted to enable the start of therapy is easy access to the medication by patients. Increased access to care has been shown to increase the use of preventative care and healthcare-seeking behavior among patients.

What is an important takeaway message from your study for managed care professionals?

Managed care professionals should assess the appropriate timing of initiating triple therapy following an exacerbation to maximize the benefit of the patient’s treatment regimen. In COPD, providers should strongly consider impact of timing on exacerbations, readmissions, and healthcare costs. •

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TRELEGY ELLIPTA was developed in collaboration with **INNOVIVA**

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