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Single-Inhaler Triple Therapies for Asthma and Chronic Obstructive Pulmonary Disease

Individual Topic Request

December 2022

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About This Research Product

An ***Individual Topics Request (ITR)*** is a brief and succinct evidence synthesis document, generally with a narrow scope and a quick timeline. The products can be requested by an individual or group of Drug Effectiveness Review Project (DERP) participants. Methods will be customized to the budget and needs of participants.

Overview of All Research Products Available to DERP

Research Product Type	Scoping	Budget	Synthesis of Findings	RoB and GRADE	About the Product Goal of Product
PICOS and Key Questions	Yes	No	No	No	• Outlines the scope of DERP's research interests • DERP uses this product to determine if they want a Topic Brief
Topic Brief	Yes	Yes	No	No	• Developed from PICOS and Key Questions and identifies eligible studies for the topic and proposes a budget • DERP uses this product to determine if they want to move the topic into the research work plan (e.g., Systematic Review)
Surveillance Report	No	No	No	No	• Identifies studies and FDA actions on existing topics (i.e., those completed in the last 3 years) since the previous research product was completed • DERP uses this product to determine if they want to commission an update or derivate of an existing research product
Individual Topic Request (ITR)	**No**	**No**	**Yes**	**Yes**	• **A brief and succinct research product synthesizing evidence on a narrow, requested topic (e.g., a new, high-cost drug)** • **DERP uses this product to better understand the evidence for a narrow topic, typically on a quick timeline**
Policy Brief	No	No	Yes	No	• A synthesis of management strategies, on things such therapies or payment models, for DERP participants to consider • DERP uses this product to evaluate what is or might be occurring in Medicaid at a programmatic and clinical level
Rapid Review	No	No	Yes	Yes	• An evidence synthesis product that is larger than an ITR, but less comprehensive than a Systematic Review (e.g., shorter search period) • DERP uses this product to better understand the body of evidence on a topic within a quick timeline
Systematic Review	No	No	Yes	Yes	• The most comprehensive evidence synthesis product that uses gold-standard methods of evidence synthesis • DERP uses this product to understand the body of evidence for a larger topic, such as a drug class review

Abbreviations. DERP: Drug Effectiveness Review Project; FDA: US Food & Drug Administration; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; ITR: individual topic request; PICOS: populations, interventions, comparators, outcomes, study designs; RoB: risk of bias.

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Overview

Medicaid administrators are interested in the effectiveness and harms of 3 single-inhaler triple therapies (SITT; Table 1) for the management of asthma and chronic obstructive pulmonary disease (COPD) compared with monotherapy, dual therapy, or multiple-inhaler triple therapies (MITT). We used Drug Effectiveness Review Project (DERP) methods to identify and evaluate relevant evidence published up to September 2022.

Table 1. Single-Inhaler Triple Therapy Medications of Interest

Brand Name	Generic Name	Generic Abbreviation
Breztri Aerosphere	Budesonide; glycopyrrolate; formoterol fumarate	BUD/GLY/FOR
Trelegy Ellipta	Fluticasone furoate; umeclidinium bromide; vilanterol trifenatate	FLU/UMEC/VI
Trimbow	Beclomethasone dipropionate; glycopyrronium bromide; formoterol fumarate dihydrate	BDP/GLY/FOR

Note. Glycopyrrolate and glycopyrronium bromide are used interchangeably.

We identified 1 randomized controlled trial (RCT) with a moderate risk of bias evaluating Trelegy Ellipta (Trelegy) in individuals with asthma and 11 RCTs evaluating all 3 SITTs in individuals with COPD (7 with moderate risk of bias and 4 with high risk of bias). The majority of participants in the asthma study identified as White and female. Meanwhile, most participants in the COPD studies identified as White, male, and former smokers.

In general, the SITTs demonstrated significant improvements in lung function, symptom control, and health-related quality of life (HRQoL) compared with mono- or dual therapies, though some of these differences were very small, particularly as they related to the volume of rescue medicine used per day (e.g., a difference of 0.6 puffs per day). However, for individuals treated for COPD, SITTs provided substantially significant differences in lung function, rate of moderate-to-severe exacerbations, and HRQoL compared with the dual therapy budesonide with formoterol (BUD/FOR). In particular, users of Trimbow and Trelegy were approximately 2.5 to 5 times more likely, respectively, to achieve a minimal clinically important difference (MCID; Table 2) in lung function (i.e., trough forced expiratory volume in 1 second [FEV_1]) and 25% to 50% more likely to achieve an MCID in HRQoL measures. SITTs were found to be non-inferior when compared with MITTs. Adverse events (AE), including serious AEs (SAE) and AEs of special interest (AESI; e.g., pneumonia), occurred in similar proportions across treatments both within and between studies. Early withdrawal from studies due to AEs were rare, as were deaths.

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Table 2. Established Minimal Clinically Important Differences

Measure	Condition(s)	Score Range	MCID (from baseline)
Trough FEV_1	Asthma COPD	N/A	≥ 100 ml increase[1]
TDI focal score	COPD	−9 to 9 Lower score indicates more severity	≥ 1 unit increase[1]
ACQ-7 total score	Asthma	0 to 6 Higher score indicates more severely uncontrolled	≥ 0.5 point decrease[2]
SGRQ total score	Asthma COPD	0 to 100 Higher score indicates more limitations	≥ 4 unit decrease[1]

Abbreviations. ACQ-7: Asthma Control Questionnaire, 7-item; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; MCID: minimal clinically important differences; N/A: not applicable; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnea Index.

Key Findings

SITTs were compared to a variety of monotherapies (e.g., tiotropium [TIO]), dual therapies administered with 1 or 2 inhalers (e.g., fluticasone with vilanterol [FLU/VI]), or MITTs (e.g., FLU/VI with umeclidinium [UMEC]). Table 3 provides abbreviations of the generic drug names.

Table 3. Abbreviations of Generic Drug Components

Abbreviation	Generic Drug
BDP	Beclomethasone dipropionate
BUD	Budesonide
FLU	Fluticasone furoate
FOR	Formoterol fumarate
GLY	Glycopyrronium bromide (or glycopyrrolate)
TIO	Tiotropium
UMEC	Umeclidinium bromide
VI	Vilanterol trifenatate

Note. Breztri is BUD/GLY/FOR; Trelegy is FLU/UMEC/VI; Trimbow is BDP/GLY/FOR.

Asthma Findings

1 RCT, CAPTAIN, in 2,436 people with inadequately controlled asthma

- Trelegy (containing 31.25 or 62.5 µg UMEC) compared with FLU/VI for a minimum of 24 weeks; risk of bias: moderate
- Significant improvements in favor of Trelegy were seen in:
  - Lung function (i.e., trough FEV_1; $P < .001$)
  - Frequency and volume of rescue medication with the 31.25 µg dose of UMEC ($P \leq .02$)
  - Achievement of a clinically significant response, based on the MCID (Table 2), for HRQoL was more likely with the 62.5 µg dose of UMEC when measured with the Asthma Control Questionnaire, 7-item (ACQ-7; $P < .001$)
- No significant differences were observed between Trelegy and FLU/VI in the number or frequency of severe exacerbations

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Chronic Obstructive Pulmonary Disease (COPD) Findings

Breztri Aerosphere

2 RCTs in 10,490 individuals with moderate-to-very-severe COPD

- ETHOS (N = 8,588) and compared Breztri Aerosphere (Breztri; containing 160 or 320 µg BUD) to GLY/FOR or BUD/FOR over 52 weeks; risk of bias: high
- KRONOS (N = 1,902) compared Breztri to GLY/FOR or BUD/FOR over 24 weeks; risk of bias: moderate
- Significant improvements in favor of Breztri were seen in:
  - Lung function (trough FEV_1; $P \leq .01$)
  - Symptom control (e.g., frequency of moderate-to-severe exacerbations; $P \leq .01$)
  - Frequency and volume of rescue medication ($P \leq .04$)
  - HRQoL per the St. George's Respiratory Questionnaire (SGRQ; $P \leq .03$)
- Individuals receiving Breztri were less likely to experience a clinically important deterioration (e.g., FEV_1 decrease of ≥ 100 ml, ≥ 4 point increase on SGRQ) for:
  - Lung function compared with BUD/FOR over 24 weeks (trough FEV_1; $P \leq .03$)
  - Shortness of breath measures per the Transition Dyspnea Index (TDI; $P \leq .02$)
  - HRQoL per the SGRQ ($P < .001$)

Trelegy

7 RCTs with study sizes of 729 to 10,355 (total N = 18,590) for 12 to 52 weeks

- Trelegy compared with several monotherapies, dual therapies, or physician-prescribed MITTs; risk of bias was moderate for 4 and high for 3
- No statistically significant differences for any outcomes of interest were observed when Trelegy was compared with the MITTs (BUD/FOR+TIO and FLU/VI+UMEC)
- Significant improvements in favor of Trelegy for:
  - Lung function compared with BUD/FOR, FLU/VI, TIO alone, or UMEC/VI (trough FEV_1; all, $P < .001$)
  - Symptom control compared with BUD/FOR, FLU/VI, or UMEC/VI (all, $P \leq .02$)
  - Use of rescue medication compared with BUD/FOR, FLU/VI, or UMEC/VI (all, $P \leq .02$)
  - HRQoL compared with BUD/FOR, FLU/VI, TIO alone, or UMEC/V (all, $P \leq .001$)
  - A 50% risk reduction of developing pneumonia compared with FLU/VI or UMEC/VI (both, $P < .001$)
- Individuals receiving Trelegy were also more likely to achieve a clinically significant response, based on the MCID (Table 2), in:
  - Lung function, by a factor of 4 to 5, compared with BUD/FOR (trough FEV_1; $P \leq .03$)
  - Shortness of breath severity compared with FLU/VI or UMEC/VI by approximately 30% ($P < .001$) and 60% compared with BUD/FOR (over 24 weeks only)
  - HRQoL per the SGRQ compared with BUD/FOR, FLU/VI, UMEC/VI, or MITTs by approximately 40% to 60% (all, $P < .001$)

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Trimbow

2 RCTs with moderate risk of bias

- TRINITY (N = 2,691) with TIO alone or BDP/FOR+TIO over 52 weeks
- TRIVERSYTI (N = 708) with BUD/FOR over 24 weeks
- No statistically significant differences for any outcomes of interest were observed when Trimbow was compared with the MITT composed of BDP/FOR+TIO
- Significant improvements in favor of Trimbow compared with TIO alone or BUD/FOR were seen in lung function (trough FEV_1), symptom control, and use of rescue medications (all, $P \leq .01$)
- Individuals using Trimbow were more likely to achieve a clinically significant response, based on the MCID (Table 2), for lung function and HRQoL per SGRQ

State Considerations Overview

SITTs can improve the management of asthma or COPD, including adherence and persistence of treatment. Consistent treatment may improve other aspects of asthma and COPD care (e.g., health care utilization) as well as care and outcomes for comorbid conditions. Consider the individual patient disease profile (e.g., disease severity) and patient preferred outcomes to determine if SITTs may be an appropriate management approach. Consider reviewing the benchmark document and other materials from the American Lung Association Asthma Guidelines-Based Care Coverage Project, which provides information on key aspects of the management of asthma and addresses barriers to treatment, particularly for Medicaid beneficiaries. Revisit the National Heart, Lung, and Blood Institute's national plan for COPD, (updated in 2019) and the 2020 updates to asthma management guidelines.

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Background

Asthma and chronic obstructive pulmonary disease (COPD) are chronic conditions that affect the lungs and cause breathing difficulties. Individuals living with these conditions experience similar symptoms (e.g., coughing, shortness of breath), but the risk factors vary.

Asthma

Asthma causes chronic inflammation of the lungs, which increases sensitivity to airborne particulates (e.g., pollen, viruses), often referred to as triggers.[3] Exposure to a trigger can cause an asthma flare-up, which leads to asthmatic symptoms (e.g., shortness of breath, coughing), which can be life-threatening.[3] An analysis of US National Health Interview Survey (NHIS) data for the 3-year period covering 2016 to 2018 found approximately 1 in every 13 (around 8%) Americans are currently living with asthma.[4] The prevalence of asthma has remained relatively steady since 2006, but there has been a decrease in asthma of about 4% in children living in large metropolitan areas.[4] In general, individuals living with asthma are more likely to[4]:

- Be female (across all ages, 9.4% vs. 6.5% male)
- Identify as non-White and non-Hispanic
- Identify as Puerto Rican
- Meet the federal poverty threshold

Social Determinants of Health

Recent studies found that children with asthma that live in urban areas and attend schools with poor infrastructure have worse health and academic outcomes (e.g., higher rates of asthma-related hospitalization and absenteeism).[13,14] Similarly, other studies have found higher rates of asthma-related emergency department visits, hospital admissions, and health care utilization in children and adults living in large urban areas.[15,16] These studies highlight that asthma-related disparities are not limited to geography (urban vs. rural) but have other common social determinants including race, ethnicity, low socioeconomic status, and access to health care.

Chronic Obstructive Pulmonary Disease (COPD)

COPD refers to a group of diseases that cause airflow blockage and breathing-related problems such as emphysema and chronic bronchitis.[5] The 2020 NHIS estimated 12.5 million US adults (approximately 5%)[6] are currently diagnosed with COPD, with the highest prevalence in the South and Midwest, where it's estimated that 5.5% to 12% of adults are living with COPD, respectively.[7] While COPD is commonly considered a disease caused by smoking, nearly 25% of COPD cases are not directly associated with smoking.[8] COPD is more common in urban environments, but COPD-related mortality is nearly double in rural communities. A comparison of US COPD-related deaths in 1999 and 2019 found a decrease from about 52 to 40 (per 100,000) in large urban areas, but an increase from 51 to 74 in rural areas, and more deaths in women than men.[9]

COPD is the fourth leading cause of death in the US and is more prevalent in[5]:

- Women
- Individuals who identify as Native American, Alaskan Native, or multiracial non-Hispanic
- People aged 65 and older
- Current or former smokers

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- People with a history of asthma
- People with low socioeconomic status

COPD interferes with multiple aspects of an individual's life. An individual with COPD frequently has limitations related to activities of daily living (e.g., walking, bathing), as well as the ability to work and socialize.[5] Comorbidities are common and can include diabetes, arthritis, cardiovascular diseases (e.g., congestive heart failure), and mental health conditions.[5]

Treatment

Beyond lifestyle changes (e.g., quitting smoking) and pulmonary rehabilitation, these conditions are treated with medications to manage symptoms. These medications include inhaled corticosteroids (ICS; e.g., budesonide [BUD]), long-acting muscarinic antagonists (LAMA; e.g., tiotropium [TIO]), and long-acting $ß_2$ agonists (LABA; e.g., vilanterol [VI]), which may be prescribed on their own or in combination.[10] Individuals prescribed more than 1 management medication may be required to take the medication 1 or more times per day and use 1 or more inhalers.[10] In 2017 Trelegy was approved by the US Food & Drug Administration (FDA), making it the first single-inhaler triple therapy (SITT) available for COPD and asthma (in adults aged 18 years and older only); Breztri, for the management of COPD, followed in 2020.[11,12]

Medicaid

An analysis of 2 years of Behavioral Risk Factor Surveillance System data of nearly 6,500 low-income adults with asthma found that Medicaid expansion allowed more individuals to gain health insurance coverage, but costs related to seeing a health care provider and purchasing asthma medications were still a barrier.[17] The American Lung Association began a review of guidelines-based asthma care in 2015. In 2018, researchers reviewed the American Lung Association findings for Medicaid coverage of guidelines-based asthma care and found that coverage is inconsistent and generally lacking.[18]

Annual Medicaid spending on inhalers to manage asthma or COPD has more than doubled between 2012 and 2018 from $2.1 billion to $4.6 billion, respectively, with a total spend of $26.2 billion over the 7-year period.[19] In the same period, the number of prescriptions filled by Medicaid beneficiaries for ICS-containing inhalers increased by 77%.[19] The increase in spending is in part due to Medicaid expansion, which provided more individuals with access to inhaled medications to manage asthma or COPD.[20,21]

Aim of This Report

Drug Effectiveness Review Project (DERP) participants are interested in understanding the effectiveness and harms of triple therapies for asthma or COPD that are delivered with a single inhaler compared with monotherapy or dual or triple therapies administered with 2 or more inhalers. The aim of this report is to review evidence related to 2 FDA-approved SITTs, Breztri and Trelegy, and the pipeline SITT, Trimbow (Table 4).

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Populations

- Adults and children with COPD or asthma

Interventions

- See Table 4 for SITTs of interest.

Table 4. Single-Inhaler Triple Therapy Treatments of Interest

Brand Name	Generic Name	Generic Name Abbreviation	Indication(s)	FDA Approval Date
Breztri Aerosphere[11]	Budesonide; glycopyrrolate; formoterol fumarate	BUD/GLY/FOR	• COPD	07/23/2020
Trelegy Ellipta[12]	Fluticasone furoate; umeclidinium bromide; vilanterol trifenatate	FLU/UMEC/VI	• COPD • Asthma (aged ≥ 18 years)	09/18/2017
Pipeline Therapies				
Breztri Aerosphere[11]	Budesonide; glycopyrrolate; formoterol fumarate	BUD/GLY/FOR	• Asthma	N/A
Trimbow[22]	Beclomethasone dipropionate; glycopyrronium bromide; formoterol fumarate dihydrate	BDP/GLY/FOR	• COPD • Asthma	N/A

Abbreviations. BDP: beclomethasone; BUD: budesonide; COPD: chronic obstructive pulmonary disease; FDA: US Food & Drug Administration; FOR: formoterol; FLU: fluticasone; GLY: glycopyrronium; N/A: not applicable; UMEC: umeclidinium; VI: vilanterol.

Comparators

- Another listed intervention
- Standard of care (e.g., monotherapy, dual therapy, or multiple-inhaler triple therapy [MITT])

Outcomes

- Forced expiratory volume in 1 second (FEV_1)
- Severe exacerbations
- Symptom control
- Use of rescue medications
- Quality of life, using validated scales (e.g., St. George's Respiratory Questionnaire [SGRQ])
- All-cause emergency department visits or hospital admissions
- Mortality
- Adverse events (AE), including AEs of special interest (AESI; e.g., pneumonia)
- Withdrawals due to AEs
- Serious AEs (SAE)

Study Designs

- Randomized controlled trials (RCT)

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Key Questions

KQ1. What is the efficacy of triple-combination therapies for COPD and asthma?

KQ2. What are the harms of triple-combination therapies for COPD and asthma?

KQ3. Do the effectiveness and harms vary by subgroup (e.g., severity of disease, adherence to therapy)?

KQ4. What are the ongoing studies of triple-combination therapies for COPD and asthma?

Methods

We conducted a systematic search using Ovid MEDLINE ALL, Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews for any RCTs or systematic reviews (with or without meta-analyses) evaluating a listed intervention (Table 4) for the treatment of asthma or COPD. Systematic reviews were used for reference list searching and not as evidence sources. We did not include papers or data reporting post hoc analyses. Additional eligibility criteria were studies on human participants and publication in English. We also searched clinical trial registries (e.g., ClinicalTrials.gov) for ongoing studies for SITTs for asthma or COPD. Searches were conducted on September 16, 2022.

One independent researcher conducted risk-of-bias assessments and a second senior researcher reviewed them; conflicts were handled through discussion. A full description of our methods can be found in Appendix A.

Findings

We identified 12 head-to-head RCTs reported in 26 publications.[23-48] There was 1 study for the treatment of asthma[35] and 11 (in 25 publications) for the treatment of COPD[23,25,28,29,32,36,37,42,47,48]; 2 COPD studies were reported in a single publication. The asthma study compared Trelegy to the dual therapy FLU/VI. Studies examining SITT in COPD participants included 2 comparing Breztri[29,42], 7 comparing Trelegy[23,25,28,32,36,37], and 2 comparing Trimbow[47,48] to various single, dual, or MITTs. Most of the studies were multinational and included participants from the US; US participants were not included in the 2 studies evaluating Trimbow for COPD. None of the identified studies recruited individuals under the age of 18. Studies generally reported outcomes related to lung function (e.g., trough FEV_1), rate of moderate-to-severe exacerbations, use of rescue mediation, health-related quality of life (HRQoL) using the SGRQ, and AEs.

Minimal Clinically Important Differences

A number of clinical tests and tools are used to measure outcomes (e.g., lung function, HRQoL) related to the treatment of asthma and COPD. The minimal clinically important differences (MCID) for these clinical tests and tools are reported in Table 5.

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Table 5. Minimal Clinically Important Differences for Clinical Tests and Tools

Measure	Condition(s)	Score Range	MCID (from baseline)
Lung Function			
Trough FEV_1	Asthma COPD	N/A	≥ 100 ml increase[1]
Symptoms			
Exacerbations	Asthma COPD	N/A	None currently exist
TDI focal score	COPD	−9 to 9 Lower score indicates more severity	≥ 1 unit increase[1]
Health-Related Quality of Life			
ACQ-7 total score	Asthma	0 to 6 Higher score indicates more severely uncontrolled	≥ 0.5 point decrease[2]
CAT total score	COPD	0 to 40 Higher score indicates more limitations	Not yet determined
SGRQ total score	Asthma COPD	0 to 100 Higher score indicates more limitations	≥ 4 unit decrease[1]

Abbreviations. ACQ-7: Asthma Control Questionnaire, 7-item; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; MCID: minimal clinically important difference; N/A: not applicable; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnea Index.

Generic Drug Names

Table 6 provides a list of the generic drug names and corresponding abbreviation, for reference.

Table 6. Abbreviations of Generic Drug Names

Abbreviation	Generic Drug
BDP	Beclomethasone dipropionate
BUD	Budesonide
FLU	Fluticasone furoate
FOR	Formoterol fumarate
GLY	Glycopyrronium bromide (or glycopyrrolate)
TIO	Tiotropium
UMEC	Umeclidinium bromide
VI	Vilanterol trifenatate

Note. Breztri is BUD/GLY/FOR; Trelegy is FLU/UMEC/VI; Trimbow is BDP/GLY/FOR.

Asthma

We identified 1 RCT comparing Trelegy to the dual therapy FLU/VI for the treatment of asthma.[35] We did not identify any published RCTs for the treatment of asthma with Breztri or Trimbow.

Trelegy Ellipta

We identified 1 RCT—CAPTAIN (N = 2,436)—comparing Trelegy with FLU/VI in participants with inadequately controlled asthma for a minimum of 24 weeks (Table 7).[35] Approximately half of the participants continued blinded treatment through 36 or 52 weeks, but results were generally reported at 24 weeks.[35] Trelegy was provided with 2 different doses of the UMEC component—

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31.25 or 65 µg. CAPTAIN was a 6-arm RCT conducted in the US and several other countries.[35] The mean age of participants was 53.2 years (SD, 13.1), a majority of whom identified as White (80%; 1,950 of 2,436) and female (62%; 1,514 of 2,436).[35] Further details of the treatment arms and participant characteristics are in Table 7. We also identified a 2021 publication from Nakamura and colleagues[49] reporting subgroup analyses of CAPTAIN participants recruited exclusively in Japan, but we have not included the results in this report. We determined risk of bias to be moderate due to the study being sponsored and led by employees of GlaxoSmithKline.

Brief statistical details are reported in corresponding tables with further detail available in Appendix B, Table B1.

Table 7. Participant Characteristics and Treatment Arms for Asthma RCTs

Study Name Trial Number Location(s) Study Duration Risk of Bias	N Randomized Participant Characteristics	Treatments

CAPTAIN[35]
NCT02924688
US + multinational
24 to 52 weeks
Moderate
	• N = 2,439
	• Mean age: 53.2 (SD, 13.1)
	• Male: 922 (38%)
	• Race
	  ○ White: 1,950 (80%)
	  ○ Asian: 344 (14%)
	  ○ Black/AA: 119 (5%)
	  ○ AI/AN: 4 (< 1%)
	  ○ Native Hawaiian/PI: 3 (< 1%)
	  ○ Multiple: 15 (1%)
	• Ethnicity
	  ○ Hispanic or Latino: 249 (10%)
		As randomized
		SITT
		• Trelegy (FLU/UMEC/VI)
		  ○ 100/31·25/25 µg, n = 405
		  ○ 100/62·5/25 µg, n = 406
		  ○ 200/31·25/25 µg, n = 404
		  ○ 200/62·5/25 µg, n = 408
		
		Comparator
		• FLU/VI
		  ○ 100/25 µg, n = 407
		  ○ 200/25 µg, n = 406
		
		As analyzed
		SITT
		• Trelegy (UMEC 31.25 µg), n = 809
		• Trelegy (UMEC 62.5 µg), n = 814
		
		Comparator
		• FLU/VI, n = 813

Abbreviations. AA: African American; AI/AN: American Indian/Alaska Native; FLU: fluticasone; PI: Pacific Islander; RCT: randomized controlled trial; SD: standard deviation; SITT: single-inhaler triple therapy; UMEC: umeclidinium; VI: vilanterol.

Lung Function and Symptom Control

At week 24, trough FEV_1 had significantly improved from baseline in participants treated with Trelegy, regardless of UMEC dose, compared with FLU/VI (mean between-treatment difference, 89 ml [UMEC 31.25 µg] and 101 ml [UMEC 62.5 µg]; both, $P < .001$; Table 8).[35] Additionally, participants that received Trelegy achieved the MCID for trough FEV_1 with mean changes of 139 ml (UMEC 31.25 µg) and 151 ml (UMEC 62.5 µg; *P*, not reported [NR]; Table 8).[35] The number of individuals experiencing at least 1 moderate or severe exacerbation at any time during the study period was similar across treatments (range, 40% to 47%), as was the proportion of

exacerbations considered severe (range, 47% to 55%; Appendix B, Table B1).[35] No significant difference in the annualized rate of severe exacerbations was found between Trelegy and FLU/VI (adjusted rate ratio, 0.99 [UMEC 31.25 µg] and 0.97 [UMEC 62.5 µg]; both, $P \geq .05$).[35]

Individuals receiving Trelegy had an increase of approximately 13% in the number of rescue medication-free days compared with FLU/VI (approximately 11%; Appendix B, Table B1).[35] Significant between-treatment differences in the percentage of days without the use of rescue medication (an increase of 2.8%; $P = .02$) and the number of puffs of rescue medication per day (a reduction of around 0.2 puffs; $P < .001$) were observed in individuals who received Trelegy with 31.25 µg UMEC, compared to FLU/VI alone, but not with the higher dose of UMEC (Table 4).[35]

Table 8. Lung Function and Symptom Control in Asthma RCTs of Trelegy

Study Name Trial Number Treatments	Lung Function	Symptom Response
CAPTAIN[35] NCT02924688 Trelegy vs. FLU/VI	At week 24 <u>Trough FEV_1</u> Mean CFB • Trelegy (UMEC 31.25 µg): 139 ml (95% CI, 117 to 161); *P*, NR • Trelegy (UMEC 62.5 µg): 151 ml (95% CI, 129 to 172); *P*, NR • FLU/VI: 50 ml (95% CI, 28 to 72); *P*, NR Mean between-treatment CFB • Trelegy (UMEC 31.25 µg): 89 ml (95% CI, 58 to 120); $P < .001$ • Trelegy (UMEC 62.5 µg): 101 ml (95% CI, 70 to 132); $P < .001$	<u>Exacerbations</u> Annualized rate of severe exacerbations • Trelegy (UMEC 31.25 µg): aOR, 0.99 (95% CI, 0.77 to 1.29); *P*, NSS • Trelegy (UMEC 62.5 µg): aOR, 0.97 (95% CI, 0.75 to 1.26); *P*, NSS <u>Use of rescue medication, over 24 weeks</u> Percentage of rescue-free days • Trelegy (UMEC 31.25 µg): 2.78 (95% CI, 0.45 to 5.10); $P = .02$ • Trelegy (UMEC 62.5 µg): 2.17 (95% CI, −0.15 to 4.49); *P*, NSS Puffs per day • Trelegy (UMEC 31.25 µg): −0.2 (95% CI, −0.2 to −0.1); $P < .001$ • Trelegy (UMEC 62.5 µg): 0 (95% CI, −0.1 to 0.0); *P*, NSS

Abbreviations. aOR: adjusted odds ratio; CFB: change from baseline; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FLU: fluticasone; NR: not reported; NSS: not statistically significant; RCT: randomized controlled trial; UMEC: umeclidinium; VI: vilanterol.

Health-Related Quality of Life

Clinically meaningful improvements in HRQoL, as measured with the ACQ-7 (mean range, −0.68 to −0.77) and SGRQ (mean range, −10.29 to −11.69), were seen for all treatment arms at week 24 (Appendix B, Table B1).[35] However, when compared with FLU/VI, significant between-treatment differences favoring Trelegy with 62.5 µg UMEC were observed in ACQ-7 total score ($P \leq .01$) and in responder rate (i.e., achieving the established MCID; adjusted odds ratio [OR], 1.43; 95% confidence interval [CI], 1.16 to 1.76; $P < .01$).[35] No statistically significant between-treatment differences related to ACQ-7 were found when comparing Trelegy with 31.25 µg UMEC and FLU/VI.[35]

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No statistically significant between-treatment differences in SGRQ total scores or responder rates were observed.[35]

Table 9. Health-Related Quality of Life in Asthma RCTs of Trelegy

Study Name Trial Number Treatments	ACQ-7	SGRQ
CAPTAIN[35] NCT02924688 Trelegy vs. FLU/VI	At week 24, mean between-treatment difference CFB	
	Total score • Trelegy (UMEC 31.25 µg): −0.06 (95% CI, −0.12 to 0.01); *P*, NSS • Trelegy (UMEC 62.5 µg): −0.09 (95% CI, −0.16 to −0.02); *P* = .008 Responder rate • Trelegy (UMEC 31.25 µg): OR, 1.15 (95% CI, 0.94 to 1.42); *P*, NSS • Trelegy (UMEC 62.5 µg): OR, 1.43 (95% CI, 1.16 to 1.76); *P* < .001	Total score • Trelegy (UMEC 31.25 µg): 1.10 (95% CI, −0.27 to 2.47); *P*, NSS • Trelegy (UMEC 62.5 µg): −0.30 (95% CI, −1.66 to 1.05); *P*, NSS Responder rate • Trelegy (UMEC 31.25 µg): OR, 0.86 (95% CI, 0.69 to 1.06); *P*, NSS • Trelegy (UMEC 62.5 µg): OR, 1.14 (95% CI, 0.92 to 1.42); *P*, NSS

Abbreviations. ACQ-7: Asthma Control Questionnaire, 7-item; CFB: change from baseline; CI: confidence interval; FLU: fluticasone; NSS: not statistically significant; OR: odds ratio; RCT: randomized controlled trial; SGRQ: St. George's Respiratory Questionnaire; UMEC: umeclidinium; VI: vilanterol.

Adverse Events

The number of participants experiencing any AE, treatment-emergent AE (TEAE), SAE, or withdrawing from the study due to an AE was similar across all treatment arms; fatalities due to an AE were rare, with 1 of the deaths (pulmonary embolism) being considered as related to Trelegy with 31.25 µg UMEC.[35] The number of participants experiencing specific AEs of interest (e.g., pneumonia, cardiac effects) was also similar across all treatment groups.[35]

Chronic Obstructive Pulmonary Disease (COPD)

We identified 11 studies in 25 publications. Briefly, we identified:

- 2 RCTs comparing Breztri with GLY/FOR or BUD/FOR (total N = 10,490) for 24 or 52 weeks, in 6 publications[29,39,40,42-44]
- 7 RCTs comparing Trelegy with a variety of single (e.g., TIO), dual (e.g., FLU/VI), or MITTs for 12 to 52 weeks, in 17 publications (total N = 18,590)[23-28,30-34,36-38,41,45,46]
- 2 RCTs comparing Trimbow with a variety of single (e.g., TIO), dual (e.g., FLU/VI), or MITTs for 24 or 52 weeks (total N = 3,399)[47,48]

All studies recruited participants with a minimum age of 40 years and excluded individuals with a current co-diagnosis of asthma. Most studies (6 of 9) enrolled participants in the US, although neither Trimbow study recruited US participants. Across all included studies, a majority of participants identified as male and White, with a mean age of approximately 65 years. Table 10 provides an overview of the included studies.

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Table 10. Overview of Included RCTs Comparing SITTs in Individuals With COPD

Study Details						Outcomes				
Study	Duration	Includes US	N Randomized	Comparators	Mean Age	Lung Function (e.g., FEV_1)	Symptom Control	HRQoL (e.g., SGRQ)	Adverse Events	Risk of Bias
Breztri										
ETHOS[42]	52	√	8,588	• BUD/FOR • GLY/FOR	64.6	√	√	√	√	High
KRONOS[29]	24	√	1,902	• BUD/FOR • GLY/FOR	65.2	√	√	√	√	Moderate
Trelegy										
Bansal, 2021[23]	12	√	800	• TIO	66.1	√	√	√	√	Moderate
Bremner, 2018[25]	24	X	1,055	• FLU/VI+UMEC	66.3	√	√	√	√	High
[a]Ferguson, 2020[28]	12	√	729	• BUD/FOR+TIO	65.1	√	√	√	√	Moderate
[a]Ferguson, 2020[28]	12	√	732	• BUD/FOR+TIO	65.3	√	√	√	√	Moderate
FULFIL[36]	24	X	1,810	• BUD/FOR	63.9	√	√	√	√	Moderate
IMPACT[37]	52	√	10,355	• FLU/VI • UMEC/VI	65.3	√	√	√	√	High
INTREPID[32]	24	X	3,109	• Any MITT	67.8	√	√	√	√	High
Trimbow										
TRINITY[47]	52	X	2,691	• TIO • BDP/FOR+TIO	63.2	√	√	√	√	Moderate
TRIVERSYTI[48]	24	X	708	• BUD/FOR	65.9	√	√	√	√	Moderate

Note. [a] Ferguson and colleagues report 2 replicate RCTs in the same publication.
Abbreviations. BDP: beclomethasone dipropionate; BUD: budesonide; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FLU: fluticasone; FOR: formoterol; GLY: glycopyrronium; HRQoL: health-related quality of life; MITT: multiple-inhaler triple therapy; RCT: randomized controlled trial; SGRQ: St. George's Respiratory Questionnaire; SITT: single-inhaler triple therapy; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol.

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Breztri

We identified 2 RCTs (in 9 publications) evaluating Breztri for the management of COPD—ETHOS (N = 8,588)[39,40,42-44] and KRONOS (N = 1,902).[29,50-52] Breztri was compared with dual or triple therapies delivered with multiple inhalers for 24 to 52 weeks. ETHOS and KRONOS recruited individuals with moderate-to-very-severe COPD in multiple countries, including the US. Participants were more likely to identify as male and White and as a former smoker; mean age was around 65 years (Table 11). Additional publications of subgroup analyses were identified but have not been included in this review because they evaluate participants recruited exclusively in Japan[50,51] or China.[52]

Risk of bias was determined to be high for the ETHOS study and moderate for the KRONOS study. While both studies were found to have generally sound methods (e.g., adequate blinding, appropriate analyses) and balanced groups, they were sponsored and conducted almost exclusively by industry. The ETHOS study had high discontinuation of treatment before week 52 of the trial—roughly 20% in the Breztri arms and nearly 25% in the comparator arms[42]—hence an assessment of high risk of bias. Participants were most likely to discontinue the ETHOS trial early due to lack of efficacy or AEs.

Table 11. Participant Characteristics and Treatment Arms for COPD RCTs of Breztri

Study Name Trial Number Location(s) Study Duration Risk of Bias	N Randomized Participant Characteristics	Treatments

ETHOS[42]
NCT02465567
US + multinational
52 weeks
High
	• N = 8,588[a]
	• Moderate-to-very-severe COPD
	• Mean age: 64.6 years (SD, 7.6)
	• Male: 5,081 (63%)
	• Current smoker: 3,495 (40.7%)
	• Ethnicity
	  ○ White: 7,226 (84.9%)
	  ○ Asian: 651 (7.6%)
	  ○ AI/AN/Other: 327 (3.9%)
	  ○ Black: 305 (3.6%)
		SITT
		• Breztri (BUD/GLY/FOR)
		  ○ 320/9/4.8 µg, n = 2,157
		  ○ 160/9/4.8 µg, n = 2,137
		
		Comparators
		• GLY/FOR (9/4.8 µg), n = 2,143
		• BUD/FOR (160/4.8 µg), n = 2,151

KRONOS[29]
NCT02497001
US + multinational
24 weeks
Moderate
	• N = 1,902
	• Moderate-to-very severe COPD
	• Mean age: 65.2 (SD, 7.6)
	• Male: 1,350 (71.2%)
	• Current smoker: 750 (39.5%)
	• Ethnicity
	  ○ White: 950 (50.1%)
	  ○ Asian: 852 (44.9%)
	  ○ Black: 90 (4.7%)
		SITT
		• Breztri (BUD/GLY/FOR)
		  ○ 320/14.4/10 µg, n = 639
		
		Comparators[b]
		• GLY/FOR$_{MDI}$ (18/9.6 µg), n = 625
		• BUD/FOR$_{MDI}$ (320/9.6 µg), n = 314
		• BUD/FOR$_{DPI}$ (400/12 µg), n = 318

Note. [a] ETHOS reports participant characteristics and analyses with a modified ITT population (N = 8,509).
[b] KRONOS used an MDI and DPI formulation of BUD/FOR due to differences in availability of the MDI version among participating countries.
Abbreviations. AI/AN: American Indian/Alaska Native; BUD: budesonide; COPD: chronic obstructive pulmonary

disease; DPI: dry-powder inhaler; FOR: formoterol; GLY: glycopyrrolate; ITT: intention-to-treat; MDI: metered-dose inhaler; RCT: randomized controlled trial; SD: standard deviation; SITT: single-inhaler triple therapy.

Lung Function and Symptom Control

Breztri significantly improved trough FEV_1 compared with GLY/FOR or BUD/FOR (all, $P \leq .01$; Table 8) in the KRONOS study[29] and in a subgroup of participants with very severe COPD in the ETHOS study[43]; ETHOS researchers did not report trough FEV_1 outcomes for the whole trial population. KRONOS researchers reported trough FEV_1 mean within treatment changes from baseline of 147 and 125 ml for those administered Breztri or GLY/FOR, respectively, but 73 to 88 ml for those administered BUD/FOR (Appendix B, Table B2).[29] KRONOS researchers did not conduct statistical analyses of within-treatment changes from baseline for trough FEV_1, but these observations may indicate MCIDs of trough FEV_1 were achieved for those treated with Breztri and GLY/FOR.[29] Mean between-treatment differences were statistically significant in favor of Breztri compared with GLY/FOR or BUD/FOR (range, 22 to 74 ml; all, $P \leq .02$; Table 8).[29] Individuals receiving Breztri were significantly less likely to experience a clinically important deterioration of trough FEV_1 (i.e., a decrease of ≥ 100 ml from baseline) compared with BUD/FOR ($P \leq .03$), but not GLY/FOR ($P \geq .05$). [29] ETHOS researchers did not report the responder rate for lung function (i.e., how many individuals achieved the MCID for trough FEV_1).

In general, individuals that received Breztri had a significant reduction in moderate or severe exacerbations, as well as a significant delay in the time-to-first moderate or severe exacerbation event (Table 12); however, there were some differences between the 2 studies. For example, over the 52-week ETHOS study, the annual rate of moderate or severe exacerbations were significantly reduced for individuals that received Breztri compared with GLY/FOR or BUD/FOR (rate ratios ranged from 0.76 to 0.86; all, $P \leq .01$).[42] Meanwhile, KRONOS researchers found no differences between Breztri and BUD/FOR over 24 weeks of treatment, although Breztri did significantly reduce moderate or severe exacerbations when compared with GLY/FOR (rate ratio, 0.48; $P < .001$).[29] Both studies generally found significant delays to time of first moderate or severe exacerbation event in individuals who received Breztri. Over the 24-week study period, KRONOS researchers found that individuals receiving GLY/FOR or BUD/FOR experienced a first moderate or severe exacerbation 59% to 75% earlier, respectively, than those receiving Breztri; however, this delay was only statistically significant when compared with GLY/FOR (hazard ratio [HR], 0.59; 95% CI, NR; $P < .001$; Table 12).[29] Similarly, over 52 weeks in the ETHOS study, those receiving GLY/FOR or BUD/FOR experienced a first moderate or severe exacerbation almost 90% sooner than those receiving Breztri (both, $P \leq .01$; Table 12).[42] Furthermore, ETHOS researchers found a similar 11% to 13% reduction in the time to the time to a first moderate or severe exacerbation event in individuals that received Breztri compared with BUD/FOR (HR, 0.89 for the higher dose; 95% CI, 0.81 to 0.97; HR, 0.87 for the lower dose; 95% CI, 0.80 to 0.95),[42] but KRONOS researchers found no significant difference when comparing Breztri with BUD/FOR_{MDI} (metered-dose inhaler).[29]

Significant increases in the percentage of days with no rescue medication use were observed when Breztri compared with GLY/FOR or BUD/FOR (ranging from around 2% to 5%; all, $P \leq .04$) in the ETHOS study.[40,42] After 52 weeks of treatment, individuals treated with Breztri reported a decrease of around 1 puff per day compared with a reduction of 0.6 and 0.8 puffs per day for GLY/FOR or BUD/FOR, respectively.[40] This resulted in significant between-treatment

differences when comparing Breztri to GLY/FOR (a reduction of 0.3 to 0.5 puffs per day; $P < .001$; Table 12).[42] There was also a significant between-treatment difference when comparing Breztri with 320 µg budesonide with BUD/FOR (a reduction of around 0.3 puffs per day; $P < .001$; Table 12).[42] However, in an undefined subsample of KRONOS participants (858 of 1,902), all participants, regardless of treatment, had a decrease of around 1 puff per day (range, −1.1 to −1.6), but no significant differences were observed between Breztri and any of the comparators over the 24-week study period (Appendix B, Table B2).[29]

The severity of episodes of shortness of breath, as measured with the Transition Dyspnea Index (TDI) focal score, was significantly reduced during the trial period in individuals that received Breztri compared with GLY/FOR or BUD/FOR in the ETHOS study (all, $P \leq .001$); however, the between-treatment mean differences were small, ranging from 0.26 to 0.34.[42] The severity of episodes of shortness of breath was also significantly reduced during the trial period in individuals that received Breztri compared with BUD/FOR_{DPI} (dry-powder inhaler; a difference of 0.46; $P = .003$) in the KRONOS study[29]; however, no significant differences were observed when comparing Breztri to GLY/FOR or BUD/FOR_{MDI} in the KRONOS study.[29] The ETHOS study found that individuals administered Breztri were significantly more likely to achieve response (defined as a ≥ 1 point increase on the TDI focal score) compared with those that received GLY/FOR or BUD/FOR (estimates ranged from 16% to 20%; all, $P \leq .02$; Table 12).[42]

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Table 12. Lung Function and Symptom Control in COPD RCTs of Breztri

Study Name Treatments	FEV_1	Symptom Control	Use of Rescue Medication
ETHOS[42] Breztri (BUD 160 or 320 µg) vs. GLY/FOR or BUD/FOR	Over 52 weeks, between-treatment difference CFB FEV_1, NR for whole participant population <u>Subgroup</u> Individuals with very severe COPD (n = 3,088)[43] Trough FEV_1 • Breztri (BUD 320 µg) ○ GLY/FOR: 46 ml (95% CI, 27 to 64); *P* < .001 ○ BUD/FOR: 72 ml (95% CI, 54 to 90); *P* < .001 • Breztri (BUD 160 µg) ○ GLY/FOR: 36 ml (95% CI, 18 to 54); *P* < .001 ○ BUD/FOR: 62 ml (95% CI, 45 to 80); *P* < .001	Over 52 weeks, between-treatment difference CFB Annual rate of moderate or severe exacerbations • Breztri (BUD 320 µg) ○ GLY/FOR: rate ratio, 0.76 (95% CI, 0.69 to 0.83); *P* < .001 ○ BUD/FOR: rate ratio, 0.87 (95% CI, 0.79 to 0.95); *P* = .003 • Breztri (BUD 160 µg) ○ GLY/FOR: rate ratio, 0.75 (95% CI, 0.69 to 0.83); *P* < .001 ○ BUD/FOR rate ratio, 0.86 (95% CI, 0.79 to 0.95); *P* = .002 Time-to-first moderate or severe exacerbation • Breztri (BUD 320 µg) ○ GLY/FOR: HR, 0.88 (95% CI, 0.81 to 0.96); *P* = .004 ○ BUD/FOR: HR, 0.89 (95% CI, 0.81 to 0.97); *P* = .006 • Breztri (BUD 160 µg) ○ GLY/FOR: HR, 0.87 (95% CI, 0.79 to 0.94); *P* = .001 ○ BUD/FOR: HR, 0.87 (95% CI, 0.80 to 0.95); *P* = .002 <u>Shortness of breath</u> TDI, total focal score • Breztri (BUD 320 µg) ○ GLY/FOR: 0.34 (95% CI, 0.19 to 0.49); *P* < .001	Over 52 weeks, between-treatment difference CFB Percentage of rescue-free days[40] • Breztri (BUD 320 µg) ○ GLY/FOR: 4.98 (95% CI, 2.84 to 7.12); *P* < .001 ○ BUD/FOR: 4.34 (95% CI, 2.22 to 6.47); *P* < .001 • Breztri (BUD 160 µg) ○ GLY/FOR: 2.83 (95% CI, 0.68 to 4.98); *P* = .01 ○ BUD/FOR: 2.19 (95% CI, 0.06 to 4.33); *P* = .04 Puffs per day[40] • Breztri (BUD 320 µg) ○ GLY/FOR: −0.53 (95% CI, −0.71 to −0.34); *P* < .001 *P* < .001 ○ BUD/FOR: −0.35 (95% CI, −0.53 to −0.17); *P* < .001 • Breztri (BUD 160 µg) ○ GLY/FOR: −0.34 (95% CI, −0.53 to −0.16); *P* < .001 ○ BUD/FOR: −0.16 (95% CI, −0.35 to 0.02); *P*, NSS

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Study Name Treatments	FEV_1	Symptom Control	Use of Rescue Medication
		○ BUD/FOR: 0.26 (95% CI, 0.11 to 0.41); *P* < .001 • Breztri (BUD 160 µg) ○ GLY/FOR: 0.34 (95% CI, 0.18 to 0.49); *P* < .001 ○ BUD/FOR: 0.26 (95% CI, 0.11 to 0.41); *P* < .001 Responders • Breztri (BUD 320 µg) ○ GLY/FOR: OR, 1.19 (95% CI, 1.05 to 1.35); *P* = .005 ○ BUD/FOR: OR, 1.16 (95% CI, 1.02 to 1.31); *P* = .02 • Breztri (BUD 160 µg) ○ GLY/FOR: OR, 1.20 (95% CI, 1.06 to 1.36); *P* = .004 ○ BUD/FOR: OR, 1.17 (95% CI, 1.03 to 1.32); *P* = .01	
KRONOS[29] Breztri vs. GLY/FOR or BUD/FOR_{MDI} or BUD/FOR_{DPI}	Over 24 weeks, mean between-treatment difference CFB <u>Trough FEV_1</u> • GLY/FOR: 22 ml (95% CI, 4 to 39); *P* = .01 • BUD/FOR_{MDI}: 74 ml (95% CI, 52 to 95); *P* < .001 • BUD/FOR_{DPI}: 59 ml (95% CI, 30 to 80); *P* < .001 Time to clinically important deterioration • GLY/FOR: HR, 0.88 (95% CI, 0.76 to 1.0); *P*, NSS • BUD/FOR_{MDI}: HR, 0.83 (95% CI, 0.70 to 0.98); *P* = .03	<u>Exacerbations</u> Annualized rate of moderate or severe exacerbations • GLY/FOR: rate ratio, 0.48 (95% CI, 0.37 to 0.64); *P* < .001 • BUD/FOR_{MDI}: rate ratio, 0.82 (95% CI, 0.58 to 1.17); *P*, NSS • BUD/FOR_{DPI}: rate ratio, 0.83 (0.59 to 1.18); *P*, NSS Time-to-first exacerbation • GLY/FOR: HR, 0.59 (95% CI, NR); *P* < .001 • BUD/FOR_{MDI}: HR, 0.75 (95% CI, NR); *P*, NSS • BUD/FOR_{DPI}, NR	NR for whole participant population; see Appendix B, Table B2 for details related to an undefined subgroup.

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Study Name Treatments	FEV_1	Symptom Control	Use of Rescue Medication
	• BUD/FOR_{DPI}: HR, 0.81 (95% CI, 0.69 to 0.96); *P* = .01	Shortness of breath TDI focal score, between-treatment difference • GLY/FOR: 0.18 (95% CI, −0.07 to 0.43); *P*, NSS • BUD/FOR_{MDI}: 0.24 (95% CI, −0.07 to 0.54); *P*, NSS • BUD/FOR_{DPI}: 0.46 (95% CI, 0.16 to 0.77); *P* = .003	

Abbreviations. BUD: budesonide; CFB: change from baseline; CI; confidence interval; COPD: chronic obstructive pulmonary disease; DPI: dry-powder inhaler; FEV_1: forced expiratory volume in 1 second; FOR: formoterol; GLY: glycopyrrolate; HR: hazard ratio; MDI: metered-dose inhaler; NR: not reported; NSS: not statistically significant; OR: odds ratio; RCT: randomized controlled trial; TDI: Transition Dyspnea Index.

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Health-Related Quality of Life

Regardless of treatment arm, participants in the ETHOS study achieved significant improvements in their HRQoL when the SGRQ total score from baseline was compared to the mean score over the 52-week trial (Table 13).[40] However, individuals who received Breztri were significantly more likely to have a greater reduction in the total score (all, $P \leq .002$; Table 13).[40] Individuals who received Breztri were also 24% to 46% less likely to experience a clinically important deterioration (i.e., increase of ≥ 4 units from baseline; all, $P < .001$; Table 13).[40] Conversely, at week 24 of the KRONOS study, a significant but small between-treatment difference in the SGRQ total score was observed between Breztri and GLY/FOR ($P = .03$), but not when compared with BUD/FOR.[29] Additional detail is available in Appendix B, Table B2.

Table 13. Health-Related Quality of Life in Breztri RCTs for COPD

Study Name Treatments	SGRQ

ETHOS[42]
 	
Breztri (BUD 160 or 320 µg) vs. GLY/FOR or BUD/FOR
	Over 52 weeks, mean between-treatment difference CFB[40]
	
	Total score
	• Breztri (BUD 320 µg)
	  ○ GLY/FOR: −1.59 (95% CI, −2.27 to −0.91); $P < .001$
	  ○ BUD/FOR: −1.31 (95% CI, −1.99 to −0.64); $P < .001$
	• Breztri (BUD 160 µg)
	  ○ GLY/FOR: −1.34 (95% CI, −2.02 to −0.66); $P < .001$
	  ○ BUD/FOR: −1.06 (95% CI, −1.74 to −0.39); $P = .002$
	
	Responders
	• Breztri (BUD 320 µg)
	  ○ GLY/FOR: OR, 1.46 (95% CI, 1.28 to 1.65); $P < .001$
	  ○ BUD/FOR: OR, 1.27 (95% CI, 1.12 to 1.44); $P < .001$
	• Breztri (BUD 160 µg)
	  ○ GLY/FOR: OR, 1.42 (95% CI, 1.25 to 1.61); $P < .001$
	  ○ BUD/FOR: OR, 1.24 (95% CI, 1.09 to 1.40); $P < .001$

KRONOS[29] Breztri vs. GLY/FOR or BUD/FOR_{MDI} OR BUD/FOR_{DPI}	At week 24, mean between-treatment difference CFB Total score • GLY/FOR: −1.22 (95% CI, −2.30 to −0.15); $P = .03$ • BUD/FOR_{MDI}: −0.45 (95% CI, −1.78 to 0.87); *P*, NSS • BUD/FOR_{DPI}: −1.26 (95% CI, −2.58 to 0.06); *P*, NSS

Abbreviations. BUD: budesonide; CFB: change from baseline; CI: confidence interval; COPD: chronic obstructive pulmonary disease; DPI: dry-powder inhaler; FOR: formoterol; GLY: glycopyrrolate; MDI: metered-dose inhaler; NSS: not statistically significant; OR: odds ratio; RCT: randomized controlled trial; SGRQ: St. George's Respiratory Questionnaire.

Adverse Events

The proportion of individuals experiencing an AE of any type (e.g., TEAE, SAE) was similar between treatments within and across the ETHOS and KRONOS studies, and was around 20% for any SAE[42] and around 9% for any serious TEAE[29], respectively. Likewise, AEs that led to study withdrawal (around 3% to 7%) or AESIs (e.g., pneumonia, cardiac events) were also similar between treatments within and across the ETHOS[42] and KRONOS[29] studies (around 1% to 2% for major adverse cardiovascular events [MACEs] and around 1% to 5% for pneumonia;

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Appendix B, Table B2). The ETHOS authors observed that around 2% of participants experienced a bone fracture.[42]

While all-cause mortality was rare (< 1% of participants in either study), the risk of death from any cause was significantly lower in individuals who received Breztri compared with individuals who received GLY/FOR (HR, 0.54; 95% CI, 0.34 to 0.87).[42] A subgroup analysis of all-cause mortality in the ETHOS study found a significant reduction in the time-to-death when Breztri, at either dose, was compared with GLY/FOR in individuals that had 2 or more moderate or severe exacerbations at baseline (HR, 0.36; 95% CI, 0.19 to 0.70).[39] This significant reduction was also seen with the higher dose of Breztri for individuals that had 2 or more moderate or severe exacerbations at baseline (versus 1 exacerbation), no severe exacerbations (versus 1 or more), triple therapy, and ICS at screening.[39]

Trelegy Ellipta

We identified 7 studies in 17 publications; study sizes ranged from 800 to 10,355 participants (total N = 18,590).[23-28,30-34,36-38,41,45,46] Two of the identified studies were replicate RCTs (i.e., identical study protocols and treatments) and were reported with pooled results in a single publication.[28] Mean age ranged from 63.9 to 67.8 years; a majority of the participants were male and former smokers. Participants from the US were recruited in 4 (of 7) studies, but none of the studies reported race or ethnicity. Studies compared Trelegy with a variety of single, dual, or MITTs for 12 to 52 weeks. Table 14 provides further details. We also identified 5 additional publications for the FULFIL[53] and IMPACT[54-57] studies that report subgroup analyses for participants recruited solely in China, Japan, Spain, or multiple Asian countries, but we have not included these subgroup analyses in this review.

Risk of bias was determined to be moderate for 3 RCTs[23,28,36] and high for 3 RCTs[25,32,37]; note the 2 replicate RCTs reported by Ferguson and colleagues[28] were assessed as a single RCT. Drug manufacturers (i.e., industry) sponsored and had direct involvement in the design, execution, and analyses for all included RCTs, which resulted in initial assessments of a moderate risk of bias. However, the 3 RCTs that were determined to have a high risk of bias were conducted and reported almost entirely by employees of the sponsoring agent and also had some methodological concerns (e.g., lack of blinding in the INTREPID study, early withdrawal of ≥ 20% of participants in the IMPACT study).

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Table 14. Participant Characteristics and Treatment Arms for COPD RCTs of Trelegy

Study Name or First Author Trial Number Location(s) Study Duration Risk of Bias	N Randomized Participant Characteristics	Treatments
Bansal, 2021[23] NCT03474081 US + Poland and Russia 12 weeks Moderate	• N = 800 • Moderate-to-severe COPD • Mean age: 66.2 years (SD, 7.9) • Male: 543 (68%) • Current smoker: 381 (48%)	SITT • Trelegy (FLU/UMEC/VI) ○ 100/62.5/25 µg, n = 400 Comparator • TIO 18 µg, n = 400

Bremner, 2018[25]
NCT02729051
Multinational
24 weeks
High
	• N = 1,055
	• Moderate-to-severe COPD
	• Mean age: 66.3 years (SD, 8.6)
	• Male: 785 (74.4%)
	• Current smoker: 401 (38.0%)
		SITT
		• Trelegy (FLU/UMEC/VI)
		  ○ 100/62.5/25 µg, n = 527
		
		Comparator
		• FLU/VI+UMEC
		  ○ 100/25 + 62.5 µg, n = 528

Ferguson, 2020[28]
NCT03478683
NCT03478696
US + multinational
12 weeks
Moderate
	• N = 1,461
	• COPD severity, NR
	• Mean age: 65.2 years (SD, 8.1)
	• Male: 758 (51.9%)
	• Current smoker: 714 (48.9%)
		SITT
		• Trelegy (FLU/UMEC/VI)
		  ○ 100/62.5/25 µg, n = 729
		
		Comparator
		• BUD/FOR+TIO
		  ○ 400/12 + 18 µg, n = 731

FULFIL[30,36,41,46]
NCT02345161
Multinational
24 weeks (up to 52 weeks)
Moderate
	• N = 1,810
	• COPD severity, NR
	• Mean age: 63.9 years (SD, 8.6)
	• Male: 1,341 (74.1%)
	• Current smoker: 794 (43.9%)
		SITT
		• Trelegy (FLU/UMEC/VI)
		  ○ 100/62.5/25 µg, n = 911
		
		Comparator
		• BUD/FOR
		  ○ 400/12 µg, n = 899

IMPACT[24,26,27,31,33,34,37,38,45]
NCT02164513
US + multinational
52 weeks
High
	• N = 10,355
	• Moderate-to-severe COPD
	• Mean age: 65.3 years (SD, 8.3)
	• Male: 6,870 (66.3%)
	• Current smoker: 3,587 (34.6%)
		SITT
		• Trelegy (FLU/UMEC/VI)
		  ○ 100/62.5/25 µg, n = 4,151
		
		Comparators
		• FLU/VI
		  ○ 100/25 µg, n = 4,134
		• UMEC/VI
		  ○ 62.5/25 µg, n = 2,070

INTREPID[32] NCT03467425 Multiple European countries 24 weeks High	• N = 3,109 • Moderate-to-severe COPD • Mean age: 67.8 years (SD, 8.7) • Male: 1,655 (53.5%) • Current smoker, NR	SITT • Trelegy (FLU/UMEC/VI) ○ 100/62.5/25 µg, n = 1,545 Comparator • Any MITT, n = 1,547

Abbreviations. BUD: budesonide; COPD: chronic obstructive pulmonary disease; FLU: fluticasone; FOR: formoterol; MITT: multiple-inhaler triple therapy; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; SITT: single-inhaler triple therapy; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol.

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Lung Function and Symptom Control

Lung function, as measured with trough FEV_1, was found to be significantly improved in individuals treated with Trelegy (all $P \leq .01$ unless noted; Table 15) compared with:

- TIO alone over 12 weeks (a difference of 87 ml between treatments)[23]
- BUD/FOR at 24 and 52 weeks (between-treatment differences of 171 and 131 ml, respectively)[36]
- BUD/FOR+TIO over 12 weeks (a difference of 56 ml between treatments; *P*, NR)[28]
- FLU/VI at 52 weeks (a difference of 97 ml between treatments)[37]
- UMEC/VI at 52 weeks (a difference of 54 ml between treatments)[37]
- MITTs, as prescribed by their physician over 24 weeks (a difference of 53 ml between treatments)[32]

No significant difference in trough FEV_1 was observed when Trelegy was compared with FLU/VI+UMEC over 24 weeks.[25]

The FULFIL study also reported that individuals who received Trelegy were around 4 times more likely to achieve an MCID in trough FEV_1 after 24 weeks of treatment and nearly 5 times more likely after 52 weeks of treatment, compared with individuals who were treated with BUD/FOR (Table 15).[36] Furthermore, the FULFIL study found individuals treated with Trelegy had significant improvements in trough FEV_1 at 24 and 52 weeks compared with BUD/FOR (all, $P \leq .01$) regardless of prior year exacerbation severity and frequency (Appendix B, Table B3).[30] Ferguson and colleagues found significant differences in trough FEV_1 after 12 weeks of treatment with Trelegy compared with BUD/FOR+TIO when analyses were stratified by those under the age of 65 or those aged 65 or older (differences of 74 and 41 ml, respectively; *P*, NR; Table 15).[28]

The annualized rate of exacerbations was reported by the FULFIL and IMPACT studies. Trelegy was found to provide a significant reduction in the annual rate of moderate or severe exacerbations when compared to BUD/FOR at 24 and 52 weeks (a 35% and 44% reduction, respectively; both, $P < .01$)[36] and FLU/VI or UMEC/VI at 52 weeks (15% and 25% reduction, respectively; both, $P < .001$; Table 15).[37] Individuals who received Trelegy for 24 weeks and experienced 1 or fewer moderate exacerbations or more than 1 severe exacerbations in the prior 12 months had significant reductions in their annual rate of moderate or severe exacerbations compared with BUD/FOR (a 45% and 27% reduction, respectively; both, $P \leq .01$; Appendix B, Table B3).[30] Time-to-first moderate or severe exacerbation was found to be significantly delayed by approximately 15% for individuals treated with Trelegy compared with FLU/VI or UMEC/VI (both, $P < .001$; Table 15) in the IMPACT study.[37] However, Bremner and colleagues found no significant differences in time-to-first moderate or severe exacerbation when Trelegy was compared with FLU/VI+UMEC (Table 15).[25] Bansal and colleagues observed a slightly lower proportion of individuals who received Trelegy (27 of 400; 7%) experienced a moderate-to-severe exacerbation during the 12-week study period compared with those who received TIO alone (43 of 400; 11%); however, no formal statistical testing was reported.[23] Similarly, the INTREPID study reported an annualized rate of moderate-to-severe exacerbations of 1.2 in the Trelegy group and 1.1 in the MITT group; however, no formal statistical testing was reported.[32]

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No significant differences in achieving an MCID for shortness of breath (i.e., response), as measured with the TDI, were found when comparing Trelegy with FLU/VI+UMEC for 24 weeks[25] or BUD/FOR for 52 weeks (Table 15).[46] However, it was found that Trelegy significantly increased the likelihood of response for shortness of breath by (all, $P < .001$; Table 11):

- 60% compared with BUD/FOR over 24 weeks[46]
- 36% compared with FLU/VI over 52 weeks[45]
- 33% compared with UMEC/VI over 52 weeks[45]

Use of rescue medication was infrequently reported. The FULFIL study found a small but significant reduction of −0.2 uses per day over 24 ($P < .001$) and 52 weeks ($P = .02$) for those using Trelegy compared with BUD/FOR.[46] There was a slight increase in rescue medication use, regardless of treatment, in the IMPACT study, but the level of use was significantly lower for user of Trelegy compared with FLU/VI or UMEC/VI (at all time points, $P < .001$).[45] In addition, over the last 4 weeks of the IMPACT study, there was a significant reduction in percentage of days requiring rescue medication use (around 4% to 5%) for users of Trelegy compared with FLU/VI or UMEC/VI (both, $P < .001$).[45]

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Table 15. Lung Function and Symptom Control in COPD RCTs of Trelegy

Study Name Treatments	Lung Function	Exacerbations	Other Symptom Control
Bansal, 2021[23] Trelegy, n = 400 TIO, n = 400	At 12 weeks, between-treatment difference CFB Trough FEV_1 • 87 ml (95% CI, 56 to 118); *P* < .001	Exacerbations • Annualized rate of exacerbations, NR	NR
Bremner, 2018[25] Trelegy, n = 527 FLU/VI+UMEC, n = 528	At 24 weeks, between-treatment difference CFB Trough FEV_1 • 26 ml (95% CI, −2 to 53); *P*, NSS	Exacerbations • Annualized rate of exacerbations, NR • Time-to-first moderate/severe exacerbation: HR, 0.87 (95% CI, 0.68 to 1.12); *P*, NSS	Shortness of breath, at week 24 • TDI responder rate: OR, 0.95 (95% CI, 0.72 to 1.25); *P*, NSS
Ferguson, 2020[28] Trelegy, n = 729 BUD/FOR+TIO, n = 731	At 12 weeks, between-treatment difference CFB Trough FEV_1 • 56 ml (95% CI, 37 to 75); *P*, NR Subgroups • Age < 65: 74 ml (95% CI, 46 to 102); *P*, NR • Age ≥ 65: 41 ml (95% CI, 15 to 67); *P*, NR	NR	NR
FULFIL[30,36,41,46] For main 24-week study: Trelegy, n = 911 BUD/FOR, n = 899 For extension through 52 weeks Trelegy, n = 210 BUD/FOR, n = 220	Between-treatment difference CFB • 171 ml (95% CI, 148 to 194); *P* < .001 Trough FEV_1 Responder rate • At week 24: OR, 4.03 (95% CI, 3.27 to 4.97); *P* < .001 • At week 52: OR, 4.79 (3.02 to 7.61); *P* < .001	Exacerbations Annualized rate of moderate and severe exacerbations • Up to week 24: rate ratio, 0.65 (95% CI, 0.49 to 0.86); *P* = .002 • Up to week 52: rate ratio, 0.56 (95% CI, 0.37 to 0.85); *P* = .006	Shortness of breath (TDI) Responder rate • At week 24: OR, 1.61 (95% CI, 1.33 to 1.95); *P* < .001 • At week 52: OR, 1.35 (95% CI, 0.91 to 1.99); *P*, NSS Use of rescue medication • Over 24 weeks: −0.2 occasions per day; *P* < .001 • Over 52 weeks: −0.2 occasions per day; *P* = .02

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Study Name Treatments	Lung Function	Exacerbations	Other Symptom Control
IMPACT[24,26,27,31,33,34,37,38,45] Trelegy, n = 4,151 FLU/VI, n = 4,134 UMEC/VI, n = 2,070	At week 52, between-treatment difference CFB Trough FEV_1 • FLU/VI: 97 ml (95% CI, 85 to 109); *P* < .001 • UMEC/VI: 54 ml (95% CI, 39 to 69); *P* < .001	Exacerbations Annualized rate of moderate or severe exacerbations • FLU/VI: rate ratio, 0.85 (95% CI, 0.80 to 0.90); *P* < .001 • UMEC/VI: rate ratio, 0.75 (95% CI, 0.70 to 0.81); *P* < .001 Time-to-first moderate or severe exacerbation • FLU/VI: HR, 0.85 (95% CI, 0.80 to 0.91); *P* < .001 • UMEC/VI: HR, 0.84 (95% CI, 0.78 to 0.91) *P* < .001	Shortness of breath At 52 weeks[45] TDI responders • FLU/VI: OR, 1.36 (95% CI, 1.19 to 1.55); *P* < .001 • UMEC/VI: OR, 1.33 (95% CI, 1.13 to 1.57); *P* < .001 Use of rescue medications Weeks 49 to 52[45] Percentage of rescue medication-free days, between-treatment difference • FLU/VI: 5.2% (95% CI, 3.5 to 6.9); *P* < .001 • UMEC/VI: 4.4% (95% CI, 2.3 to 6.5); *P* < .001
INTREPID[32] Trelegy, n = 301 MITT, n = 292	At week 24, between-treatment difference CFB Trough FEV_1 • 53 ml (95% CI, 9 to 96); *P* = .01	Annualized rate of moderate or severe exacerbations • Trelegy, mean 1.2 (SD, 3.65) • MITT: 1.1 (SD, 5.57)	NR

Abbreviations. BUD: budesonide; CFB: change from baseline; CI; confidence interval; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FLU: fluticasone; FOR: formoterol; HR: hazard ratio; MITT: multiple-inhaler triple therapy; NR: not reported; NSS: not statistically significant; OR: odds ratio; RCT: randomized controlled trial; SD: standard deviation; TDI: Transition Dyspnea Index; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol.

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Health-Related Quality of Life

In the included studies reporting the effectiveness of Trelegy, HRQoL was reported using the SGRQ or the COPD Assessment Test (CAT). In many instances a significant decrease in SGRQ total score from baseline was seen in all treatment groups, with small but significant between-treatment differences observed in individuals receiving Trelegy compared with (all, $P < .001$; Table 16):

- BUD/FOR at 24 weeks (a reduction of 6.6 vs. 4.3)[36]
- FLU/VI at 52 weeks (a reduction of 5.5 vs. 3.7)[37]
- TIO at 12 weeks (reduction from baseline reported graphically only)[23]
- UMEC/VI at 52 weeks (a reduction of 5.5 vs. 3.7)[37]between treatment

No significant between-treatment differences in SGRQ total score were observed when Trelegy was compared with (Table 16):

- BUD/FOR at 52 weeks[36]
- BUD/FOR+TIO at 12 weeks[28]
- FLU/VI+UMEC at 24 weeks[25]

A decrease of at least 4 units in the SGRQ total score is considered an MCID and therefore a significant treatment response.[1] Participants treated with Trelegy were significantly more likely to respond, as measured by the SGRQ total score, by (Table 16):

- 62% compared with TIO at 12 weeks ($P < .001$)[23]
- 50% compared with BUD/FOR at 52 weeks ($P = .05$)[36]
- 41% compared with UMEC/VI at 52 weeks ($P < .001$)[37]
- 41% compared with FLU/VI at 52 weeks ($P < .001$)[37]
- 41% compared with BUD/FOR at 24 weeks ($P < .001$)[36]

No significant difference was seen in response, as measured by the SGRQ total score, in the studies by Bremner and colleagues[25] and Ferguson and colleagues[28] for Trelegy when compared with other therapies.

Some studies also measured HRQoL with the CAT. No MCID for CAT score has been defined, but some studies[23,28,45,46] have defined a decrease of 2 or more units from baseline to be a significant change and therefore a response to treatment. In the studies that used the CAT, it was found that when Trelegy was compared with (Table 16):

- TIO for 12 weeks: Trelegy significantly improved CAT score (reduction from baseline reported graphically only; $P = .001$), but Trelegy users were not significantly more likely to be treatment responders.[23]
- BUD/FOR+TIO for 12 weeks: No significant between-treatment differences were observed in total CAT score nor in being a treatment responder.[28]
- BUD/FOR for 24 weeks: Trelegy significantly improved CAT score (a reduction of 2.5 vs. 1.6), and those administered Trelegy were 44% more likely to be treatment responders (both, $P < .001$).[46]
- BUD/FOR for 52 weeks: No significant between-treatment differences in CAT score were observed, but those using Trelegy were 50% more likely to be treatment responders ($P = .048$).[46]

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- FLU/VI for 52 weeks: Trelegy users were 24% more likely to be treatment responders ($P < .001$).[45]
- UMEC/VI for 52 weeks: Trelegy users were 28% more likely to be treatment responders ($P < .001$).[45]
- MITT for 24 weeks: Trelegy users were 31% more likely to be treatment responders ($P < .001$).[32]

The FULFIL study examined SGRQ total score and SGRQ responders by prior 12-month exacerbation history. At week 24, regardless of exacerbation history, Trelegy users had improved SGRQ total scores compared with BUD/FOR. However, significant improvements in SGRQ total score were observed for those using Trelegy compared with BUD/FOR in those with a history of (Appendix B, Table B3)[30]:

- 1 or fewer moderate exacerbations, but no severe exacerbations (at 24 weeks, $P < .001$)
- 2 or more moderate exacerbations, but no severe exacerbations (at 24 weeks, $P = .01$)
- 2 or more moderate exacerbations, but no severe exacerbations (at 52 weeks, $P = .03$)

Table 16. Health-Related Quality of Life in Trelegy RCTs for COPD

Study Name Treatments	SGRQ	CAT
Bansal, 2021[23] Trelegy, n = 400 TIO, n = 400	At 12 weeks, mean between-treatment difference CFB SGRQ • Total score: −3.2 (−5.0 to −1.4); $P < .001$ • Responder rate: OR, 1.62 (95% CI, 1.22 to 2.17); $P = .001$	At 12 weeks, mean between-treatment difference CFB CAT • Total score: −1.2 (95% CI, −1.9 to −0.5); $P = .001$ • Responder rate: OR, 1.15 (95% CI, 0.86 to 1.53); $P = .3$
Bremner, 2018[25] Trelegy, n = 527 FLU/VI+UMEC, n = 528	At week 24, mean between-treatment difference CFB SGRQ • Total score: −0.9 (95% CI, −2.5 to 0.7); *P*, NSS • Responder rate: OR, 0.92 (95% CI, 0.71 to 1.20); *P*, NSS	NR
Ferguson, 2020[28] Trelegy, n = 729 BUD/FOR+TIO, n = 731	At week 12, mean between-treatment difference CFB SGRQ • Total score: 0.0 (95% CI, −1.0 to 1.1); $P = .9$ • Responder rate: OR, 1.05 (95% CI, 0.84 to 1.31); $P = .7$	At week 12, mean between-treatment difference CFB CAT • Total score: −0.3 (95% CI, −0.9 to 0.2); $P = .2$ • Responder rate: OR, 1.04 (95% CI, 0.83 to 1.30); $P = .7$
FULFIL[30,36,41,46] For main 24-week study: Trelegy, n = 911 BUD/FOR, n = 899 For extension through 52 weeks	At week 24, mean between-treatment difference CFB SGRQ • Total score: −2.2 (95% CI, −3.5 to −1.0); $P < .001$ • Responder rate: OR, 1.41 (95% CI, 1.16 to 1.70); $P < .001$	At week 24, mean between-treatment difference CFB[46] CAT • Total score: −0.9 (95% CI, −1.4 to −0.4); $P < .001$ • Responder rate: OR, 1.44 (95% CI, NR); $P < .001$

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Study Name Treatments	SGRQ	CAT
Trelegy, n = 210 BUD/FOR, n = 220	At week 52, mean between-treatment difference CFB SGRQ • Total score: −2.7 (95% CI, −5.5 to 0.2); *P* = .06 • Responder rate: OR, 1.50 (95% CI, 1.01 to 2.24); *P* = .05	At week 52, mean between-treatment difference CFB[46] CAT • Total score: Details, NR; *P*, NSS • Responder rate: OR, 1.50 (95% CI, NR); *P* = .048

IMPACT[24,26,27,31,33,34,37,38,45]
 	
Trelegy, n = 4,151
FLU/VI, n = 4,134
UMEC/VI, n = 2,070
	At week 52, mean between-treatment difference CFB
	
	SGRQ total score
	• FLU/VI: −1.8 (95% CI, −2.4 to −1.1); *P* < .001
	  ○ Responder rate: OR, 1.41 (1.29 to 1.55); *P* < .001
	• UMEC/VI: −1.8 (95% CI, −2.6 to −1.0); *P* < .001
	  ○ Responder rate: OR, 1.41 (1.26 to 1.57); *P* < .001
		At week 52, mean between-treatment difference CFB[45]
		
		CAT
		Responder rate:
		• FLU/VI: OR, 1.24 (95% CI, 1.14 to 1.36); *P* < .001
		• UMEC/VI: OR, 1.28 (95% CI, 1.15 to 1.43); *P* < .001

INTREPID[32] Trelegy, n = 301 MITT, n = 292	NR	At week 24 • CAT responder rate: OR, 1.31 (95% CI, 1.13 to 1.51); *P* < .001

Abbreviations. BUD: budesonide; CFB: change from baseline; CI: confidence interval; COPD: chronic obstructive pulmonary disease; FLU: fluticasone; FOR: formoterol; GLY: glycopyrrolate; MITT: multiple-inhaler triple therapy; NR: not reported; NSS: not statistically significant; OR: odds ratio; RCT: randomized controlled trial; SGRQ: St. George's Respiratory Questionnaire; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol.

Adverse Events

AEs were common in all studies, regardless of treatment. Within the individual studies, the proportions of AEs were similar between treatments. The proportion of participants who experienced at least 1 AE ranged from 10% to 50%. TEAEs and SAEs were also similar between treatment groups within the studies, with SAEs generally affecting less than 10% of all participants. Similarly, AESIs (e.g., pneumonia, cardiac events, decreased bone mineral density) were similar between treatments. However, the IMPACT study found that individuals administered Trelegy had a significant reduction of 53% in their risk of developing pneumonia and a 53% delay in time to first pneumonia event when compared with UMEC/VI (both, *P* < .001).[27] Hospitalizations related to exacerbations or AEs were only reported in the FULFIL and IMPACT studies. FULFIL researchers briefly reported that there were fewer exacerbation-related hospitalizations in individuals receiving Trelegy (12 of 911; 1.3%) compared with BUD/FOR (22 of 899; 2.4%), but did not provide further details.[36] IMPACT researchers found Trelegy reduced hospitalizations related to severe exacerbations by 34% (rate ratio, 0.66; 95% CI, 0.56 to 0.78; *P* < .001) and delayed pneumonia-related hospitalization or death by 62% compared with UMEC/VI (*P* < .001; Appendix B, Table B3).[27] Deaths were rare and occurred in less than 1% of the participants. Withdrawal from the study due to an AE generally occurred in 1% to 2% of participants, regardless of treatment. Appendix B, Table B3 provides more detail of AEs.

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Trimbow

We identified 2 RCTs—TRINITY (N = 2,691)[47] and TRIVERSYTI (N = 708)[48]—that compared Trimbow with BUD/FOR, TIO, or BDP/FOR+TIO. Study duration was 24 to 52 weeks. The majority of participants were male and former smokers with a mean age of approximately 65 (Table 17). Both studies were conducted outside the US. TRIVERSYTI[48] recruited participants exclusively in China, Korea, or Taiwan, while participants of the multinational TRINITY study were almost exclusively identified as White (99.2%; 2,670 of 2,691).[47] Severity of COPD at recruitment was not reported in either study. Risk of bias for both studies was determined to be moderate due to industry sponsorship and heavy involvement of sponsor employees in conducting and analyzing the study. Additionally, there were some conflict-of-interest concerns surrounding the receipt of non-grant monies from the sponsor to non-sponsor researchers during the study period.

Table 17. Participant Characteristics and Treatment Arms for Trimbow RCTs for COPD

Study Name Trial Number Location(s) Study Duration Risk of Bias	N Randomized Participant Characteristics	Treatments

TRINITY[47]
NCT01911364
Multinational
52 weeks
Moderate
	• N = 2,691
	• COPD severity, NR
	• Mean age: 63.2 (SD, 8.6)
	• Male: 2,056 (76.4%)
	• Current smoker: 1,286 (47.8%)
	• Ethnicity
	  ○ White: 2,670 (99.2%)
	  ○ Black/African American: 1 (0.03%)
	  ○ Other: 19 (0.7%)
		SITT
		• Trimbow (BDP/FOR/GLY), 2 puffs twice per day
		  ○ 100/6/12.5 µg, n = 1,078
		
		Comparators
		• TIO only, 1 puff once per day
		  ○ 18 µg, n = 1,075
		• BDP/FOR+TIO, 2 puffs twice per day
		  ○ 100/6 + 18 µg, n = 538

TRIVERSYTI[48]
NCT03197818
China, Korea, Taiwan
24 weeks
Moderate
	• N = 708
	• COPD severity, NR
	• Mean age: 65.9 (SD, 7.4)
	• Male: 673 (95.0%)
	• Current smoker: 174 (24.5%)
	• Nationality
	  ○ Chinese: 576 (81.3%)
	  ○ Korean: 108 (15.2%)
	  ○ Taiwanese: 22 (3.1%)
		SITT
		• Trimbow (BDP/FOR/GLY)
		  ○ 100/6/10 µg, n = 353
		
		Comparator
		• BUD/FOR
		  ○ 160/4.5 µg, n = 355

Abbreviations. BDP: beclomethasone dipropionate; BUD: budesonide; COPD: chronic obstructive pulmonary disease; FOR: formoterol; GLY: glycopyrronium; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; SITT: single-inhaler triple therapy; TIO: tiotropium.

Lung Function and Symptom Control

Significant between-treatment differences in trough FEV_1 were observed when comparing Trimbow with BUD/FOR over 24 weeks (mean difference, 70 ml; $P < .001$)[48] or TIO alone over 52 weeks (mean difference, 58 ml; $P < .001$; Table 18).[47] Individuals treated with Trimbow were also significantly more likely to achieve an MCID in trough FEV_1 compared to those treated with

BUD/FOR (26% vs. 12%; OR, 2.58; $P < .001$)[48] or TIO alone (38% vs. 27%; OR, 1.62; $P < .001$).[47] However, when Trimbow was compared with BDP/FOR+TIO there was no significant between-treatment difference in trough FEV_1 or in the likelihood of achieving an MCID in trough FEV_1.[47]

The annual rate of moderate-to-severe COPD exacerbations were significantly reduced in individuals who received Trimbow compared with TIO alone (0.46 vs. 0.57; $P = .002$)[47] or BUD/FOR (0.52 vs. 0.91; $P < .001$; Table 18).[48] Similarly, individuals who were randomized to TIO alone[47] or BUD/FOR[48] were significantly more likely to experience their first moderate-to-severe COPD exacerbation earlier than those treated with Trimbow ($P = .01$ and $P < .001$, respectively; Table 18). No significant differences in the rate of moderate-to-severe COPD exacerbations or time-to-first moderate or severe exacerbation were observed when Trimbow was compared with BDP/FOR+TIO.[47]

Individuals that received Trimbow had significantly fewer days that required the use of rescue medication (around 7% to 9% across both studies), and required fewer puffs per day when it was needed, than those that received TIO alone (around 0.6 puffs fewer)[47] or BUD/FOR[48] (around 0.1 puffs fewer; all, $P < .001$; Table 18) over the study periods. No significant differences in the percentage of rescue medication-free days or average number of puffs per day were observed between Trimbow and BDP/FOR+TIO at any time point.[47]

Additional statistical details can be found in Appendix B, Table B2.

Table 18. Lung Function and Symptom Control for Trimbow RCTs for COPD

Study Name Trial Number Treatments	FEV_1	Symptom Control
TRINITY[47] NCT01911364 Trimbow vs. TIO or BDP/FOR+TIO	Trough FEV_1, over 52 weeks Mean between-treatment difference • TIO: 58 ml (95% CI, 39 to 77); $P < .001$ • BDP/FOR+TIO, NSS Responder rate • TIO: OR, 1.62 (95% CI, 1.35 to 1.95); $P < .001$ • BDP/FOR+TIO: −11 ml (−34 ml to 12 ml); *P*, NSS	Exacerbations Annualized rate of moderate-to-severe exacerbations • TIO: rate ratio, 0.80 (95% CI, 0.69 to 0.92); $P = .002$ • BDP/FOR+TIO: rate ratio, 1.01 (95% CI, 0.85 to 1.21); *P*, NSS Time-to-first moderate-to-severe exacerbation • TIO: HR, 0.84 (95% CI, 0.72 to 0.97); $P = .01$ • BDP/FOR+TIO: HR, 1.06 (95% CI, 0.88 to 1.27); *P*, NSS Use of rescue medication, at weeks 41 to 52, mean between-treatment difference Percentage of rescue-free days • TIO: 8.78 (95% CI, 5.74 to 11.81); $P < .001$ • BDP/FOR+TIO: −1.24 (95% CI, −4.92 to 2.44); *P*, NSS

Study Name Trial Number Treatments	FEV_1	Symptom Control
		Puffs per day • TIO: −0.61 (95% CI, −0.78 to −0.44); *P* < .001 • BDP/FOR+TIO: 0.05 (95% CI, −0.16 to 0.25); *P*, NSS
TRIVERSYTI[48] NCT03197818 Trimbow vs. BUD/FOR	Trough FEV_1, at week 24 Adjusted mean between-treatment difference • 70 ml (95% CI, 53 to 88); *P* < .001 Responder rate • OR, 2.58 (95% CI, 1.72 to 3.85); *P* < .001	Exacerbations Annualized rate of moderate-to-severe exacerbations • Rate ratio, 0.57 (95% CI, 0.42 to 0.77); *P* < .001 Time-to-first moderate/severe exacerbation • HR, 0.55 (95% CI, 0.51 to 0.75); *P* < .001 Use of rescue medication, over 24 weeks, between-treatment difference Percentage of rescue-free days • 6.7 (95% CI, 3.9 to 9.4); *P* < .001 Puffs per day • −0.15 (95% CI, −0.23 to −0.06); *P* < .001

Abbreviations. BDP: beclomethasone dipropionate; BUD: budesonide; CFB: change from baseline; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FOR: formoterol; HR: hazard ratio; NR: not reported; NSS: not statistically significant; OR: odds ratio; TIO: tiotropium.

Health-Related Quality of Life

Individuals that received Trimbow had significantly improved SGRQ and CAT scores when compared with BUD/FOR (reported graphically only; both, *P* < .001)[48] and were more likely to respond (i.e., reach the MCID for SGRQ) compared with TIO alone (46% vs. 39%; *P* = .002; Table 19).[47] No significant difference was observed between Trimbow and BDP/FOR+TIO.[47]

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Table 19. Health-Related Quality of Life Outcomes for Trimbow RCTs for COPD

Study Name Trial Number Treatments	SGRQ	CAT
TRINITY[47] NCT01911364 Trimbow vs. TIO or BDP/FOR+TIO	Responder rate • TIO: OR, 1.33 (95% CI, 1.11 to 1.59); *P* = .002 • BDP/FOR+TIO: OR, 0.91 (95% CI, 0.73 to 1.13); *P*, NSS	NR
TRIVERSYTI[48] NCT03197818 Trimbow vs. BUD/FOR	Total score, between-treatment mean difference, overall • −3.18 (95% CI, −4.99 to −1.37); *P* < .001	CAT, adjusted between-treatment mean difference, overall • −1.01 (95% CI, −1.63 to −0.39); *P* < .001

Abbreviations. BDP: beclomethasone dipropionate; BUD: budesonide; CAT: COPD Assessment Test; CI: confidence interval; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FOR: formoterol; NR: not reported; NSS: not statistically significant; OR: odds ratio; RCT: randomized controlled trial; SGRQ: St. George's Respiratory Questionnaire; TIO: tiotropium.

Adverse Events

The proportion of individuals experiencing an AE of any type (e.g., TEAE, SAE) was similar between treatments within and across the TRINITY and TRIVERSYTI studies.[47,48] Likewise, AEs that led to study withdrawal, death, or AESIs (e.g., pneumonia, cardiac events) were also similar between-treatments within and across the TRINITY and TRIVERSYTI studies.[47,48] Further details are available in Appendix B, Table B4.

Ongoing Studies

We identified 7 ongoing studies: 3 studying individuals with asthma and 4 studying individuals with COPD (Table 20).

Ongoing Studies for the Treatment of Asthma With SITT

The KALOS (N = 2,200)[58] and LOGOS (N = 2,200)[59] studies are recruiting participants aged 12 to 80 with asthma and treating participants with Breztri, BUD/FOR, or Symbicort for 52 weeks. KALOS and LOGOS include participants from the US and have primary completion dates in the first quarter of 2024. A third ongoing study is recruiting adults aged 18 years and over with asthma (N = 356) for a 12 week trial comparing Trelegy to FLU/VI in China; the primary completion date is September 2024.[60] Further details are in Table 20.

Ongoing Studies for the Treatment of COPD With SITT

The TRIMICU study (N = 200) is recruiting participants in Belgium over age 18 who were admitted to the hospital for a COPD exacerbation.[61] TRIMICU will compare Trimbow plus standard of care to standard of care alone over a period of 2 years.[61] The TRITON study (N = 2,934) is recruiting adults aged 40 years and older with COPD and comparing Trimbow to BDP/FOR for 52 weeks.[62] TRITON includes participants in the US and has a primary completion date in mid-2024. The TRICOLON (N = 300)[63] and TRACkER (N = 316)[64] studies are being conducted in the Netherlands and recruiting adults aged 40 years and older. TRICOLON and

TRACkER are comparing Trimbow to a variety of other treatments for 52 or 26 weeks, respectively. Further details are in Table 20.

Table 20. Ongoing RCTs

Trial Name Trial Number Location(s)	Expected Enrollment Participant Characteristics Duration	Treatment Groups	Relevant Outcomes	Primary Completion Date
Asthma				
KALOS[58] NCT04609878 US + multinational Phase 3	• N = 2,200 • Aged 12 to 80 years • 52 weeks	• Breztri • BUD/FOR	• AEs • Efficacy • Exacerbations • FEV_1 • QoL	January 2024
LOGOS[59] NCT04609904 US + multinational Phase 3	• N = 2,200 • Aged 12 to 80 years • 52 weeks	• Breztri • BUD/FOR	• AEs • Efficacy • Exacerbations • FEV_1 • QoL	March 2024
NCT04937387[60] China Phase 3	• N = 356 • Aged ≥ 18 years • 12 weeks	• Trelegy • FLU/VI	• Efficacy • FEV_1	September 2024
COPD				
TRIMICU[61] NCT04737655 Belgium Phase 4	• N = 200 • Aged > 18 years, admitted to hospital for COPD exacerbation • 2 years	• Trimbow + SOC • SOC	• Exacerbations • Length of stay in hospital	February 2023
TRITON[62] NCT04320342 US + multinational Phase 3	• N = 2,934 • Aged ≥ 40 years • 52 weeks	• Trimbow • BDP/FOR	• AEs • Efficacy • Exacerbations • FEV_1 • Use of rescue medications	July 2024
TRICOLON[63] NCT05495698 Netherlands	• N = 300 • Aged ≥ 40 years • 52 weeks	• Trimbow • Qvar + Bevespi • Trimbow + health app	• Efficacy • Exacerbations • QoL	September 2024
TRACkER[64] 2019-003351-11 Netherlands	• N = 316 • Aged ≥ 40 years, with COPD with characteristics of asthma • 26 weeks	• Trimbow • SOC (e.g., Duaklir inhaler)	• Efficacy • Exacerbations • QoL • SAEs	Not stated (registered December 2019)

Abbreviations. AE: adverse event; BDP: beclomethasone dipropionate; BUD: budesonide; COPD: chronic obstructive pulmonary disorder; FEV_1: forced expiratory volume in 1 second; FLU: fluticasone; FOR: formoterol; QoL: quality of life; RCT: randomized controlled trial; SAE: serious adverse event; SOC: standard of care; VI: vilanterol.

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Conclusions

The RCTs included in this report were generally large and multinational with most enrolling US participants, though the proportion of US participants was not always clear. The participants also tended to have moderate-to-severe disease.

When compared with mono- or dual therapies, individuals who used the SITTs—Breztri, Trelegy, and Trimbow—generally experienced greater improvements in lung function, HRQoL, and reductions in the severity and frequency of moderate-to-severe exacerbations and in the use of rescue medications. While those treated with SITTs frequently had larger changes over the trial period, and were generally more likely to achieve clinically meaningful differences where these have been established (e.g., FEV_1, SGRQ), these between-treatment differences could be relatively small (e.g., decreases of 0.9 and 0.25 points on the SGRQ and TDI, respectively). Furthermore, several studies observed participants were able to achieve clinically meaningful differences for outcomes regardless of treatment. It should be noted that when the dual therapy BUD/FOR was compared to Breztri, Trelegy, or Trimbow for the treatment of COPD, substantially significant differences in several clinically important outcomes favored the SITT (Table 21).

Table 21. Substantially Significant Outcomes Favoring SITTs Compared With BUD/FOR

SITT	BUD/FOR
Breztri	• 20% less likely to experience FEV_1 deterioration (decrease ≥ 100 ml) • 25% more likely to increase SGRQ ≥ 4 points
Trelegy	• FEV_1 mean between-group difference of 170 to 180 ml • 4 to 5 times more likely to increase FEV_1 by ≥ 100 ml • Experience half the rate of exacerbations • 40% to 50% more likely to increase HRQoL scores to meet MCIDs
Trimbow	• 2.6 times more likely to increase trough FEV_1 by ≥ 100 ml • 45% delay in time to first moderate or severe exacerbation • Larger improvements in SGRQ scores

Abbreviations. BUD: budesonide; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FOR: formoterol; HRQoL: health-related quality of life; MCID: minimal clinically important difference; SGRQ: St. George's Respiratory Questionnaire; SITT: single-inhaler triple therapy.

The evidence is mixed when comparing SITTs to MITTs, with some studies finding no significant between-treatment differences and others finding some very small significant between-treatment differences. Unfortunately, AEs (including SAEs and AESIs) are still common with SITTs, but the proportions of individuals affected and the type of AE are similar to other treatments. In a few instances, SITTs offered a significant reduction in risk for pneumonia. Withdrawals due to an AE and treatment-related deaths were rare.

Discussion

Asthma and COPD are common conditions that can greatly interfere with an individual's life despite numerous pharmaceutical options available to manage the conditions. Individuals living with asthma or COPD frequently have additional chronic conditions, which may impact treatment options and outcomes. Asthma and COPD are more likely to affect individuals who identify as non-White and female and who have a lower socioeconomic status, yet the vast majority of study participants identify as male and White. The Centers for Disease Control and

Prevention suspect the condition is underdiagnosed, particularly among women and other minority populations,[6] which can translate to more severe disease when a diagnosis is eventually made.

Patient-reported outcomes (e.g., SGRQ, ACQ-7) were measured by nearly all of the included studies, but these instruments may not effectively capture patient-important outcomes. In the last few years, more researchers have begun to study outcomes important to patients and have found that these do not always align with commonly reported clinical outcomes. For example, a survey of 1,050 individuals living with moderate-or-severe COPD found that they valued improvements in daily symptoms rather than a reduction in exacerbations.[65]

Limitations

Condition-related hospitalizations or emergency department visits were rarely reported, making it difficult to determine the impact of SITTs on these outcomes. Analyses by subgroups of interest were lacking in part because many were done via post hoc analyses, which were excluded in this report. Additionally, neither certainty of evidence assessments nor meta-analyses were conducted due to this report not being a full systematic review (i.e., rapid review methods were employed), both of which may improve interpretation of the results, especially considering the small but significant between-treatment differences observed. While none of the included studies investigated treatment adherence, recent studies[66,67] have found that individuals using SITTs are more likely to adhere and persist with management treatments compared with those prescribed treatments that require the use of 2 or more inhalers, which may explain some of the mixed results seen in this report.

State Considerations

The Medicaid population has higher proportions of individuals with asthma or COPD compared with private insurers, and the Medicaid population has more severe disease with less management due to various barriers (e.g., medication costs). SITT treatments can result in some positive impacts on the management of asthma or COPD for beneficiaries; there may also be benefits to some patients in terms of adherence and persistence of treatment. Consistent treatment that helps an individual manage their condition may in turn improve other aspects of asthma and COPD care (e.g., reduced utilization of services), as well as care and outcomes for comorbid conditions.

Medicaid administrators might consider reviewing the benchmark document[68] and other materials from the American Lung Association Asthma Guidelines-Based Care Coverage Project,[69] which provides information on key aspects of the management of asthma and addresses barriers to treatment, particularly for Medicaid beneficiaries. Medicaid administrators might also revisit the National Heart, Lung, and Blood Institute's national plan for COPD,[8] which was updated in 2019, and the 2020 updates to asthma management guidelines.[70] Medicaid administrators may consider the individual patient disease profile (e.g., disease severity, medication adherence) and patient-important outcomes to determine if SITTs may be an appropriate management approach.

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Appendix A. Clinical Evidence Methods

Search Strategy

We searched Drug Effectiveness Review Project (DERP) bibliographic database (e.g., Ovid MEDLINE; Table A1) and gray literature clinical evidence sources to identify randomized controlled trials (RCTs) and systematic reviews (with and without meta-analyses), including the terms *single-inhaler triple therapy*, *SITT*, *asthma*, *COPD*, *Breztri*, *Trelegy*, *Trimbow*, generic drug names, and known trial names or numbers. We limited records retrieved to those studies focused on human subjects and published in the English language. No additional search limits were applied. Systematic reviews were used for reference list searching and not as evidence sources. Searches were conducted on September 16, 2022.

Table A1. Bibliographic Databases

Database	Platform	Issue/Version	Total Number of Records Retrieved
CENTRAL	Wiley	Issue 9 of 12, September 2022	582
CDSR	Wiley	Issue 9 of 12, September 2022	23
MEDLINE ALL	Ovid	1946 to September 14, 2021	409

Abbreviations. CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CINAHL: Cumulative Index to Nursing and Allied Health Literature.

Gray Literature Sources

- Agency for Healthcare Research and Quality (AHRQ)
  - Effective Health Care (EHC) Program
  - Evidence-based Practice Centers (EPC) Reports
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Health Evidence Review Commission (HERC)
- Institute for Clinical and Economic Review (ICER)
- International HTA Database
- Veterans Administration Evidence-based Synthesis Program (VA-ESP)
- Washington Health Technology Assessment (WA HTA)

We conducted general internet searches using DuckDuckGo and Google Scholar for background and gray literature searches. We also searched AHRQ, CADTH, HERC, ICER, the International HTA Database, VA-ESP, and WA HTA to identify systematic reviews and gray literature using the following search terms: *Breztri*, *Trelegy*, and *Trimbow*.

Ovid MEDLINE ALL Search Strategy

1. (copd or Chronic Obstructive Pulmonary or asthma*).ti,ab.

2. Asthma/ or Asthma, Exercise-Induced/ or Asthma, Occupational/ or Asthma, Aspirin-Induced/ or Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome/ or Pulmonary Disease, Chronic Obstructive/

3. or/1-2

4. ((single* or one*) adj2 inhale* adj3 triple).mp.

5. ((one* or single*) adj1 device* adj9 triple).mp.

6. sitt device*.mp.

7. Triple Inhaled Therap*.mp.

8. or/4-7

9. ((TRIGGER or TRIMARAN or CAPTAIN or TRIBUTE or TRILOGY or TRINITY or INTREPID or CTT200812 or FULFIL or IMPACT or KRONOS or ETHOS or KALOS or LOGOS) adj1 (trial or study or random* or RCT)).ti,ab.

10. 3 and (8 or 9)

11. ((Budesonide adj4 Glycopyrrolate adj4 Formoterol) or Budesonide-Glycopyrrolate-Formoterol or Budesonide-Formoterol-Glycopyrrolate or Glycopyrrolate-Formoterol-Budesonide or Glycopyrrolate-Budesonide-Formoterol or Formoterol-Glycopyrrolate-Budesonide or Formoterol-Budesonide-Glycopyrrolate or BGFF or (BUD adj2 GLY adj2 FOR) or BUD-GLY-FOR or BUD-FOR-GLY or GLY-FOR-BUD or GLY-BUD-FOR or FOR-BUD-GLY or FOR-GLY-BUD).mp.

12. ((Fluticasone adj4 umeclidinium adj4 vilanterol) or Fluticasone furoate-umeclidinium bromide-vilanterol or Fluticasone furoate-vilanterol-umeclidinium or vilanterol-umeclidinium bromide-Fluticasone or vilanterol-Fluticasone furoate-umeclidinium or umeclidinium bromide-vilanterol-Fluticasone or umeclidinium bromide-Fluticasone furoate-vilanterol or Fluticasone-umeclidinium bromide-vilanterol or Fluticasone-vilanterol-umeclidinium or vilanterol-umeclidinium-Fluticasone or vilanterol-Fluticasone-umeclidinium or umeclidinium-vilanterol-Fluticasone or umeclidinium-Fluticasone-vilanterol or FF-UMEC-VI or FF-VI-UMEC or VI-UMEC-FF or VI-FF-UMEC or UMEC-FF-VI or UMEC-VI-FF or (FF adj2 UMEC adj2 VI)).mp.

13. ((beclometasone adj4 formoterol adj4 glycopyrronium) or beclometasone-formoterol-glycopyrronium or beclometasone-glycopyrronium-formoterol or formoterol-glycopyrronium-beclometasone or formoterol-beclometasone-glycopyrronium or glycopyrronium-formoterol-beclometasone or glycopyrronium-beclometasone-formoterol or (BEC adj2 FOR adj2 GLY) or BEC-FOR-GLY or BEC-GLY-FOR or GLY-FOR-BEC or GLY-BEC-FOR or FOR-BEC-GLY or FOR-GLY-BEC).mp.

14. ((Budesonide adj4 Glycopyrrolate adj4 Formoterol) or beclometasone dipropionate-formoterol fumarate-glycopyrronium or beclometasone dipropionate-glycopyrronium-formoterol fumarate or formoterol fumarate-glycopyrronium-beclometasone dipropionate or formoterol fumarate-beclometasone dipropionate-glycopyrronium or glycopyrronium-formoterol fumarate-beclometasone dipropionate or glycopyrronium-beclometasone dipropionate-formoterol fumarate or (BDP adj2 FF adj2 G$3) or BDP-FF-G$3 or BDP-G*-FF or G*-FF-BDP or G*-BDP-FF or FF-BDP-G$3 or FF-G*-BDP).mp.

15. ((UM adj2 FF adj2 VI) or UM-FF-VI or UM-VI-FF or FF-VI-UM or FF-UM-VI or VI-UM-FF or VI-FF-UM).mp.

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16. (ics adj2 laba adj2 lama).mp.

17. (Breztri* or Trixeo* or Riltrava* or Trelegy* or Elebrato* or Temybric* or Trimbow* or Trydonis* or Riarify*).mp.

18. or/11-17

19. (NCT01911364 or NCT01917331 or NCT02164513 or NCT02197975 or NCT02345161 or NCT02465567 or NCT02497001 or NCT02536508 or NCT02579850 or NCT02676076 or NCT02676089 or NCT02729051 or NCT02731846 or NCT02924688 or NCT02982187 or NCT03081247 or NCT03184987 or NCT03250182 or NCT03262012 or NCT03376932 or NCT03467425 or NCT03474081 or NCT03478683 or NCT03478696 or NCT03662711 or NCT03842904 or NCT03859414 or NCT03906045 or NCT03949842 or NCT04606394 or NCT04609878 or NCT04609904 or NCT04671355 or NCT04675463 or NCT05097014 or NCT05292053 or NCT05495698 or NCT05535972).af.

20. 8 or 18 or 19

21. limit 20 to english language

CDSR and CENTRAL via the Cochrane Library Search Strategy

1 (copd or Chronic Obstructive Pulmonary or asthma*):ti,ab

2 [mh Asthma] or [mh "Asthma, Exercise-Induced"] or [mh "Asthma, Occupational"] or [mh "Asthma, Aspirin-Induced"] or [mh "Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome"] or [mh "Pulmonary Disease, Chronic Obstructive"]

3 or 1-2

4 ((single* or one*) near/2 inhale* near/9 triple)

5 ((one* or single*) near/2 device* near/9 triple)

6 sitt device*

7 ("Triple Inhaled" near/3 Therap*) or (Triple-Inhaled near/3 Therap*)

8 or 4-7

9 ((TRIGGER or TRIMARAN or CAPTAIN or TRIBUTE or TRILOGY or TRINITY or INTREPID or CTT200812 or FULFIL or IMPACT or KRONOS or ETHOS or KALOS or LOGOS) near/1 (trial or study or random* or RCT)):ti,ab

10 3 and (8 or 9)

11 ((Budesonide near/4 Glycopyrrolate near/4 Formoterol) or Budesonide-Glycopyrrolate-Formoterol or Budesonide-Formoterol-Glycopyrrolate or Glycopyrrolate-Formoterol-Budesonide or Glycopyrrolate-Budesonide-Formoterol or Formoterol-Glycopyrrolate-Budesonide or Formoterol-Budesonide-Glycopyrrolate or BGFF or (BUD near/2 GLY near/2 FOR) or BUD-GLY-FOR or BUD-FOR-GLY or GLY-FOR-BUD or GLY-BUD-FOR or FOR-BUD-GLY or FOR-GLY-BUD)

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12 ((Fluticasone near/4 umeclidinium near/4 vilanterol) or Fluticasone furoate-umeclidinium bromide-vilanterol or Fluticasone furoate-vilanterol-umeclidinium or vilanterol-umeclidinium bromide-Fluticasone or vilanterol-Fluticasone furoate-umeclidinium or umeclidinium bromide-vilanterol-Fluticasone or umeclidinium bromide-Fluticasone furoate-vilanterol or Fluticasone-umeclidinium bromide-vilanterol or Fluticasone-vilanterol-umeclidinium or vilanterol-umeclidinium-Fluticasone or vilanterol-Fluticasone-umeclidinium or umeclidinium-vilanterol-Fluticasone or umeclidinium-Fluticasone-vilanterol or FF-UMEC-VI or FF-VI-UMEC or VI-UMEC-FF or VI-FF-UMEC or UMEC-FF-VI or UMEC-VI-FF or (FF near/2 UMEC near/2 VI))

13 ((beclometasone near/4 formoterol near/4 glycopyrronium) or beclometasone-formoterol-glycopyrronium or beclometasone-glycopyrronium-formoterol or formoterol-glycopyrronium-beclometasone or formoterol-beclometasone-glycopyrronium or glycopyrronium-formoterol-beclometasone or glycopyrronium-beclometasone-formoterol or (BEC near/2 FOR near/2 GLY) or BEC-FOR-GLY or BEC-GLY-FOR or GLY-FOR-BEC or GLY-BEC-FOR or FOR-BEC-GLY or FOR-GLY-BEC)

14 ((Budesonide near/4 Glycopyrrolate near/4 Formoterol) or beclometasone NEXT dipropionate-formoterol fumarate-glycopyrronium or beclometasone NEXT dipropionate-glycopyrronium-formoterol NEXT fumarate or formoterol NEXT fumarate-glycopyrronium-beclometasone dipropionate or formoterol NEXT fumarate-beclometasone dipropionate-glycopyrronium or glycopyrronium-formoterol NEXT fumarate-beclometasone NEXT dipropionate or glycopyrronium-beclometasone NEXT dipropionate-formoterol NEXT fumarate or (BDP near/2 FF near/2 GLY) OR (BDP near/2 FF near/2 GB))

15 BDP-GB-FF or GB-FF-BDP or GB-BDP-FF or FF-GB-BDP or BDP-FF-GLY or BDP-GLY-FF or GLY-FF-BDP or GLY-BDP-FF or FF-BDP-GLY or FF-GLY-BDP OR BDP-FF-GLY OR BDP-FF-GB OR FF-BDP-GLY OR FF-BDP-GB

16 ((UM near/2 FF near/2 VI) or UM-FF-VI or UM-VI-FF or FF-VI-UM or FF-UM-VI or VI-UM-FF or VI-FF-UM)

17 (ics near/2 laba near/2 lama)

18 (Breztri* or Trixeo* or Riltrava* or Trelegy* or Elebrato* or Temybric* or Trimbow* or Trydonis* or Riarify*)

19 or 11-18

20 (NCT01911364 or NCT01917331 or NCT02164513 or NCT02197975 or NCT02345161 or NCT02465567 or NCT02497001 or NCT02536508 or NCT02579850 or NCT02676076 or NCT02676089 or NCT02729051 or NCT02731846 or NCT02924688 or NCT02982187 or NCT03081247 or NCT03184987 or NCT03250182 or NCT03262012 or NCT03376932 or NCT03467425 or NCT03474081 or NCT03478683 or NCT03478696 or NCT03662711 or NCT03842904 or NCT03859414 or NCT03906045 or NCT03949842 or NCT04606394 or NCT04609878 or NCT04609904 or NCT04671355 or NCT04675463 or NCT05097014 or NCT05292053 or NCT05495698 or NCT05535972)

21 10 OR 19 OR 20

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22 10 OR 19 OR 20 in Cochrane Reviews

23 10 or 19 or 20 in Trials

Gray Literature Search Terms

- Asthma
- Breztri Aerosphere
- Chronic obstructive pulmonary disease
- COPD
- Single device triple therapy
- Single-inhaler triple therapy
- Trelegy
- Trimbow

Ongoing Studies

We searched the following DERP sources for ongoing studies using the search terms *asthma*, *COPD*, *triple therapy*, *single inhaler*, *single device*, and various abbreviations of the interventions of interest (e.g., FOR/GLY, FF/GLY):

- Astra Zeneca (for Breztri Aerosphere)
- Chiesi (for Trimbow)
- ClinicalTrials.gov
- GSK (formerly GlaxoSmithKline; for Trelegy Ellipta)
- International Clinical Trials Registry Platform (WHO)
- ScanMedicine
- US Food & Drug Administration (FDA)

Inclusion Criteria

Populations

- Adults and children with COPD or asthma

Interventions

- See Table A2 for SITTs of interest.

Table A2. Single-Inhaler Triple Therapy Treatments of Interest

Brand Name	Generic Name	Generic Name Abbreviation	Indication(s)	FDA Approval Date
Breztri Aerosphere[11]	Budesonide; glycopyrrolate; formoterol fumarate	BUD/GLY/FOR	• COPD	07/23/2020
Trelegy Ellipta[12]	Fluticasone furoate; umeclidinium bromide; vilanterol trifenatate	FLU/UMEC/VI	• COPD • Asthma (aged ≥ 18 years)	09/18/2017
Pipeline Therapies				
Breztri Aerosphere[11]	Budesonide; glycopyrrolate; formoterol fumarate	BUD/GLY/FOR	• Asthma	N/A
Trimbow[22]	Beclomethasone dipropionate; glycopyrronium bromide; formoterol fumarate dihydrate	BDP/GLY/FOR	• COPD • Asthma	N/A

Abbreviations. BDP: beclomethasone; BUD: budesonide; COPD: chronic obstructive pulmonary disease; FDA: US Food & Drug Administration; FOR: formoterol; FLU: fluticasone; GLY: glycopyrronium; N/A: not applicable; UMEC: umeclidinium; VI: vilanterol.

Comparators

- Another listed intervention
- Standard of care (e.g., monotherapy, dual therapy, or multiple-inhaler triple therapy [MITT])

Outcomes

- Forced expiratory volume in 1 second (FEV_1)
- Severe exacerbations
- Symptom control
- Use of rescue medications
- Quality of life, using validated scales (e.g., St. George's Respiratory Questionnaire [SGRQ])
- All-cause emergency department visits or hospital admissions
- Mortality
- Adverse events (AE), including AEs of special interest (e.g., pneumonia)
- Withdrawals due to AEs
- Serious adverse events (SAEs)

Study Designs

- Randomized controlled trials (RCTs)

Exclusion Criteria

We excluded studies if they were not published in English or were conducted in non-human animals. We also excluded studies and data of post hoc analyses.

Screening

One experienced researcher independently screened all titles and abstracts of identified documents. A second experienced researcher reviewed the results of the screening. Disagreement was managed by discussion. This method was repeated for full-text review of documents that could not be excluded by title and abstract screening.

Data Abstraction

One experienced researcher abstracted and entered data from eligible studies in a standardized way using Microsoft Word. A second experienced researcher reviewed all the data entered. We attempted to resolve discrepancies through discussion. When discussion did not resolve the issue, a third experienced researcher settled disagreements.

Participant Characteristics and Association with Outcomes

When discussing risk and protective factors or variables in statistical models in DERP research products, in almost all cases, we are referring to associations of participant characteristics with outcomes, and not causation of outcomes. This is important because participant characteristics, such as race and ethnicity, serve as proxy or surrogate measures for underlying etiological factors not measured or evaluated in analyses. Etiological factors that might cause differences in

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outcomes for subgroups of participants could include systemic racism or other forms of systemic discrimination, stress, poverty, housing instability, or epigenetics. For example, by describing any differences in outcomes by race and ethnic groups, we are noting observed associations; these associations are not caused by biological determinants of being Black, White, or Hispanic.

Risk of Bias Assessment

We assessed the risk of bias of the included RCTs using standard instruments developed and adapted by DERP that are modifications of instruments used by national and international standards for quality.[71,72] One experienced researcher independently rated the risk of bias of included studies. A second experienced researcher reviewed each assessment. Disagreement was managed by discussion.

Randomized Controlled Trials

Low-risk-of-bias RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Low-risk-of-bias RCTs also have low potential for bias from conflicts of interest and funding source(s). Moderate-risk-of-bias RCTs have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. High-risk-of-bias RCTs have clear flaws that could introduce significant bias.

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Appendix B. Full Evidence Tables

Table B1. Full Evidence Table for Asthma RCTs

Study Name Trial Number Location Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
CAPTAIN[35] NCT02924688 US + multinational 24 to 52 weeks Trelegy (UMEC 31.25 µg), n = 809 Trelegy (UMEC 62.5 µg), n = 814 FLU/VI, n = 813	Trough FEV_1, between-treatment difference, mean CFB at week 24 • Trelegy (UMEC 31.25 µg) vs. FLU/VI: 89 ml (95% CI, 58 to 120); *P* < .001 • Trelegy (UMEC 62.5 µg) vs. FLU/VI: 101 ml (95% CI, 70 to 132); *P* < .001 Trough FEV_1 mean CFB at week 24 • Trelegy (UMEC 31.25 µg): 151 ml (95% CI, 129 to 172); *P*, NR • Trelegy (UMEC 62.5 µg): 139 ml (95% CI, 117 to 161); *P*, NR • FLU/VI: 50 ml (95% CI, 28 to 72); *P*, NR	Experienced ≥ 1 moderate or severe exacerbations at any time during study, n (%) • Trelegy (UMEC 31.25 µg): 367 (45.4%); 185 severe events • Trelegy (UMEC 62.5 µg): 329 (40.4%); 182 severe events • FLU/VI: 379 (46.6%); 179 severe events Annualized rate of severe exacerbation, over 52 weeks • Trelegy (UMEC 31.25 µg) vs. FLU/VI: adjusted rate ratio, 0.99 (95% CI, 0.77 to 1.29); *P* = 1.0 • Trelegy (UMEC 62.5 µg) vs. adjusted rate ratio, 0.97 (95% CI, 0.75 to 1.26); *P* = .8 Annualized rate of moderate or severe exacerbations, weeks 1 to 52 • Trelegy (UMEC 31.25 µg) vs. FLU/VI: adjusted rate ratio, 0.97 (95% CI, 0.81 to 1.17); *P* = .8 • Trelegy (UMEC 61.5 µg) vs. FLU/VI: adjusted rate ratio, 0.87 (95% CI, 0.72 to 1.05); *P* = .1	ACQ-7, at week 24 Mean CFB • Trelegy (UMEC 31.25 µg): −0.73 (95% CI, −0.78 to −0.69); *P*, NR • Trelegy (UMEC 62.5 µg): −0.77 (95% CI, −0.81 to −0.72); *P*, NR • FLU/VI: −0.68 (95% CI, −0.73 to −0.63); *P*, NR Mean between-treatment difference CFB • Trelegy (UMEC 31.25 µg) vs. FLU/VI: −0.06 (95% CI, −0.12 to 0.01); *P* = .1 • Trelegy (UMEC 62.5 µg) vs. FLU/VI: −0.09 (95% CI, −0.16 to −0.02); *P* = .008 Responders (decrease of ≥ 0.5 CFB) • Trelegy (UMEC 31.25 µg) vs. FLU/VI: aOR, 1.15 (95% CI, 0.94 to 1.42); *P* = .2	Any AE • FLU/VI: 468 of 813 (57.6%) • Trelegy (UMEC 31.25 µg), 465 of 810 (57.4%) • Trelegy (UMEC 62.5 µg), 456 of 814 (56.0%) Any TEAE • FLU/VI: 38 of 813 (4.7%) • Trelegy (UMEC 31.25 µg), 36 of 810 (4.4%) • Trelegy (UMEC 62.5 µg), 48 of 814 (5.9%) Any SAE • FLU/VI: 46 of 813 (4.6%) • Trelegy (UMEC 31.25 µg), 41 of 810 (5.1%)

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Study Name Trial Number Location Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
		Use of Rescue Medication, over 24 weeks Percentage of rescue-free days Mean CFB • Trelegy (UMEC 31.25 µg): 13.72 (95% CI, 12.08 to 15.35); *P*, NR • Trelegy (UMEC 62.5 µg): 13.11 (95% CI, 11.48 to 14.74); *P*, NR • FLU/VI: 10.94 (95% CI, 9.29 to 12.59); *P*, NR Mean between-treatment difference CFB • Trelegy (UMEC 31.25 µg): 2.78 (95% CI, 0.45 to 5.10); *P* = .02 • Trelegy (UMEC 62.5 µg): 2.17 (95% CI, −0.15 to 4.49); *P* = .07 Daily rescue medication use, puffs per day • Trelegy (UMEC 31.25 µg): mean 1.5 (SD, 2.04); mean CFB, −0.5 (95% CI, −0.6 to −0.5); *P*, NR • Trelegy (UMEC 62.5 µg): mean 1.4 (SD, 1.92); mean CFB, −0.4 (95% CI, −0.5 to −0.4); *P*, NR • FLU/VI: mean, 1.4 (SD, 1.95); mean CFB, −0.4 (95% CI, −0.4 to −0.3); *P*, NR	• Trelegy (UMEC 62.5 µg) vs. FLU/VI: aOR, 1.43 (95% CI, 1.16 to 1.76); *P* < .001 SGRQ, at week 24 Mean CFB • Trelegy (UMEC 31.25 µg): −10.29 (95% CI, −11.26 to −9.32); *P*, NR • Trelegy (UMEC 62.5 µg): −11.69 (95% CI, −12.64 to −10.73); *P*, NR • FLU/VI: −11.39 (95% CI, −12.35 to −10.42); *P*, NR Mean between-treatment difference CFB • Trelegy (UMEC 31.25 µg) vs. FLU/VI: 1.10 (95% CI, −0.27 to 2.47); *P* = .1 • Trelegy (UMEC 62.5 µg) vs. FLU/VI: −0.30 (95% CI, −1.66 to 1.05); *P* = .7 Responders (decrease of ≥ 4 CFB) • Trelegy (UMEC 31.25 µg) vs. FLU/VI: OR, 0.86 (95% CI, 0.69 to 1.06); *P* = .1	• Trelegy (UMEC 62.5 µg), 44 of 814 (5.4%) Withdrawal due to AE • FLU/VI: 16 of 813 (2.0%) • Trelegy (UMEC 31.25 µg), 11 of 810 (1.3%) • Trelegy (UMEC 62.5 µg), 10 of 814 (1.2%) Fatalities due to AE • FLU/VI: 1 of 814 (< 1%) • Trelegy (UMEC 31.25 µg), 2 of 810 (< 1%) • Trelegy (UMEC 62.5 µg), 0 AESIs MACEs • FLU/VI: 7 of 814 (< 1%) • Trelegy (UMEC 31.25 µg), 6 of 810 (< 1%)

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Study Name Trial Number Location Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
		Mean between-treatment difference CFB at week 24 • Trelegy (UMEC 31.25 µg) vs. FLU/VI: −0.2 (95% CI, −0.2 to −0.1); *P* < .001 • Trelegy (UMEC 62.5 µg) vs. FLU/VI: 0 (95% CI, −0.1 to 0.0); *P* = .3	• Trelegy (UMEC 62.5 µg) vs. FLU/VI: OR, 1.14 (95% CI, 0.92 to 1.42); *P* = .2	• Trelegy (UMEC 62.5 µg), 7 of 813 (< 1%) Pneumonia • FLU/VI: 14 of 814 (2%) • Trelegy (UMEC 31.25 µg), 13 of 809 (1%) • Trelegy (UMEC 62.5 µg), 9 of 814 (1%)

Note. CAPTAIN was a 6-arm RCT, but researchers pooled groups for analyses: Trelegy (UMEC 31.25 µg), n = 809; Trelegy (UMEC 62.5 µg), n = 814; FLU/VI, n = 813.

Abbreviations. ACQ-7: Asthma Control Questionnaire, 7-item; AE: adverse event; AESI: adverse event of special interest; CFB: change from baseline; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FLU: fluticasone; HRQoL: health-related quality of life; MACE: major adverse cardiovascular event; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; SGRQ: St. George's Respiratory Questionnaire; TEAE: treatment-emergent adverse event; UMEC: umeclidinium; VI: vilanterol.

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Table B2. Full Evidence Table of RCTs Comparing Breztri to Other COPD Treatments

Study Name Trial Number Location Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
ETHOS[42] NCT02465567 US + multinational 52 weeks Breztri (BUD 320 µg), n=2,157 Breztri (BUD 160 µg), n=2,137 GLY/FOR, n=2,143 BUD/FOR, n=2,151	FEV_1, NR for whole participant population Very-severe COPD subgroup (n = 3,088)[43] Breztri (BUD 320 µg, n = 747) Breztri (BUD 160 µg, n = 807) GLY/FOR (n = 779) BUD/FOR (n = 755) Trough FEV_1, between-treatment difference CFB, over 24 weeks[43] • Breztri (BUD 320 µg) vs. GLY/FOR: 43 ml (95% CI, 25 to 60); *P* < .001 • Breztri (BUD 160 µg) vs. GLY/FOR: 30 ml (95% CI, 12 to 47); *P* < .001 • Breztri (BUD 320 µg) vs. BUD/FOR: 76 ml (95% CI, 58 to 94); *P* < .001 • Breztri (BUD 160 µg) vs. BUD/FOR: 63 ml (95% CI, 46 to 81); *P* < .001	Annual rate of moderate or severe exacerbations, between • Breztri (BUD 320 µg) vs. GLY/FOR: rate ratio, 0.76 (95% CI, 0.69 to 0.83); *P* < .001 • Breztri (BUD 320 µg) vs. BUD/FOR: rate ratio, 0.87 (95% CI, 0.79 to 0.95); *P* = .003 • Breztri (BUD 160 µg) vs. GLY/FOR: rate ratio, 0.75 (95% CI, 0.69 to 0.83); *P* < .001 • Breztri (BUD 160 µg) vs. BUD/FOR: rate ratio, 0.86 (95% CI, 0.79 to 0.95); *P* = .002 Time-to-first moderate or severe COPD exacerbation over 52 weeks • Breztri (BUD 320 µg) vs. GLY/FOR: HR, 0.88 (95% CI, 0.81 to 0.96); *P* = .004 • Breztri (BUD 320 µg) vs. BUD/FOR: HR,	SGRQ mean CFB at week 52 • Breztri (BUD 320 µg), −6.4 (SE, 0.35) vs. GLY/FOR, −4.5 (SE, 0.36); mean difference, −1.88 (95% CI, −2.84 to −0.91) • Breztri (BUD 320 µg), −6.4 (SE, 0.35) vs. BUD/FOR, −4.9 (SE, 0.36); mean difference, −1.47 (95% CI, −2.43 to −0.51) • Breztri (BUD 160 µg), −6.0 (SE, 0.36) vs. GLY/FOR, −4.5 (SE, 0.36); mean difference, −1.51 (95% CI, −2.48 to −0.54) • Breztri (BUD 160 µg), −6.0 (SE, 0.36) vs. BUD/FOR, −4.9 (SE, 0.36); mean difference, −1.10 (95% CI, −2.06 to −0.14) • Breztri (BUD 320 µg), −6.4 (SE, 0.35) vs Breztri (BUD 160 µg), −6.0 (SE, 0.36); mean difference, −0.37 (95% CI, −1.32 to 0.59) SGRQ	Safety population Breztri (BUD 320 µg), n = 2,144 Breztri (BUD 160 µg), n = 2,124 GLY/FOR, n = 2,125 BUD/FOR, n = 2,136 Any AE • Breztri (BUD 320 µg): 1,368 (63.8%); 4,527 events • Breztri (BUD 160 µg): 1,356 (63.8%); 4,382 events • GLY/FOR: 1,312 (61.7%); 4,074 events • BUD/FOR: 1,377 (64.5%); 4,746 events Any SAE • Breztri (BUD 320 µg): 426 (19.9%); 664 events • Breztri (BUD 160 µg): 445 (21.0%); 681 events • GLY/FOR: 433 (20.4%); 639 events • BUD/FOR: 440 (20.6%); 653 events

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Study Name Trial Number Location Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs

	Trough FEV_1, between-treatment difference CFB, over 52 weeks[43]
	• Breztri (BUD 320 µg) vs. GLY/FOR: 46 ml (95% CI, 27 to 64); *P* < .001
	• Breztri (BUD 160 µg) vs. GLY/FOR: 36 ml (95% CI, 18 to 54); *P* < .001
	• Breztri (BUD 320 µg) vs. BUD/FOR: 72 ml (95% CI, 54 to 90); *P* < .001
	• Breztri (BUD 160 µg) vs. BUD/FOR: 62 ml (95% CI, 45 to 80); *P* < .001
	
	<u>Subgroup analyses</u>
	Trough FEV_1, between-treatment difference, over 24 weeks
	
	Prior ICS[44]
	Breztri (BUD 320 µg, n = 538)
	Breztri (BUD 160 µg, n = 596)
	GLY/FOR (n = 538)
	
	• Breztri (BUD 320 µg) vs. GLY/FOR: 42 ml (95% CI, 22 to 62); *P* < .001
	• Breztri (BUD 160 µg) vs. GLY/FOR: 31 ml (95% CI, 12 to 51); *P* = .002
		0.89 (95% CI, 0.81 to 0.97); *P* = .006
		• Breztri (BUD 160 µg) vs. GLY/FOR: HR, 0.87 (95% CI, 0.79 to 0.94); *P* = .001
		• Breztri (BUD 160 µg) vs. BUD/FOR: HR, 0.87 (95% CI, 0.80 to 0.95); *P* = .002
		
		Patients with ≥ 2 exacerbations in previous year (n = 4,810)
		Annual rate of moderate or severe exacerbations
		• Breztri (BUD 320 µg) vs. GLY/FOR: rate ratio, 0.73 (95% CI, 0.65 to 0.83)
		• Breztri (BUD 320 µg) vs. BUD/FOR: rate ratio, 0.89 (95% CI, 0.79 to 1.01); *P*, NR
		• Breztri (BUD 160 µg) vs. GLY/FOR: rate ratio, 0.72 (95% CI, 0.64 to 0.81); *P*, NR
		• Breztri (BUD 160 µg) vs. BUD/FOR: rate ratio, 0.88 (95% CI, 0.77 to 0.99); *P*, NR
			Responders (CFB decrease of ≥ 4 units)
			• Breztri (BUD 320 µg) vs. GLY/FOR: OR, 1.4 (95% CI, 1.2 to 1.6); *P*, NR
			• Breztri (BUD 320 µg) vs. BUD/FOR: OR, 1.2 (95% CI, 1.1 to 1.4); *P*, NR
			• Breztri (BUD 160 µg) vs. GLY/FOR: OR, 1.3 (95% CI, 1.1 to 1.5); *P*, NR
			• Breztri (BUD 160 µg) vs. BUD/FOR: OR, 1.2 (95% CI, 1.0 to 1.3); *P*, NR
			
			Total score, mean between-treatment difference CFB, over 52 weeks[40]
			• Breztri (BUD 320 µg)
			  ○ GLY/FOR: −1.59 (95% CI, −2.27 to −0.91); *P* < .001
			  ○ BUD/FOR: −1.31 (95% CI, −1.99 to −0.64); *P* < .001
			• Breztri (BUD 160 µg)
			  ○ GLY/FOR: −1.34 (95% CI, −2.02 to −0.66); *P* < .001
			  ○ BUD/FOR: −1.06 (95% CI, −1.74 to −0.39); *P* = .002
				Withdrawal due to AE
				• Breztri (BUD 320 µg): 119 (5.6%); 150 events
				• Breztri (BUD 160 µg): 112 (5.3%); 146 events
				• GLY/FOR: 146 (6.9%); 187 events
				• BUD/FOR: 140 (6.6%); 160 events
				
				AESIs
				MACEs
				• Breztri (BUD 320 µg): 31 (1.4%); 32 events
				• Breztri (BUD 160 µg): 30 (1.4%); 31 events
				• GLY/FOR: 44 (2.1%); 47 events
				• BUD/FOR: 23 (1.1%); 24 events
				
				Pneumonia
				• Breztri (BUD 320 µg): 90 (4.2%); 93 events
				• Breztri (BUD 160 µg): 75 (3.5%); 78 events
				• GLY/FOR: 48 (2.3%); 51 events
				• BUD/FOR: 96 (4.5%); 106 events

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Study Name Trial Number Location Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs

	• Breztri (BUD 320 µg) vs. BUD/FOR: NR
	
	No Prior ICS[44]
	Breztri (BUD 320 µg, n = 184)
	Breztri (BUD 160 µg, n = 169)
	GLY/FOR (n = 175)
	
	• Breztri (BUD 320 µg) vs. GLY/FOR: 44 ml (95% CI, 7 to 81); *P* = .02
	• Breztri (BUD 160 µg) vs. GLY/FOR: 32 ml (95% CI, −6 to 70); *P* = .1
		<u>Use of rescue medication, mean between-treatment difference, over 52 weeks</u>
		Percentage of rescue-free days
		• Breztri (BUD 320 µg) vs. GLY/FOR: 4.98 (95% CI, 2.84 to 7.12); *P* < .001
		• Breztri (BUD 320 µg) vs. BUD/FOR: 4.34 (95% CI, 2.22 to 6.47); *P* < .001
		• Breztri (BUD 160 µg) vs. GLY/FOR: 2.83 (95% CI, 0.68 to 4.98); *P* = .01
		• Breztri (BUD 160 µg) vs. BUD/FOR: 2.19 (95% CI, 0.06 to 4.33); *P* = .04
		
		Puffs per day, CFB
		• Breztri (BUD 320 µg) vs. GLY/FOR: −0.53 (95% CI, −0.71 to −0.34); *P* < .001
		• Breztri (BUD 320 µg) vs. BUD/FOR: −0.35 (95% CI, −0.53 to −0.17); *P* < .001
			SGRQ, responders, over 52 weeks[40]
			• Breztri (BUD 320 µg)
			  ○ GLY/FOR: OR, 1.46 (95% CI, 1.28 to 1.65); *P* < .001
			  ○ BUD/FOR: OR, 1.27 (95% CI, 1.12 to 1.44); *P* < .001
			• Breztri (BUD 160 µg)
			  ○ GLY/FOR: OR, 1.42 (95% CI, 1.25 to 1.61); *P* < .001
			  ○ BUD/FOR: OR, 1.24 (95% CI, 1.09 to 1.40); *P* < .001
				Risk of death from any cause
				• Breztri (BUD 320 µg) vs. GLY/FOR: HR, 0.54 (95% CI, 0.34 to 0.87); *P*, NR
				• Breztri (BUD 320 µg) vs. BUD/FOR: HR, 0.78 (95% CI, 0.47 to 1.30); *P*, NR
				• Breztri (BUD 160 µg) vs. GLY/FOR: HR, 0.79 (95% CI, 0.52 to 1.20); *P*, NR
				• Breztri (BUD 160 µg) vs. BUD/FOR: HR, 1.13 (95% CI, 0.72 to 1.80); *P*, NR
				
				Bone fracture
				• Breztri (BUD 320 µg): 46 (2.1%)
				• Breztri (BUD 160 µg): 38 (1.8%)
				• GLY/FOR: 44 (2.1%)
				• BUD/FOR: 46 (2.2%)

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Study Name Trial Number Location Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
		• Breztri (BUD 160 µg) vs. GLY/FOR: −0.34 (95% CI, −0.53 to −0.16); *P* < .001 • Breztri (BUD 160 µg) vs. BUD/FOR: −0.16 (95% CI, −0.35 to 0.02); *P* = .08 <u>Shortness of breath, over 52 weeks</u> TDI, focal score, between-treatment difference • Breztri (BUD 320 µg) vs. GLY/FOR: 0.34 (95% CI, 0.19 to 0.49); *P* < .001 • Breztri (BUD 320 µg) vs. BUD/FOR: 0.26 (95% CI, 0.11 to 0.41); *P* < .001 • Breztri (BUD 160 µg) vs. GLY/FOR: 0.34 (95% CI, 0.18 to 0.49); *P* < .001 • Breztri (BUD 160 µg) vs. BUD/FOR: 0.26 (95% CI, 0.11 to 0.41); *P* < .001		

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Study Name Trial Number Location Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
		TDI, responders • Breztri (BUD 320 µg) vs. GLY/FOR: OR, 1.19 (95% CI, 1.05 to 1.35); *P* = .005 • Breztri (BUD 320 µg) vs. BUD/FOR: OR, 1.16 (95% CI, 1.02 to 1.31); *P* = .02 • Breztri (BUD 160 µg) vs. GLY/FOR: OR, 1.20 (95% CI, 1.06 to 1.36); *P* = .004 Breztri (BUD 160 µg) vs. BUD/FOR: OR, 1.17 (95% CI, 1.03 to 1.32); *P* = .01		
KRONOS[29] NCT02497001 US + multinational 24 weeks Breztri, n=639 GLY/FOR_{MDI}, n=625 BUD/FOR_{MDI}, n=314 BUD/FOR_{DPI}, n=318	Trough FEV_1, mean CFB at week 24 • Breztri: 147 ml (SE, 6.5) • GLY/FOR_{MDI}: 125 ml (SE, 6.6) • BUD/FOR_{MDI}: 73 ml (SE, 9.2) • BUD/FOR_{DPI}: 88 ml (SE, 9.1) Trough FEV_1, between-treatment difference, CFB at week 24 • GLY/FOR_{MDI}: 22 ml (95% CI, 4 to 39); *P* = .01	Annualized rate of moderate or severe exacerbations • Breztri, 0.46 vs. GLY/FOR_{MDI}, 0.95; rate ratio, 0.48 (95% CI, 0.37 to 0.64); *P* < .001 • Breztri, 0.46 vs. BUD/FOR_{MDI}, 0.56; rate ratio, 0.82 (95% CI, 0.58 to 1.17); *P* = 0.3 • Breztri, 0.46 vs. BUD/FOR_{DPI}, 0.55;	<u>SGRQ</u> Total score, mean between-treatment difference CFB at week 24 • GLY/FOR_{MDI}: −1.22 (95% CI, −2.30 to −0.15); *P* = .03 • BUD/FOR_{MDI}: −0.45 (95% CI, −1.78 to 0.87); *P* = .5 • BUD/FOR_{DPI}: −1.26 (95% CI, −2.58 to 0.06); *P* = .06 <u>Rescue medication</u> Note: Breztri, n = 293; GLY/FOR_{MDI}, n = 269;	Any TEAE • Breztri: 388 (61%) • GLY/FOR_{MDI}:384 (61%) • BUD/FOR_{MDI}: 175 (56%) • BUD/FOR_{DPI}: 183 (58%) Serious TEAEs • Breztri: 55 (9%) • GLY/FOR_{MDI}: 68 (11%) • BUD/FOR_{MDI}: 21 (7%) • BUD/FOR_{DPI}: 29 (9%) Withdrawal due to TEAEs • Breztri: 30 (5%) • GLY/FOR_{MDI}: 30 (5%)

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Study Name Trial Number Location Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
	• BUD/FOR_{MDI}: 74 ml (95% CI, 52 to 95); *P* < .001 • BUD/FOR_{DPI}: 59 ml (95% CI, 30 to 80); *P* < .001 Time to clinically important deterioration • GLY/FOR_{MDI}: HR, 0.88 (95% CI, 0.76 to 1.0); *P* = .06 • BUD/FOR_{MDI}: HR, 0.83 (95% CI, 0.70 to 0.98); *P* = .03 • BUD/FOR_{DPI}: HR, 0.81 (95% CI, 0.69 to 0.96); *P* = .01 In US population only, trough FEV_1, between-treatment difference CFB, overall • GLY/FOR_{MDI}: 22 ml (95% CI, 4 to 39); *P* = .01 • BUD/FOR_{MDI}: 74 ml (95% CI, 52 to 95); *P* < .001 • BUD/FOR_{DPI}: NR	rate ratio, 0.83 (0.59 to 1.18); *P* = .3 Time-to-first exacerbation • GLY/FOR_{MDI}: HR, 0.59 (95% CI, NR); *P* < .001 • BUD/FOR_{MDI}: HR, 0.75 (95% CI, NR); *P* = .06 • BUD/FOR_{DPI}: NR <u>Shortness of breath</u> TDI focal score, between-treatment difference CFB, overall • GLY/FOR_{MDI}: 0.18 (95% CI, −0.07 to 0.43); *P* = .1 • BUD/FOR_{MDI}: 0.24 (95% CI, −0.07 to 0.54); *P* = .1 • BUD/FOR_{DPI}: 0.46 (95% CI, 0.16 to 0.77); *P* = .003	BUD/FOR_{MDI}, n = 141; BUD/FOR_{DPI}, n = 155 Average puffs per day • Breztri, −1.3 (SE, 0.13) vs. GLY/FOR_{MDI}, −1.1 (SE, 0.13); −0.25 (95% CI, −0.60 to 0.09); *P* = .14 • Breztri, −1.3 (SE, 0.13 vs. BUD/FOR_{MDI}, −1.1 (SE, 0.18); −0.24 (95% CI, −0.65 to 0.18); *P* = .3 • Breztri, −1.3 (SE, 0.13 vs. BUD/FOR_{DPI}, −1.6 (SE, 0.17); 0.23 (95% CI, −0.17 to 0.63); *P* = .3	• BUD/FOR_{MDI}: 11 (4%) • BUD/FOR_{DPI}: 11 (3%) All-cause deaths • Breztri: 6 (1%) • GLY/FOR_{MDI}: 3 (< 1%) • BUD/FOR_{MDI}: 2 (1%) • BUD/FOR_{DPI}: 1 (< 1%) <u>AESIs</u> Pneumonia • Breztri: 12 (2%) • GLY/FOR_{MDI}: 10 (2%) • BUD/FOR_{MDI}: 6 (2%) • BUD/FOR_{DPI}: 4 (1%) MACEs • Breztri: 2 (< 1%) • GLY/FOR_{MDI}: 3 (< 1%) • BUD/FOR_{MDI}: 2 (1%) • BUD/FOR_{DPI}: 2 (1%)

Abbreviations. AE: adverse event; AESI: adverse event of special interest; BUD: budesonide; CFB: change from baseline; CI: confidence interval; COPD: chronic obstructive pulmonary disease; DPI: dry-powder inhaler; FEV_1: forced expiratory volume in 1 second; FOR: formoterol; GLY: glycopyrrolate; HR: hazard ratio; HRQoL: health-related quality of life; ICS: inhaled corticosteroids; MACE: major adverse cardiovascular event; MDI: metered-dose inhaler; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; SAE: serious adverse event; SE: standard error; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnea Index; TEAE: treatment-emergent adverse event.

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Table B3. Full Evidence Table of RCTs Comparing Trelegy to Other COPD Treatments

Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
Bansal, 2021[23] NCT03474081 US + Poland and Russia 12 weeks Trelegy, n = 400 TIO, n = 400	Trough FEV_1, between-treatment difference, mean CFB • At 12 weeks: 87 ml (95% CI, 56 to 118); *P* < .001 • At 12 weeks + 1 day: 95 ml (95% CI, 62 to 128); *P* < .001	Experienced an exacerbation at any time during trial • Moderate/severe: Trelegy, 27 of 400 (6.7%) vs. TIO, 43 of 400 (10.7%) • Severe: Trelegy, 5 of 400 (1.2%) vs. TIO, 3 of 400 (0.7%)	At 12 weeks SGRQ • Total score, between-treatment difference, mean CFB: −3.2 (−5.0 to −1.4); *P* < .001 • Responder (score CFB ≥ 4 unit decrease): OR, 1.62 (95% CI, 1.22 to 2.17); *P* = .001 CAT • Score, between-treatment difference, mean CFB: −1.2 (95% CI, −1.9 to −0.5); *P* = .001 • Responder (score decrease ≥ 2 CFB): OR, 1.15 (95% CI, 0.86 to 1.53); *P* = .35	Any AE: • Trelegy, 127 of 400 (31.7%); number of events, 236 • TIO, 115 of 400 (28.7%); number of events, 248 Any TEAE: • Trelegy 11 of 400 (2.7%); number of events, 18 • TIO, 4 of 400 (1.0%); number of events, 21 Any SAE: • Trelegy, 13 of 400 (3.2%); number of events, 17 • TIO, 10 of 400 (2.5%); number of events, 12 Withdrawal due to AE: • Trelegy, 7 of 400 (1.7%); number of events, 10

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
				• TIO, 3 of 400 (0.7%); number of events, 3 AESIs Cardiovascular effects: • Trelegy, 11 of 400 (2.7%); number of events, 13 • TIO, 11 of 400 (2.7%); number of events, 18 Decreased BMD and associated fractures: • Trelegy, 2 of 400 (0.5%); number of events, 2 • TIO, 0 Pneumonia: • Trelegy, 3 of 400 (0.7%); number of events, 3 • TIO, 3 (0.7%); number of events, 3
Bremner, 2018[25] NCT02729051 Multinational 24 weeks	Trough FEV_1, between-treatment difference, mean CFB at week 24	Exacerbations At any time during trial period	SGRQ • Total score, mean: Trelegy, -5.8 (95% CI, -7.0 to -4.7) vs.	Any AE: • Trelegy, 255 of 527 (48.4%)

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
Trelegy, n = 527 FLU/VI+UMEC, n = 528	• 26 ml (95% CI, −2 to 53); *P*, NSS	• Moderate/severe: Trelegy, 129 of 527 (24.4%) vs. FLU/VI+UMEC, 142 of 528 (26.9%) • Severe: Trelegy, 22 of 527 (4%) vs. FLU/VI+UMEC, 31 of 528 (6%) Time-to-first moderate/severe exacerbation • HR, 0.87 (95% CI, 0.68 to 1.12); *P*, NR <u>TDI, at week 24</u> Focal score, mean: • Trelegy, 2.0 (95% CI, 1.8 to 2.3) vs. FLU/VI+UMEC, 1.9 (95% CI, 1.6 to 2.1); between-treatment difference, 0.1 (95% CI −0.2 to 0.5); *P*, NR Responders • Trelegy, 295 of 527 (56%) vs. FLU/VI+UMEC, 296 of 528 (56%); OR, 0.95 (95% CI, 0.72 to 1.25); *P*, NR	FLU/VI+UMEC, -4.9 (95% CI, -6.1 to -3.8); between-treatment difference, at week 24: −0.9 (95% CI, −2.5 to 0.7) • Responder (score CFB ≥ 4 unit decrease): Trelegy, 263 of 527 (50%) vs. FLU/VI+UMEC, 269 of 528 (51%); OR, 0.92 (95% CI, 0.71 to 1.20); *P*, NR	• FLU/VI+UMEC, 253 of 528 (47.9%) Any TEAE: • Trelegy, 27 of 527 (5.1%) • FLU/VI+UMEC, 19 of 528 (3.6%) Any SAE: • Trelegy, 52 of 527 (9.9%) • FLU/VI+UMEC, 57 of 528 (10.8%) Fatal SAE: • Trelegy, 4 of 527 (0.7%) • FLU/VI+UMEC, 4 of 528 (0.7%) <u>AESIs</u> Cardiovascular events: • Trelegy, 30 of 527 (5.7%) • FLU/VI+UMEC, 28 of 528 (5.3%)

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
				Decreased BMD and associated fractures: • Trelegy, 5 of 527 (0.9%) • FLU/VI+UMEC, 6 of 528 (1.1%) Pneumonia: • Trelegy, 14 of 527 (2.6%) • FLU/VI+UMEC, 21 of 528 (4.0%)
Ferguson, 2020[28] NCT03478683 NCT03478696 US + multinational 12 weeks Trelegy, n = 729 BUD/FOR+TIO, n = 731	At 12 weeks Trelegy, n = 690; BUD/FOR+TIO, n = 683 Trough FEV_1, Mean CFB, • At day 84: Trelegy, 32 ml (95% CI, 18 to 46) vs. BUD/FOR+TIO, −24 ml (95% CI, −37 to −10); between-treatment difference, 56 ml (95% CI, 37 to 75); *P*, NR • At day 85: Trelegy, 28 ml (95% CI, 13 to 42) vs. BUD/FOR+TIO, −17 ml (95% CI, −32 to −2); between-treatment difference,	NR	At week 12 <u>SGRQ</u> Total score • Mean CFB: Trelegy, −1.4 (95% CI, −2.1 to −0.6) vs. BUD/FOR+TIO, −1.4 (95% CI, −2.1 to −0.6); between-treatment difference, 0.0 (95% CI, −1.0 to 1.1); *P* = .9 Responders • Trelegy, 241 of 688 (35%) vs. BUD/FOR+TIO, 236 of 687 (34%); OR, 1.05 (95% CI, 0.84 to 1.31); *P* = .7	Any AE • Trelegy, 223 (30.6%); 449 events • BUD/FOR+TIO, 230 (31.5%); 408 events Drug-related AE • Trelegy, 32 (4.4%); 46 events • BUD/FOR+TIO, 26 (3.5%); 31 events Any SAE • Trelegy, 37 (5.1%); 60 events

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
	45 ml (95% CI, 24 to 65); *P*, NR <u>Subgroup analyses</u> Trough FEV_1 at day 84, Between-treatment difference CFB • Age < 65: 74 ml (95% CI, 46 to 102); *P*, NR • Age ≥ 65: 41 ml (95% CI, 15 to 67); *P*, NR Trough FEV_1 at day 85, Between-treatment difference CFB • Age < 65: 65 ml (95% CI, 34 to 95); *P*, NR • Age ≥ 65: 28 ml (95% CI, 0 to 56); *P*, NR		<u>CAT</u> Score • Mean CFB: Trelegy, −0.5 (95% CI, −0.9 to −0.2) vs. BUD/FOR+TIO, −0.2 (95% CI, −0.6 to 0.2); between-treatment difference, −0.3 (95% CI, −0.9 to 0.2); *P* = .20 Responders • Trelegy, 263 of 693 (38%) vs. BUD/FOR+TIO, 256 of 692 (37%); OR, 1.04 (95% CI, 0.83 to 1.30); *P* = .7	• BUD/FOR+TIO, 31 (4.2%); 40 events Fatal SAE • Trelegy, 0 • BUD/FOR+TIO, 1 (< 1%) Withdrawal due to any AE • Trelegy, 9 (1.2%) • BUD/FOR+TIO, 12 (1.6%) <u>AESIs</u> Cardiovascular effects • Trelegy, 21 (2.9%); 24 events • BUD/FOR+TIO, 16 (2.2%); 21 events Pneumonia • Trelegy, 7 (1.0%); 7 events • BUD/FOR+TIO, 9 (1.2%); 11 events

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
				Decreased BMD and associated fractures • Trelegy, 7 (1.0%); 9 events • BUD/FOR+TIO, 7 (< 1%); 7 events
FULFIL[30,36,41,46] NCT02345161 Multinational 24 weeks Trelegy, n = 911 BUD/FOR, n = 899 Extension study (up to 52 weeks) Trelegy, n = 210 BUD/FOR, n = 220 Note: CID defined as: moderate/severe exacerbation and/ or ≥ 4-unit deterioration from baseline in SGRQ total score and/or ≥ 100 ml deterioration from baseline in FEV_1 (SGRQ-containing CID)	At week 24 Trough FEV_1, mean CFB • Trelegy, 142 ml (95% CI, 126 to 158) vs. BUD/FOR, −29 ml (95% CI, −46 to −13); mean between-treatment difference, 171 ml (95% CI, 148 to 194); *P* < .001 Responders • Trelegy, 453 of 907 (49.9%) vs. BUD/FOR, 184 of 892 (20.6%); OR, 4.03 (95% CI, 3.27 to 4.97); *P* < .001 At week 52 (extension study, n = 430) Trough FEV_1, mean CFB • Trelegy, 126 ml (95% CI, 92 to 159) vs. BUD/FOR, −53 ml (95% CI, −87 to −20);	Up to week 24, mean annualized exacerbation rate • Moderate and severe exacerbations: Trelegy, 0.22 vs. BUD/FOR, 0.34; rate ratio, 0.65 (95% CI, 0.49 to 0.86); *P* = .002 Up to week 52 • Moderate and severe exacerbations: Trelegy, 0.20 vs. BUD/FOR, 0.36; rate ratio, 0.56 (95% CI, 0.37 to 0.85); *P* = .006 <u>TDI[46]</u> At 24 weeks • Total focal score: Trelegy, 2.29 vs. BUD/FOR, 1.72; between-treatment difference CFB: 0.57 (95% CI, 0.30 to 0.84); *P* < .001	At week 24 SGRQ total score, mean CFB • Trelegy, −6.6 (95% CI, −7.4 to −5.7) vs. BUD/FOR, −4.3 (95% CI, −5.2 to −3.4); mean between-treatment difference CFB, −2.2 (95% CI, −3.5 to −1.0); *P* < .001 Responders • Trelegy 448 of 904 (49.5%) vs. BUD/FOR, 368 of 893 (41.2%); OR, 1.41 (95% CI, 1.16 to 1.70); *P* < .001 At week 52 (extension study, n = 430) SGRQ total score, mean CFB • Trelegy, −4.6 (95% CI, −6.5 to −2.6) vs. BUD/FOR, −1.9 (95% CI, −3.9 to 0.1); mean	At week 24 Any TEAE • Trelegy: 354 (38.9%) • BUD/FOR: 339 (37.7%) Any serious TEAE • Trelegy 49 (5.4%) • BUD/FOR: 51 (5.7%) All-cause mortality • Trelegy: 6 (0.6%) • BUD/FOR: 6 (0.6%) Withdrawals due to AEs, NR <u>AESIs</u> MACEs • Trelegy: 39 (4.3%) • BUD/FOR: 47 (5.2%)

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
	mean between-treatment difference CFB, 179 ml (95% CI, 131 to 226); *P* < .001 Responders • Trelegy, 96 of 210 (45.7%) vs. BUD/FOR, 34 of 219 (15.4%); OR, 4.79 (3.02 to 7.61); *P* < .001 <u>Subgroup analyses (pre-specified)[30]</u> At 24 weeks Trough FEV_1, mean between-treatment difference CFB <u>Baseline disease severity</u> • Predicted FEV_1 < 50% no moderate/severe exacerbations (n = 626): 178 ml (95% CI, 0.14 to 0.22); *P* < .001 • Predicted FEV_1 < 50% with ≥ 1 moderate/severe exacerbations (n = 589): 118 ml	• Responders: Trelegy, 556 of 911 (61%) vs. BUD/FOR, 458 of 899 (51%); OR, 1.61 (95% CI, 1.33 to 1.95); *P* < .001 At 52 weeks • Total focal score: Trelegy, 1.74 vs. BUD/FOR, 1.39; between-treatment difference CFB: 0.34 (95% CI, −0.28 to 0.97); *P* = .3 • Responders: Trelegy, 111 of 210 (53%) vs. BUD/FOR, 101 of 220 (46%); OR, 1.35 (95% CI, 0.91 to 1.99); *P* = .1 <u>Use of Rescue Medication</u> Treatment difference • Over 24 weeks: −0.2 occasions per day; *P* < .001 • Over 52 weeks (n = 430): −0.2 occasions per day; *P* = .02	difference, −2.7 (95% CI, −5.5 to 0.2); *P* = .06 Responders • Trelegy 91 of 209 (43.5%) vs. BUD/FOR, 73 of 219 (33.3%); OR, 1.50 (95% CI, 1.01 to 2.24); *P* = .05 CAT score[46] • Treatment difference, at 24 weeks: Trelegy, −2.5 (95% CI, reported graphically) vs. BUD/FOR, −1.6 (95% CI, reported graphically); mean difference, −0.9 (95% CI, −1.4 to −0.4); *P* < .001 • Treatment difference, at 52 weeks: Details NR; *P*, NSS Responders: • At week 24: OR, 1.44 (95% CI, NR); *P* < .001 • At week 52: OR, 1.50 (95% CI, NR); *P* = .048	Pneumonia • Trelegy: 20 (2.2%) • BUD/FOR: 7 (0.8%) Decreased BMD • Trelegy: 4 (0.4%) • BUD/FOR: 6 (0.7%) At week 52 (extension study, n = 430) Any serious TEAE • Trelegy: 21 (10.0%) • BUD/FOR: 28 (12.7%) <u>AESIs</u> CV effects • Trelegy: 18 (8.6%) • BUD/FOR: 22 (10.0%) Pneumonia • Trelegy: 4 (1.9%) • BUD/FOR: 4 (1.8%)

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
	(95% CI, 0.08 to 0.16); *P* < .001 • Predicted FEV_1 50% to 79% with ≥ 2 moderate or ≥ 1 severe exacerbation (n = 585): 215 ml (95% CI, 176 to 255); *P* < .001 Exacerbation history (in 12 months prior to randomization) • ≤ 1 moderate (n = 1,213): 157 ml (95% CI, 129 to 186); *P* < .001 • ≥ 2 moderate (n = 597): 199 ml (95% CI, 158 to 240); *P* < .001 • ≥ 1 severe (n = 385): 146 ml (95% CI, 87 to 205); *P* < .001 At 52 weeks Baseline disease severity • Predicted FEV_1 < 50% no moderate/severe exacerbations (n = 133): 224 ml (95%	Subgroup analyses (pre-specified)[30] At 24 weeks, mean annualized moderate/severe exacerbation rate Baseline disease severity • Predicted FEV_1 < 50% no moderate/severe exacerbations (n = 626): rate reduction, 33% (95% CI, −4 to 57; *P*, NSS); rate ratio, NR • Predicted FEV_1 < 50% with ≥ 1 moderate/severe exacerbations (n = 589): rate reduction, 45% (95% CI, 11 to 66; *P* < .05); rate ratio, 0.55 (95% CI, 0.34 to 0.89); *P* = .01 • Predicted FEV_1 50% to 79% with ≥ 2 moderate or ≥ 1 severe exacerbation (n = 585): rate reduction, 27% (95% CI, −21 to 56; *P*, NSS); rate ratio, NR	Composite CID[41] Time-to-first composite CID event (SGRQ), at 24 weeks • Trelegy, median 170 days vs. BUD/FOR, median 30 days; risk reduction, 52%; *P* < .001 Time-to-first composite CID event (SGRQ), at 52 weeks • Trelegy, median 170 days vs. BUD/FOR, median 31 days; risk reduction, 48%; *P* < .001 Subgroup analyses (pre-specified)[30] At 24 weeks SGRQ, mean between-treatment difference CFB Baseline disease severity • Predicted FEV_1 < 50% no moderate/severe exacerbations (n = 626): −1.9 (95% CI, −4.1 to −0.3); *P* < .001 • Predicted FEV_1 < 50% with ≥ 1 moderate/severe exacerbations (n = 589):	Decreased BMD • Trelegy: 1 (< 1%) • BUD/FOR: 1 (< 1%)

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
	CI, 135 to 313); *P* < .001 • Predicted FEV_1 < 50% with ≥ 1 moderate/severe exacerbations (n = 143): 140 ml (95% CI, 59 to 221); *P* < .001 • Predicted FEV_1 50% to 79% with ≥ 2 moderate or ≥ 1 severe exacerbation (n = 150): 179 ml (95% CI, 100 to 258); *P* < .001 <u>Exacerbation history (in 12 months prior to randomization)</u> • ≤ 1 moderate (n = 307): 170 ml (95% CI, 113 to 227); *P* < .001 • ≥ 2 moderate (n = 123): 199 ml (95% CI, 111 to 287); *P* < .001 • ≥ 1 severe (n = 115): 129 ml (95% CI, 30 to 227); *P* = .01	<u>Exacerbation history (in 12 months prior to randomization)</u> • ≤ 1 moderate (n = 1,213): rate reduction, 36% (95% CI, 11 to 54; *P* < .01); rate ratio, 0.64 (95% CI, 0.46 to 0.89); *P* = .008 • ≥ 2 moderate (n = 597): rate reduction, 25% (95% CI, −23 to 55; *P*, NSS); rate ratio, NR • ≥ 1 severe (n = 385): rate reduction, 59% (95% CI, 17 to 80); *P* < .05); rate ratio, 0.41 (95% CI, 0.20 to 0.83); *P* = .01 At 52 weeks, NR for any subgroups.	−2.5 (95% CI, −4.7 to −0.3); *P* < .001 • Predicted FEV_1 50% to 79% with ≥ 2 moderate or ≥ 1 severe exacerbation (n = 585): −2.2 (95% CI, −4.4 to 0); *P* < .001 Responders • Predicted FEV_1 < 50% no moderate/severe exacerbations (n = 626): *P* = .08 • Predicted FEV_1 < 50% with ≥ 1 moderate/severe exacerbations (n = 589): *P* = .03 • Predicted FEV_1 50% to 79% with ≥ 2 moderate or ≥ 1 severe exacerbation (n = 585): *P* = .05 <u>Exacerbation history (in 12 months prior to randomization)</u> • ≤ 1 moderate (n = 1,213): −2.6 (95% CI, −4.0 to −1.1); *P* < .001	

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
			• ≥ 2 moderate (n = 597): −3.3 (95% CI, −5.9 to −0.7); *P* = .01 • ≥ 1 severe (n = 385): −1.5 (95% CI, −3.9 to 0.9); *P* = .2 Responders • ≤ 1 moderate (n = 1,213): *P* < .001 • ≥ 2 moderate (n = 597): *P* = .2 • ≥ 1 severe (n = 385): *P* = .01 At 52 weeks <u>Baseline disease severity</u> • Predicted FEV_1 < 50% no moderate/severe exacerbations (n = 133): −1.7 (95% CI, −7.0 to 3.6); *P* = .5 • Predicted FEV_1 < 50% with ≥ 1 moderate/severe exacerbations (n = 143): −2.1 (95% CI, −6.9 to 2.7); *P* = .4 • Predicted FEV_1 50% to 79% with ≥ 2 moderate or ≥ 1 severe exacerbation (n = 150):	

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
			−3.8 (95% CI, −8.5 to 0.8); *P* = .1 <u>Exacerbation history (in 12 months prior to randomization)</u> • ≤ 1 moderate (n = 307): −1.0 (95% CI, −4.3 to 2.3); *P* = .5 • ≥ 2 moderate (n = 123): −6.2 (95% CI, −11.6 to −0.7); *P* = .03 • ≥ 1 severe (n = 115): −0.8 (95% CI, −6.1 to 4.5); *P* = .7	
IMPACT[24,26,27,31,33,34,37,38,45] NCT02164513 US + multinational 52 weeks Trelegy, n = 4,151 FLU/VI, n = 4,134 UMEC/VI, n = 2,070	Trough FEV_1 Mean CFB at week 52 • Trelegy, 94 ml (95% CI, 86 to 102) vs. FLU/VI, −3 ml (95% CI, −12 to 6); between treatment difference, 97 (95% CI, 85 to 109); *P* < .001 • Trelegy, 94 ml (95% CI, 86 to 102) vs. UMEC/VI, 40 ml (95% CI, 28 to 52); between treatment difference, 54 (95% CI, 39 to 69); *P* < .001	<u>Exacerbations</u> Annualized rate of moderate or severe exacerbations: • Trelegy, 0.91 vs. FLU/VI, 1.07; rate ratio, 0.85 (95% CI, 0.80 to 0.90); *P* < .001 • Trelegy, 0.91 vs. UMEC/VI, 1.21; rate ratio, 0.75 (95% CI, 0.70 to 0.81); *P* < .001 Annualized rate of severe exacerbations • Trelegy, 0.13 vs. FLU/VI, 0.15; rate ratio, 0.87	SGRQ, at week 52 Total score, mean CFB • Trelegy, −5.5 (95% CI, −5.9 to −5.0) vs. FLU/VI, −3.7 (95% CI, −4.2 to −3.2); between treatment difference, −1.8 (95% CI, −2.4 to −1.1); *P* < .001 • Trelegy, −5.5 (95% CI, −5.9 to −5.0) vs. UMEC/VI, −3.7 (95% CI, −4.4 to −3.0); between treatment difference, −1.8 (95% CI, −2.6 to −1.0); *P* < .001	Any TEAE Trelegy, 2,897 (70%); 9,765 events FLU/VI, 2,800 (68%); 8,969 events UMEC/VI, 1,429 (69%); 4,382 events Any drug-related AE • Trelegy, 478 (12%); 675 events • FLU/VI, 492 (12%); 719 events • UMEC/VI, 214 (10%); 298 events

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
		(95% CI, 0.76 to 1.01); *P* = .06 • Trelegy, 0.13 vs. UMEC/VI, 0.19; rate ratio, 0.66 (95% CI, 0.56 to 0.78); *P* < .001 Time-to-first moderate or severe exacerbation • Trelegy vs. FLU/VI: HR, 0.85 (95% CI, 0.80 to 0.91); *P* < .001 • Trelegy vs. UMEC/VI: HR, 0.84 (95% CI, 0.78 to 0.91) *P* < .001 <u>Shortness of breath</u> TDI focal score, at week 52[45] Responders, n (%) Trelegy, 730 (36) • vs. FLU/VI, 591 (29); OR, 1.36 (95% CI, 1.19 to 1.55); *P* < .001 • vs. UMEC/VI, 302 (30); OR, 1.33 (95% CI, 1.13 to 1.57); *P* < .001 <u>Use of rescue medications, weeks 49 to 52[45]</u>	Responders, n (%) Trelegy, 1,723 (42%) • vs. FLU/VI, 1,390 (34%); OR, 1.41 (1.29 to 1.55); *P* < .001 • vs. UMEC/VI, 696 (34%); OR, 1.41 (1.26 to 1.57); *P* < .001 CAT score, at week 52[45] Responders, n (%) Trelegy, 1,698 (42%) • vs. FLU/VI, 1,491 (37%); OR, 1.24 (95% CI, 1.14 to 1.36); *P* < .001 • vs. UMEC/VI, 730 (36%); OR, 1.28 (95% CI, 1.15 to 1.43); *P* < .001	Any TE-SAE • Trelegy, 895 (22%); 1,604 events • FLU/VI, 850 (21%); 1,465 events • UMEC/VI, 470 (23%); 753 events Withdrawal due to TEAE • Trelegy, 252 (6%) • FLU/VI, 327 (8%) • UMEC/VI, 187 (9%) All-cause mortality, on treatment Trelegy, 50 (1%) • FLU/VI, 49 (1%); HR, 0.58 (95% CI, 0.38 to 0.88); *P* = .02 • UMEC/VI, 39 (2%); HR, 0.61 (95% CI, 0.40 to 0.93); *P* = .02 <u>AESIs</u> CV effects[26]

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
		Percentage of rescue medication-free days, Mean CFB Trelegy, −1.9% • vs. FLU/VI, −7.1%; between treatment difference, 5.2% (95% CI, 3.5 to 6.9); *P* < .001 • vs. UMEC/VI, −6.3%; between treatment difference, 4.4% (95% CI, 2.3 to 6.5); *P* < .001 <u>Subgroup analyses</u> 1 moderate/0 severe exacerbations in prior year[31] Annualized rate of moderate or severe exacerbations: Trelegy, 0.85 (95% CI, 0.78 to 0.92) • vs. FLU/VI, 1.06 (95% CI, 0.97 to 1.15); rate ratio, 0.80 (95% CI, 0.71 to 0.90); *P* < .001 • vs. UMEC/VI, 1.03 (95% CI, 0.92 to 1.16); rate ratio, 0.82 (95% CI, 0.71 to 0.95); *P* = .007 Time-to-first moderate or severe exacerbation		Trelegy, 450 (11%); 621 events • vs. FLU/VI, 430 (10%); 543 events; HR, 0.98 (95% CI, 0.85 to 1.11); *P* = .7 • vs. UMEC/VI, 224 (11%; 283 events); HR, 0.92 (95% CI, 0.78 to 1.08); *P* = .3 Risk of CV effect leading to hospitalization or death[26] Trelegy, 150 (4%) • vs. FLU/VI, 118 (3%); HR, 1.19 (95% CI, 0.93 to 1.51); *P* = .2 • vs. UMEC/VI, 72 (3%); HR, 0.96 (95% CI, 0.72 to 1.27); *P* = .8 Pneumonia • Trelegy, 317 (8%); 356 events • FLU/VI, 292 (7%); 334 events

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
		• Trelegy vs. FLU/VI: HR, 0.81 (95% CI, 0.72 to 0.91); *P* < .001 • Trelegy vs. UMEC/VI: HR, 0.92 (95% CI, 0.79 to 1.06); *P* = .2 ≥ 2 moderate, no severe exacerbations in prior year[31] Trelegy, 0.85 (95% CI, 0.80 to 0.91) • vs. FLU/VI, 0.96 (95% CI, 0.90 to 1.03); rate ratio, 0.89 (95% CI, 0.81 to 0.98); *P* = .02 • vs. UMEC/VI, 1.21 (95% CI, 1.10 to 1.32); rate ratio, 0.71 (95% CI, 0.63 to 0.79); *P* < .001 Time-to-first moderate or severe exacerbation • Trelegy vs. FLU/VI: HR, 0.92 (95% CI, 0.83 to 1.01); *P* = .07 • Trelegy vs. UMEC/VI: HR, 0.80 (95% CI, 0.72 to 0.90); *P* < .001 ≥ 1 severe, any moderate exacerbations in prior year[31]		• UMEC/VI, 97 (5%); 104 events Time-to-first event for pneumonia (investigator-reported)[27] • Trelegy vs. FLU/VI: HR, 1.02 (95% CI, 0.87 to 1.19); *P* = .8 • Trelegy vs. UMEC/VI: HR, 1.53 (95% CI, 1.22 to 1.92); *P* < .001 Risk of pneumonia (investigator-reported)[27] • Trelegy vs. FLU/VI: rate ratio, 0.99 (95% CI, 0.84 to 1.17); *P* = .9 • Trelegy vs. UMEC/VI: rate ratio, 1.53 (95% CI, 1.21 to 1.94); *P* < .001 Time-to-first investigator-reported pneumonia resulting

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
		Annualized rate of moderate or severe exacerbations: Trelegy, 1.06 (95% CI, 0.98 to 1.16) • vs. FLU/VI, 1.28 (95% CI, 1.18 to 1.39; rate ratio, 0.83 (95% CI, 0.74 to 0.93); *P* = .002 • vs. UMEC/VI, 1.43 (95% CI, 1.27 to 1.61); rate ratio, 0.74 (95% CI, 0.65 to 0.86); *P* < .001 Time-to-first moderate or severe exacerbation • Trelegy vs. FLU/VI: HR, 0.81 (95% CI, 0.72 to 0.91): *P* < .001 • Trelegy vs. UMEC/VI: HR, 0.81 (95% CI, 0.70 to 0.93); *P* = .003 By smoking history[37] Current smoker: Trelegy, 0.92 (95% CI, 0.86 to 0.99) • vs. FLU/VI, 1.09 (95% CI, 1.01 to 1.17); 15% reduction (95% CI, 6% to 24%); *P* < .01 • vs. UMEC/VI, 1.07 (95% CI, 0.96 to 1.19);		in hospitalization or death[27] • Trelegy, 199 (5%) vs. FLU/VI, 170 (4%); HR, 1.10 (95% CI, 0.89 to 1.34); *P* = .38 • Trelegy, 199 (5%) vs. UMEC/VI, 57 (3%); HR, 1.62 (95% CI, 1.21 to 2.17); *P* < .001 Risk of investigator-reported pneumonia resulting in hospitalization, death or severe exacerbation[27] • Trelegy vs. FLU/VI: rate ratio, 0.93 (95% CI, 0.82 to 1.06); *P* = .29 • Trelegy vs. UMEC/VI: rate ratio, 0.76 (95% CI, 0.65 to 0.89); *P* < .001 On-treatment cardiovascular AESI leading to

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
		14% reduction (95% CI, 2% to 24%); *P* < .05 Former smoker: Trelegy, 0.89 (95% CI, 0.85 to 0.95) • vs. FLU/VI, 1.06 (95% CI, 1.00 to 1.12); 15% reduction (95% CI, 9% to 22%); *P* < .001 • vs. UMEC/VI, 1.28 (95% CI, 1.18 to 1.38); 30% reduction (95% CI, 23% to 36%); *P* < .001		hospitalization, prolonged hospitalization, or death[26] • Trelegy, 150 of 4,151 (4%) vs. FLU/VI, 118 of 4,134 (3%); HR, 1.19 (95% CI, 0.93 to 1.51); *P* = .17 • Trelegy, 150 of 4,151 (4%) vs. UMEC/VI: 72 of 2,070 (3%); HR, 0.96 (95% CI, 0.72 to 1.27); *P* = .76
INTREPID[32] NCT03467425 Multiple European countries 24 weeks Trelegy, n = 1,545 MITT, n = 1,547	Trelegy n = 301 vs. MITT n = 292 Trough FEV_1, between-treatment mean CFB at week 24 • Trelegy: mean, 100 ml (95% CI, 64 to 135) • MITT: mean, 47 ml (95% CI, 6 to 88) • Between-treatment difference, 53 ml (95% CI, 9 to 96); *P* = .02	Annualized moderate/severe exacerbation rate • Trelegy: mean 1.2 (SD, 3.65) • MITT: 1.1 (SD, 5.57)	CAT • Responder (score decrease ≥ 2 CFB) at week 24: 731 (47%) vs. 616 (40%); OR, 1.31 (95% CI, 1.13 to 1.51); *P* < .001 CAT responder by prior treatment type • ICS+LAMA+LABA: OR, 1.28 (95% CI, 1.08 to 1.51); *P* = .004 • ICS+LABA: OR, 2.13 (95% CI, 1.24 to 3.66); *P* = .006	Trelegy, n = 1,545; MITT, n = 1,547 Any AE • Trelegy: 250 (16%); 376 events • MITT: 151 (10%); 221 events Any TEAE • Trelegy: 145 (9%); 210 events • MITT: 44 (3%); 53 events

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
			• LAMA+LABA: OR, 1.15 (95% CI, 0.75 to 1.75); *P* = .5	Any SAE • Trelegy: 114 (7%); 164 events • MITT: 114 (7%); 175 events Fatal TE-SAE: None Any AE leading to withdrawal • Trelegy: 115 (7%); 178 events • MITT: 32 (2%); 48 events <u>AESIs</u> Cardiovascular effects • Trelegy: 29 (2%); 35 events • MITT: 23 (1%); 27 events Decreased BMD and associated fractures • Trelegy: 6 (< 1%); 6 events • MITT: 4 (< 1%); 5 events

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Study Name or First Author Trial Number Location(s) Study Duration N by Group	FEV_1	Exacerbations Rescue Medication	HRQoL	AEs, SAEs, or AESIs
				Pneumonia • Trelegy: 27 (2%); 28 events • MITT: 32 (2%); 32 events

Abbreviations. AE: adverse event; AESI: adverse event of special interest; BMD: bone mineral density; BUD: budesonide; CAT: COPD Assessment Test; CFB: change from baseline; CI: confidence interval; CID: clinically important deterioration; COPD: chronic obstructive pulmonary disease; CV: cardiovascular; FEV_1: forced expiratory volume in 1 second; FLU: fluticasone; FOR: formoterol; HR: hazard ratio; HRQoL: health-related quality of life; ICS: inhaled corticosteroids; LABA: long-acting $ß_2$ agonists; LAMA: long-acting muscarinic antagonists; MACE: major adverse cardiovascular event; MITT: multiple-inhaler triple therapy; NR: not reported; NSS: not statistically significant; OR: odds ratio; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnea Index; TEAE: treatment-emergent adverse event; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol.

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Table B4. Full Evidence Table of RCTs Comparing Trimbow to Other COPD Treatments

Study Name Trial Number Location Duration N by Group	FEV_1	Exacerbations	HRQoL Rescue Medication	AEs, SAEs, or AESIs
TRINITY[47] NCT01911364 Multinational 52 weeks Trimbow, n = 1,078 TIO, n = 1,075 BDP/FOR+TIO, n = 538	FEV_1 responders (≥ 100 ml increase) CFB at week 52 • Trimbow vs. TIO: 408 (38%) vs. 295 (27%); OR, 1.62 (95% CI, 1.35 to 1.95); *P* < .001 • Trimbow vs. BDP/FOR+TIO: 408 (38%) vs. 210 (39%); OR, 0.95 (95% CI, 0.76 to 1.18); *P* = .6 Pre-dose FEV_1, adjusted mean and between-treatment difference CFB at week 52 • Trimbow vs. TIO: 82 ml vs. 21 ml; 61 ml (95% CI, 37 to 86); *P* < .001 • Trimbow vs. BDP/FOR+TIO: 82 ml vs. 85 ml; −3 ml (95% CI, −33 to 27); *P* = ·8 Overall FEV_1 adjusted mean CFB • Trimbow, 80 ml (95% CI, 67 to 93) vs. TIO, 22 ml (95% CI, 9 to 36); mean between-treatment difference, 58 ml (95% CI, 39 to 77); P < .001 • Trimbow, 80 ml (95% CI, 67 to 93) vs BDP/FOR+TIO, 91 ml (95% CI, 73 to 110); mean between-treatment difference,	Annualized rate of severe exacerbations, at 52 weeks • Trimbow, 0.07 (95% CI, 0.05 to 0.09) vs. TIO, 0.10 (95% CI, 0.08 to 0.12); rate ratio, 0.68 (95% CI, 0.50 to 0.94); *P* = .02 • Trimbow, 0.07 (95% CI, 0.05 to 0.09) vs. BDP/FOR+TIO, 0.06 (95% CI, 0.04 to 0.08); rate ratio, 1.18 (95% CI, 0.77 to 1.80); *P* = .45 Annualized adjusted rate of moderate-to-severe exacerbations at 52 weeks • Trimbow vs. TIO: 0.46 vs. 0.57; rate ratio, 0.80 (95% CI, 0.69 to 0.92); *P* = .002 • Trimbow, vs. BDP/FOR+TIO: 0.46 vs. 0.45; rate ratio, 1.01 (95% CI, 0.85 to 1.21); *P* = .9 Time-to-first moderate-to-severe exacerbation • Trimbow vs. TIO: HR, 0.84 (95% CI, 0.72 to 0.97); *P* = .01	SGRQ responders (≥ 4 unit decrease) CFB at week 52 • Trimbow vs. TIO: 494 (46%) vs. 423 (39%); OR, 1.33 (95% CI, 1.11 to 1.59); *P* = .002 • Trimbow vs. BDP/FOR+TIO: 494 (46%) vs. 254 (47%); OR, 0.91 (95% CI, 0.73 to 1.13); *P* = .4 <u>Use of rescue medication</u> Average number of puffs per day, adjusted between-treatment mean, CFB to weeks 41 to 52 • Trimbow vs. TIO: −0.61 (95% CI, −0.78 to −0.44); *P* < .001 • Trimbow vs. BDP/FOR+TIO: 0.05 (95% CI, −0.16 to 0.25); *P* = .6 Percentage of days without rescue medication use, adjusted between-treatment mean, CFB to weeks 41 to 52	Trimbow, n = 1,077; TIO, n = 1,076; BDP/FOR+TIO, n = 537 Any AE • Trimbow: 594 (55%) • TIO: 622 (58%) • BDP/FOR+TIO: 309 (58%) Any TEAE • Trimbow: 25 (2%) • TIO: 33 (3%) • BDP/FOR+TIO: 27 (5%) Any SAE • Trimbow: 140 (13%) • TIO: 164 (15%) • BDP/FOR+TIO: 68 (13%) Withdrawal due to AE • Trimbow: 33 (3%) • TIO: 62 (6%) • BDP/FOR+TIO: 15 (3%) AEs leading to death • Trimbow: 20 (2%)

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Study Name Trial Number Location Duration N by Group	FEV_1	Exacerbations	HRQoL Rescue Medication	AEs, SAEs, or AESIs
	−11 ml (95% CI, −34 to 12); *P* = .3	• Trimbow vs. BDP/FOR+TIO: HR, 1.06 (95% CI, 0.88 to 1.27); *P* = .6 Subgroups of interest (e.g., severity of COPD, current vs. ex-smoker) reported via forest plot only in supplemental material.	• Trimbow vs. TIO: 8.78 (95% CI, 5.74 to 11.81); *P* < .001 • Trimbow vs. BDP/FOR+TIO: −1.24 (95% CI, −4.92 to 2.44); *P* = .51	• TIO: 29 (3%) • BDP/FOR+TIO: 8 (1%) <u>AESIs</u> All MACEs • Trimbow: 20 (2%) • TIO: 23 (2%) • BDP/FOR+TIO: 7 (1%) Pneumonia • Trimbow: 21 (2%) • TIO: 14 (1%) • BDP/FOR+TIO: 9 (2%)
TRIVERSYTI[48] NCT03197818 China, Korea, Taiwan 24 weeks Trimbow, n = 353 BUD/FOR, n = 355	Pre-dose FEV_1, between-treatment difference, overall, adjusted mean • 70 ml (95% CI, 53 to 88); *P* < .001 FEV_1 responders (≥ 100 ml increase), CFB at week 24 • 91 (26%) vs. 43 (12%); OR, 2.58 (95% CI, 1.72 to 3.85); *P* < .001	Annualized rate of moderate-to-severe exacerbations • 0.52 vs. 0.91; rate ratio, 0.57 (95% CI, 0.42 to 0.77); *P* < .001 Time-to-first moderate/severe exacerbation • HR, 0.55 (95% CI, 0.40 to 0.75); *P* < .001	SGRQ adjusted between-treatment mean difference, overall • −3.18 (95% CI, −4.99 to −1.37); *P* < .001 CAT, adjusted between-treatment mean difference, overall • −1.01 (95% CI, −1.63 to −0.39); *P* < .01	Any AE • Trimbow: 215 (61.1%) • BUD/FOR: 238 (67.0%) Any TEAE • Trimbow: 9 (2.6%) • BUD/FOR: 16 (4.5%) Any SAE • Trimbow: 40 (11.4%) • BUD/FOR: 60 (16.9%)

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Study Name Trial Number Location Duration N by Group	FEV_1	Exacerbations	HRQoL Rescue Medication	AEs, SAEs, or AESIs
			Rescue medication Average number of puffs per day, adjusted between-treatment mean, overall • −0.13 (95% CI, −0.25 to −0.01); *P* < .05 Percentage of days without rescue medication use, adjusted between-treatment mean, overall • 6.7 (95% CI, 3.9 to 9.4); *P* < .001	Withdrawal due to AE • Trimbow: 8 (2.3%) • 13 (3.7%) Deaths related to AEs • Trimbow: 1 (0.3%) • BUD/FOR: 3 (0.8%) AESIs Pneumonia • Trimbow: 4 (1.1%) • BUD/FOR: 9 (2.5%)

Abbreviations. AE: adverse event; AESI: adverse event of special interest; BDP: beclomethasone dipropionate; BUD: budesonide; CAT: COPD Assessment Test; CFB: change from baseline; CI: confidence interval; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FOR: formoterol; HR: hazard ratio; HRQoL: health-related quality of life; MACE: major adverse cardiovascular event; OR: odds ratio; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; TEAE: treatment-emergent adverse event; TIO: tiotropium.

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Appendix C. List of Abbreviations

AA	African American
ACQ-7	Asthma Control Questionnaire, 7-item
AE	adverse event
AESI	adverse event of special interest
AI/AN	American Indian/Alaska Native
aOR	adjusted odds ratio
BDP	beclomethasone dipropionate
BMD	bone mineral density
BUD	budesonide
CAT	COPD Assessment Test
CFB	change from baseline
CI	confidence interval
CID	clinically important deterioration
COPD	chronic obstructive pulmonary disease
CV	cardiovascular
DPI	dry-powder inhaler
FDA	US Food & Drug Administration
FEV_1	forced expiratory volume in 1 second
FLU	fluticasone furoate
FOR	Formoterol fumarate
GLY	glycopyrronium bromide (or glycopyrrolate)
HR	hazard ratio
HRQoL	health-related quality of life
ICS	inhaled corticosteroids
ITT	intention-to-treat
LABA	long-acting $ß_2$ agonists

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LAMA	long-acting muscarinic antagonists
MACE	major adverse cardiovascular event
MCID	minimal clinically important differences
MDI	metered-dose inhaler
MITT	multiple-inhaler triple therapy
N/A	not applicable
NHIS	US National Health Interview Survey
NR	not reported
NSS	not statistically significant
OR	odds ratio
PI	Pacific Islander
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire
SITT	single-inhaler triple therapy
SOC	standard of care
TDI	Transition Dyspnea Index
TEAE	treatment-emergent adverse event
TIO	tiotropium
UMEC	umeclidinium bromide
VI	vilanterol trifenatate

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