Special Assessment to Inform CMS Drug Price Negotiations: Trelegy Ellipta and Breo Ellipta for Patients with COPD

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

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None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

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List of Acronyms and Abbreviations Used in this Report

AE	Adverse Event
AIAN	American Indian or Alaskan Native
ATS	American Thoracic Society
BD	Twice daily
BDP	Beclomethasone dipropionate
BUD	Budesonide
CAT	COPD Assessment Test
CDR	Clinical trial Diversity Rating
CE	Cost-effectiveness
CI	Confidence interval
CMS	Center for Medicare and Medicaid Services
COPD	Chronic obstructive pulmonary disease
CrI	Credible interval
DIC	Deviance information criterion
DPI	Dry powder inhalers
EMA	European Medicines Agency
ERS	European Respiratory Society
ESRD	End stage renal disease
evLY	Equal-value life year
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FEV_1/FVC	Forced expiratory volume/forced vital capacity ratio
FF	Fluticasone furoate
FFS	Fee-for-service
FOR	Formoterol
FP	Fluticasone propionate
FVC	Forced vital capacity
GLY	Glycopyrronium
GOLD	Global Initiative for Obstructive Lung Disease
HCRU	Health care resource utilization
HD	High dose
HIDI	Health Improvement Distribution Index
HRQoL	Health-Related Quality of Life
I^2	Heterogeneity statistics
ICER	Institute for Clinical and Economic Review
ICS	Inhaled corticosteroid
IRA	Inflation Reduction Act
IND	Indacaterol
KM	Kaplan-Meier
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
LD	Low dose
mcg	Micrograms
mcL	Microliters
MCID	Minimal clinically important difference
MDI	Metered dose inhalers
MITT	Multiple inhaler triple therapy
mMRC	Modified Medical Research Council Dyspnea Scale
N	Total number
n	Number

NC	Not calculated
NE	Not estimated
NHPI	Native Hawaiian or Pacific Islander
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analyses
NR	Not reported
PDC	Proportion of days covered
PDRR	Participant to Disease-prevalence Representation Ratio
PICOTS	Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design
p	P-Value
RCT	Randomized controlled trial
RR	Relative risk
SABA	Short-acting beta agonists
SAL	Salmeterol
SD	Standard deviation
SE	Standard error
SGRQ	St. George's Respiratory Questionnaire
SITT	Single inhaler triple therapy
SMI	Soft mist inhalers
TAI	Test of Adherence to Inhalers
TDI	Transitional Dyspnea Index
TIO	Tiotropium
UK	United Kingdom
US	United States
UMEC	Umeclidinium
VI	Vilanterol
vs	Versus
WAC	Wholesale acquisition cost

Executive Summary

Under the Inflation Reduction Act (IRA), the Centers for Medicare and Medicaid Services (CMS) has initiated drug price negotiations with the manufacturers of selected Medicare Part D drugs. In October 2023, the Institute for Clinical and Economic Review (ICER) published a special report on two of the 10 drugs selected for the first cycle of drug price negotiations, apixaban and rivaroxaban.[1] CMS released draft guidance for the second cycle in October 2024 and recently listed the 15 drugs for price negotiations that will take effect in 2027. This ICER special report focuses on two drugs that are subject to price negotiations in this cycle: a combination of fluticasone furoate and vilanterol (Breo Ellipta®, GSK) and a combination of fluticasone furoate, vilanterol, and umeclidinium (Trelegy Ellipta®, GSK), both as maintenance therapies for chronic obstructive pulmonary disease (COPD).

COPD is a lung disease characterized by progressive and persistent airflow obstruction in the lungs. Patients with COPD typically experience shortness of breath, fatigue, wheezing, chest tightness, and cough. Exacerbations are an important marker of disease severity, as they impact health-related quality of life, account for a large portion of COPD spending, and may accelerate disease progression.[2] The goals of pharmacologic therapy in COPD are to reduce symptoms and exacerbations. The Global Initiative for Obstructive Lung Disease (GOLD) 2025 guideline recommends dual therapy with a long-acting beta-agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) for patients initiating therapy who have significant symptoms. The GOLD guideline discourages the use of LABA plus inhaled corticosteroids (ICS); if an ICS is indicated, then triple therapy with LABA+LAMA+ICS is recommended. Those with exacerbations despite being on dual therapy should also be escalated to triple therapy.[3]

Trelegy Ellipta is a single-inhaler, triple therapy: fluticasone furoate (ICS); umeclidinium (LAMA); and vilanterol (LABA). The medications are delivered in a dry powder inhaler one puff once daily. Breo Ellipta is a single-inhaler, dual therapy: fluticasone furoate (ICS) and vilanterol (LABA). The medications are delivered in a dry powder inhaler one puff once daily. This review focuses on combinations of generic inhalers that provide triple therapy (ICS, LAMA, and LABA) as comparators for Trelegy Ellipta and generic combinations that provide dual therapy (ICS and LABA) as comparators for Breo Ellipta.

Most network meta-analyses conclude that all triple therapies have equivalent outcomes when used as prescribed. However, Trelegy Ellipta offers the advantage of requiring only one puff once a day, while the comparators require multiple inhalers administered usually twice daily. Observational data suggests that patients are poorly adherent to all therapies but modestly more adherent to once-daily therapy. This may lead to fewer COPD exacerbations, though the results have, at best, moderate certainty. Patients we spoke with also stated that they prefer once-daily therapy. There are no important differences in harms. Thus, we concluded that Trelegy Ellipta has comparable or incremental net health benefits compared with other generic triple therapies requiring multiple inhalers (Table ES1).

Current guidelines do not recommend using ICS/LABA therapy, like Breo Ellipta, for the management of COPD. However, they have been commonly used in the past and Breo Ellipta has an FDA indication for COPD. A Cochrane review found that the combination of a LAMA/LABA was superior to other dual combination therapies for COPD and that the other combinations, including ICS/LABA were equivalent to each other.[4] Breo Ellipta offers the advantage of requiring only one puff once a day, while the generic comparators require twice daily use. Observational data suggests that patients are slightly more adherent to Breo Ellipta's once-daily therapy and that this may lead to fewer COPD exacerbations, though the results have at best moderate certainty. There are no important differences in harms between dual therapies. Thus, we concluded that Breo Ellipta has comparable or incremental net health benefit compared with generic ICS/LABA dual therapies (Table ES1).

Table ES1. Evidence Ratings for Trelegy Ellipta and Breo Ellipta Compared with Generic Alternatives

Treatment	Comparator	Evidence Rating
Patients with COPD requiring Triple Therapy		
Trelegy Ellipta	Budesonide/Formoterol Fumarate with Tiotropium	C+
Trelegy Ellipta	Fluticasone Propionate/Salmeterol Xinafoate with Tiotropium	C+
Trelegy Ellipta	Fluticasone Furoate/Vilanterol Trifenatate with Tiotropium	C+
Patients with COPD requiring Dual Therapy		
Breo Ellipta	Budesonide/Formoterol Fumarate	C+
Breo Ellipta	Fluticasone Propionate/Salmeterol	C+

Economic Analyses for Trelegy Ellipta

Compared to generic alternatives, Trelegy Ellipta resulted in fewer exacerbations, increased life years, increased evLYs gained, and higher non-intervention health care sector costs (Table ES2).

Table ES2. Incremental Lifetime Results for Trelegy Ellipta Versus General Alternatives

Treatment	Exacerbations	Life Years (Discounted)	evLYs (Discounted)	Non-Intervention Health Care Sector Costs (Discounted)
FF/UMEC/VI vs. BUD/FOR + TIO	-0.32	0.06	0.05	$1,200
FF/UMEC/VI vs. FP/SAL + TIO	-0.32	0.06	0.05	$1,200
FF/UMEC/VI vs. FF/VI + TIO	-0.32	0.06	0.05	$1,200

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, LY: Life year, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Our price calculations estimated the annual cost that CMS should pay for Trelegy Ellipta based on the comparator price (Table ES3) across a range of willingness-to-pay thresholds. In these calculations, the comparator represents any potential treatment alternative, including low-cost generics, authorized generics, and heavily discounted branded triple therapies. We have included a wider range of thresholds to provide CMS with flexibility in their negotiations.

Table ES3. Estimated Annual Threshold Prices for Trelegy Ellipta across a Range of Comparator Prices and Cost-Effectiveness Benchmarks

	Annual Threshold Prices for FF/UMEC/VI			
Annual Price for Comparator	**$50,000/evLY**	**$100,000/evLY**	**$150,000/evLY**	**$200,000/evLY**
$500	$750	$1,370	$2,000	$2,600
$1,000	$1,200	$1,800	$2,400	$3,000
$1,500	$1,600	$2,200	$2,800	$3,500
$2,000	$2,000	$2,600	$3,300	$3,900
$2,500	$2,400	$3,100	$3,700	$4,300
$3,000	$2,900	$3,500	$4,100	$4,700
$3,500	$3,300	$3,900	$4,500	$5,100
$4,000	$3,700	$4,300	$5,000	$5,600
$4,500	$4,100	$4,800	$5,400	$6,000
$5,000	$4,600	$5,200	$5,800	$6,400
$5,500	$5,000	$5,600	$6,200	$6,800
$6,000	$5,400	$6,000	$6,600	$7,300
$6,500	$5,800	$6,500	$7,100	$7,700
$7,000	$6,300	$6,900	$7,500	$8,100

	Annual Threshold Prices for FF/UMEC/VI			
Annual Price for Comparator	**$50,000/evLY**	**$100,000/evLY**	**$150,000/evLY**	**$200,000/evLY**
$7,500	$6,700	$7,300	$7,900	$8,500
$8,000	$7,100	$7,700	$8,300	$9,000
$8,500	$7,500	$8,200	$8,800	$9,400
$9,000	$8,000	$8,600	$9,200	$9,800
$9,500	$8,400	$9,000	$9,600	$10,200
$10,000	$8,800	$9,400	$10,000	$10,700

evLYs: equal-value life years, FF: fluticasone furoate, UMEC: umeclidinium, VI: vilanterol
Note: Annual prices for FF/UMEC/VI are rounded to the nearest $100

Economic Analyses for Breo Ellipta

Compared to generic alternatives, Breo Ellipta resulted in fewer exacerbations, increased life years, increased evLYs gained, and higher non-intervention health care sector costs (Table ES4).

Table ES4. Incremental Lifetime Results for Breo Ellipta Versus General Alternatives

Treatment	Exacerbations	Life Years (Discounted)	evLYs (Discounted)	Non-Intervention Health Care Sector Costs (Discounted)
FF/VI vs. BUD/FOR	-0.09	0.02	0.01	$800
FF/VI vs. FP/SAL	-0.09	0.02	0.01	$800

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, LY: Life year, SAL: salmeterol, VI: vilanterol

Our price threshold calculations estimated the annual cost that CMS should pay for Breo Ellipta based on the comparator price (Table ES5) across a range of willingness-to-pay thresholds. In these calculations, the comparator represents any potential treatment alternative, including low-cost generics, authorized generics, and heavily discounted branded dual therapies. We have included a wider range of thresholds to provide CMS with flexibility in their negotiations.

Table ES5. Estimated Annual Threshold Prices for Breo Ellipta Across a Range of Comparator Prices and Cost-Effectiveness Benchmarks

	Annual Threshold Prices for FF/VI			
Annual Price for Comparator	**$50,000/evLY**	**$100,000/evLY**	**$150,000/evLY**	**$200,000/evLY**
$500	$400	$600	$800	$1,000
$1,000	$800	$1,000	$1,300	$1,500
$1,500	$1,300	$1,500	$1,700	$1,900
$2,000	$1,700	$2,000	$2,200	$2,400
$2,500	$2,200	$2,400	$2,600	$2,800
$3,000	$2,600	$2,900	$3,100	$3,300
$3,500	$3,100	$3,300	$3,500	$3,700
$4,000	$3,500	$3,700	$4,000	$4,200
$4,500	$4,000	$4,200	$4,400	$4,600
$5,000	$4,400	$4,600	$4,900	$5,000
$5,500	$4,900	$5,100	$5,300	$5,500
$6,000	$5,300	$5,500	$5,800	$6,000
$6,500	$5,800	$6,000	$6,200	$6,400
$7,000	$6,200	$6,400	$6,700	$6,900
$7,500	$6,700	$6,900	$7,100	$7,300
$8,000	$7,100	$7,300	$7,500	$7,800
$8,500	$7,600	$7,800	$8,000	$8,200
$9,000	$8,000	$8,200	$8,400	$8,700
$9,500	$8,500	$8,700	$8,900	$9,100
$10,000	$8,900	$9,100	$9,300	$9,500

evLYs: equal-value life years, FF: fluticasone furoate, VI: vilanterol

Note: Annual prices for FF/VI are rounded to the nearest $100.

1. Background

1.1 Introduction

Under the Inflation Reduction Act (IRA), the Centers for Medicare and Medicaid Services (CMS) has initiated drug price negotiations on selected Medicare Part D drugs with participating drug manufacturers. In October 2023, the Institute for Clinical and Economic Review (ICER) published a special report on two of the 10 drugs selected for the first cycle of drug price negotiations, apixaban and rivaroxaban.[1] CMS released draft guidance for the second cycle in October 2024 and recently released the list of 15 drugs for price negotiations which set to take effect in 2027. This ICER special report will focus on two drugs that are subject to price negotiations in this next cycle: a combination of fluticasone furoate and vilanterol (Breo Ellipta®, GSK) and a combination of fluticasone furoate, vilanterol, and umeclidinium (Trelegy Ellipta®, GSK), both as maintenance therapies for chronic obstructive pulmonary disease (COPD).

COPD is a lung disease characterized by progressive and persistent airflow obstruction in the lungs. It affects approximately 11.7 million (4.6%) of adults in the United States (US), with higher rates among non-Hispanic white individuals, American Indian/Alaska Native individuals, women, and adults older than 65.[5,6] In 2018, 10.4 million (16.5%) Medicare beneficiaries had a diagnosis of COPD.[7] In addition, there are a substantial number of patients with COPD who remain undiagnosed.[8] COPD is the sixth leading cause of death among Americans and is the cause of over half-a-million hospitalizations, one million emergency department visits, and 16.4 million lost working days per year.[9-11] The total economic burden of COPD is estimated to be almost $50 billion per year, with $24 billion attributable to direct medical costs. This is based on pre-pandemic estimates because the COVID-19 pandemic disrupted more recent data.[12]

Patients with COPD typically experience shortness of breath, fatigue, wheezing, chest tightness, and cough. Symptom burden is high, with about half of COPD patients reporting near-daily symptoms and the majority reporting that symptoms have a moderate-to-great impact on everyday life.[13] In very severe COPD, patients may lose weight and/or develop right-sided heart failure. Women with COPD have been observed to be younger, smoke less, and have more dyspnea than men; women also account for a higher proportion of hospitalizations.[14,15] Lower socioeconomic status has been linked with greater disease progression.[16]

The diagnosis of COPD is based on symptoms and evidence of airflow obstruction, defined as a post-bronchodilator forced expiratory volume/forced vital capacity ratio (FEV_1/FVC) of <0.7.[3] Exacerbations are an important marker of disease severity, as they impact health-related quality of life, account for a large portion of COPD spending, and may accelerate disease progression.[2] The goals of pharmacologic therapy in COPD are to reduce symptoms and exacerbations. The Global Initiative for Obstructive Lung Disease (GOLD) 2025 guideline recommends dual therapy with a

long-acting beta-agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) for patients initiating therapy who have significant symptoms (either based on their daily symptom scores or their exacerbation history). LAMA+LABAs are also recommended for patients who start on single therapy but do not have adequate control (i.e., patients with persistent symptoms or exacerbations). The GOLD guideline discourages the use of a LABA plus inhaled corticosteroids (ICS); if an ICS is indicated, then triple therapy with LABA+LAMA+ICS is recommended. Patients with COPD who have frequent exacerbations and high eosinophil counts should initiate therapy with LABA+LAMA+ICS. Those with exacerbations despite being on dual therapy should be escalated to triple therapy.[3]

There appear to be no intraclass differences among dual LABA+ICS therapies.[4] Triple therapies have demonstrated better outcomes for patients with severe COPD compared to dual therapies.[17-21] However, it remains uncertain whether variations exist in efficacy and safety among different triple therapy combinations and their delivery devices.[22-24] Additionally, some dual or triple therapies require multiple inhalations every day, sometimes with different inhalers, which can lead to poor adherence among patients with COPD.[25] Once-daily therapy has been associated with better adherence compared to twice-daily dosing in those with COPD.[26]

Inhalers use three different delivery systems. Metered dose inhalers (MDI) are pressurized canisters that deliver a puff of medication when you press on the inhaler canister. Dry powder inhalers (DPI) deliver a dose of the medication when you breathe in with sufficient force to activate the inhaler. Finally, soft mist inhalers (SMI) turn liquid medication into a mist when you press on the dose release button. Proper inhaler technique is essential for effective delivery of inhaled medications to the lungs. Common co-morbidities of aging, such as arthritis, muscle weakness, and cognitive decline contribute to the challenges in proper use of inhalers.[27]

1.2 Trelegy Ellipta and Breo Ellipta for COPD

Trelegy Ellipta

This assessment focuses on the use of Trelegy Ellipta as maintenance therapy for patients with COPD. Trelegy Ellipta is a combination of three medications: fluticasone furoate, an inhaled corticosteroid (ICS); umeclidinium, a long-acting muscarinic agent (LAMA); and vilanterol, a long-acting beta-agonist (LABA). The medications are delivered in a single dry powder inhaler one puff once daily. It comes in two strengths: either 100 mcg or 200 mcg of fluticasone furoate (ICS) combined with 62.5 mcg of umeclidinium (LAMA), and 25 mcg of vilanterol (LABA). Only the 100 mcg dose is indicated for COPD.

Breo Ellipta

This assessment focuses on the use of Breo Ellipta as maintenance therapy for patients with COPD. Breo Ellipta is a combination of two medications: fluticasone furoate, an inhaled corticosteroid (ICS) and vilanterol, a long-acting beta-agonist (LABA). The medications are delivered as an inhaled powder one puff once daily. It comes in two strengths: either 100 mcg or 200 mcg of fluticasone furoate (ICS) combined with 25 mcg of vilanterol (LABA). Only the 100 mcg dose is indicated for COPD.

It is worth highlighting that none of the current key guidelines (since 2023) for managing COPD (GOLD, American Thoracic Society, National Institute for Health and Clinical Excellence) recommend the use of the combination of an ICS with a LABA. If two medications are required, the recommendation is to use a combination of a LABA plus a LAMA, preferably as one inhaler. If additional therapy is needed, then an ICS is added to the LABA plus LAMA.[3,28,29]

2. Potential Therapeutic Alternatives

2.1 Therapeutic Alternatives for Trelegy Ellipta

We focused on combinations of generic inhalers, including authorized generics, that provide triple therapy with a combination of an ICS, LAMA, and LABA as therapeutic alternatives for Trelegy Ellipta. There is also a branded triple therapy (Breztri). Three generic triple therapy combinations are described below.

Budesonide/Formoterol Fumarate in Combination with Tiotropium

Generic budesonide 320 mcg/formoterol fumarate 9 mcg (ICS/LABA) delivered via a metered dose inhaler (MDI) two puffs twice daily in combination with generic tiotropium 18 mcg (LAMA) delivered via a dry powder inhaler (DPI) two puffs once daily.

Fluticasone Propionate/Salmeterol Xinafoate in Combination with Tiotropium

Either true generic (Wixela) or authorized generic (Advair) fluticasone propionate 250 or 500 mcg/salmeterol xinafoate 50 mcg (ICS/LABA) DPI one puff every 12 hours in combination with generic tiotropium 18 mcg (LAMA) DPI two puffs once daily.

Fluticasone Furoate/Vilanterol Trifenatate in Combination with Tiotropium

Authorized generic fluticasone furoate 100 mcg/vilanterol trifenatate 25 mcg (ICS/LABA) via a DPI one puff once daily in combination with generic tiotropium 18 mcg (LAMA) via a DPI two puffs once daily.

2.2 Therapeutic Alternatives for Breo Ellipta

There are two generic inhalers that deliver an ICS plus LABA as alternatives to Breo Ellipta.

Budesonide/Formoterol Fumarate

Generic budesonide 320 mcg/formoterol fumarate 9 mcg (ICS/LABA) delivered via a metered dose inhaler (MDI) two puffs twice daily.

Fluticasone Propionate/Salmeterol Xinafoate

Either true generic (Wixela) or authorized generic (Advair) fluticasone propionate 250 or 500 mcg/salmeterol xinafoate 50 mcg (ICS/LABA) delivered via a dry powder inhaler (DPI) one puff every 12 hours.

2.3 Clinical Outcomes

Trelegy Ellipta

Clinical Efficacy

We focused on outcomes important to patients in our assessment of therapies for COPD.[28-30] Patient-important outcomes include COPD exacerbations, COPD symptoms (e.g., dyspnea), health-related quality of life, functional status (e.g., completion of daily activities), and mortality. The use of rescue medications and oxygen therapy are also important to patients with COPD.

COPD exacerbations are defined in the 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report as episodes of acute worsening of respiratory symptom (dyspnea and/or cough and sputum production).[3] A moderate exacerbation is defined as worsening of COPD symptoms for >2 days requiring a minimum of three days of therapy with oral or systemic corticosteroids with or without antibiotics; a severe exacerbation is defined as worsening of symptoms requiring inpatient hospitalization. Rates of moderate to severe exacerbations are of particular concern to patients with COPD. Observational studies report that COPD exacerbations are associated with worsening lung function, symptoms, quality of life, and functioning (e.g., time spent outdoors),[31] and can predict future exacerbations.[32-34] Exacerbations also increasing health care resource utilization including office visits, emergency room visits, and hospitalizations.[35,36]

Clinical trials of pharmacological treatments for COPD, including Trelegy Ellipta and its therapeutic alternatives, demonstrate reductions in the number of exacerbations compared with monotherapy.[4,22,37,38] However, trials of short duration (e.g., 12 weeks) may not be powered to demonstrate reductions in COPD exacerbations. Thus, outcomes that may be more sensitive to change in the short term (e.g., symptoms) are also important in assessing trial results.

Symptoms of COPD can be measured using the Transitional Dyspnea Index (TDI). The TDI is an interviewer-administered rating used to measure change in dyspnea in three categories (functional impairment, magnitude of task, and magnitude of effort). A one-unit change has been determined to be a minimal clinically important difference (MCID) for those with a COPD diagnosis.[39]

The COPD Assessment Test (CAT) score and St. George's Respiratory Questionnaire (SGRQ) are the most commonly used measures of quality of life in studies of patients with COPD. The COPD Assessment Test (CAT) score is a self-administered questionnaire that assesses eight symptoms including coughing, phlegm, chest tightness, breathlessness, limitation to daily activities, confidence to leave home, sleep, and energy.[40] A two-point change is the MCID for patients with COPD.[41] The St. George's Respiratory Questionnaire (SGRQ) is a questionnaire designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. The self-reported questionnaire consists of 50 items evaluating symptoms (frequency and severity) and

other components (social functioning, psychological disturbances).[42] A therapy associated with a mean change of 4 units is considered slightly efficacious; eight units is moderately efficacious; and 12 units is very efficacious.[43] A recent thesis reported that the MCID should be at least seven points in patients with moderate to very severe COPD.[42]

COPD is the sixth overall leading cause of death,[5] so mortality is an essential outcome to consider.

Change in lung function is the primary outcome in many clinical trials of Trelegy Ellipta and its therapeutic alternatives. While the Food and Drug Administration (FDA) focuses on changes in lung function for approval for COPD treatments, lung function does not fully capture how the treatments help patients and is only a weak predictor of improvement in patient-reported outcomes at an individual level.[44] Thus, we are not prioritizing lung function changes in our review.

Safety

Pneumonia is a known complication of inhaled corticosteroids (ICS) and is listed in the FDA warning label for Trelegy Ellipta.[45,46] Studies also report that patients with COPD are twice as likely to be diagnosed with cardiovascular disease.[47] In addition, there are associations between COPD exacerbations and cardiovascular events.[48] Thus, cardiovascular outcomes (e.g., myocardial infarction, ischemic heart disease, stroke) are important safety outcomes to consider.

Adherence

Adherence and persistence are of particular relevance in this review because the once-daily dosing of Trelegy Ellipta may provide a significant advantage compared with therapeutic alternatives that require multiple inhalers to be used several times a day. Trelegy Ellipta is a once-daily single inhaler triple therapy while its therapeutic alternatives are administered via multiple inhalers (a dual inhaler plus a single inhaler) once or twice daily. In randomized trials, investigators teach proper inhaler use and reinforce adherence closely to optimize drug delivery. In blinded trials all groups are required to use equal number of inhalations so there is no adherence advantage to once-daily inhalers. However, in the real-world setting, patients may not receive as much coaching and adherence is usually lower. Thus, real-world effectiveness studies may be needed to assess the comparative clinical effectiveness of inhalers outside of the clinical trial setting. In this review, we used high-quality observational studies to supplement data from randomized controlled trials with particular attention to longer-term outcomes, adherence, and low-frequency harms.

Observational studies in COPD estimate adherence using the proportion of days covered (calculated using the percentage of days within a period where a patient has access to the medication based on refill dates and supply).[49] Observational studies estimated discontinuation or persistence of therapy based on a gap (>30, >45, or >60 days) between the date a prescription is filled and the next refill date.[49] However, there are challenges with the validity of these measures. Patients may refill their

medications regularly but not use them consistently and the number of doses per inhalation per canister may be higher or lower than the prescribed amount. Adherence outcomes in observational studies should be interpreted with caution and as only an approximation of consistent medication use. In addition, not all patients can effectively actuate a dry powder inhaler due to insufficient peak inspiratory flow rate, improper training, and/or dexterity issues, and may as a result not receive the full dose.

In conclusion, patient-important outcomes that are relevant for clinical efficacy include COPD exacerbations, COPD symptoms, health-related quality of life, and mortality. Safety outcomes such as serious AEs, pneumonia, and cardiovascular outcomes are also important. Finally, real-world effectiveness could be used for adherence but should be interpreted cautiously.

Breo Ellipta

Clinical Efficacy

We focused on outcomes important to patients in our assessment of therapies for COPD.[28-30] Patient-important outcomes include COPD exacerbations, COPD symptoms (e.g., dyspnea), health-related quality of life, functional status (e.g., completion of daily activities), and mortality. The use of rescue medications and oxygen therapy are also important to patients with COPD.

COPD exacerbations are defined in the 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report as episodes of acute worsening of respiratory symptom (dyspnea and/or cough and sputum production).[3] A moderate exacerbation is defined as worsening of COPD symptoms for >2 days requiring a minimum of three days of therapy with oral or systemic corticosteroids with or without antibiotics; a severe exacerbation is defined as worsening of symptoms requiring inpatient hospitalization. Rates of moderate to severe exacerbations are of particular concern to patients with COPD. Observational studies report that COPD exacerbations are associated with worsening lung function, symptoms, quality of life, and functioning (e.g., time spent outdoors),[31] and can predict future exacerbations.[32-34] Exacerbations also increasing health care resource utilization including office visits, emergency room visits, and hospitalizations.[35,36]

Clinical trials of pharmacological treatments for COPD, including Breo Ellipta and its therapeutic alternatives, demonstrate reductions in the number of exacerbations compared with monotherapy.[4,22,37,38] However, trials of short duration (e.g., 12 weeks) may not be powered to demonstrate reductions in COPD exacerbations. Thus, outcomes that may be more sensitive to change in the short term (e.g., symptoms) are also important in assessing trial results.

Symptoms of COPD can be measured using the Transitional Dyspnea Index (TDI). The TDI is an interviewer-administered rating used to measure change in dyspnea in three categories (functional

impairment, magnitude of task, and magnitude of effort). A one-unit change has been determined to be a minimal clinically important difference (MCID) for those with a COPD diagnosis.[39]

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Safety

Pneumonia is a known complication of inhaled corticosteroids (ICS) and is listed in the FDA warning label for Breo Ellipta.[50] Studies also report that patients with COPD are twice as likely to be diagnosed with cardiovascular disease.[47] In addition, there are associations between COPD exacerbations and cardiovascular events.[48] Thus, cardiovascular outcomes (e.g., myocardial infarction, ischemic heart disease, stroke) are important safety outcomes to consider.

Adherence

Adherence and persistence are of particular interest relevance in this review because the once-daily dosing of Breo Ellipta may provide a significant advantage compared with therapeutic alternatives that require multiple inhalers to be used several times a day. Breo Ellipta is a once-daily single inhaler dual therapy, while its therapeutic alternatives are used twice daily (generic SYMBICORT or ADVAIR DISKUS). In randomized trials, investigators teach proper inhaler use and reinforce adherence closely to optimize drug delivery. In blinded trials all groups are required to use equal number of inhalations so there is no adherence advantage to once-daily inhalers. However, in the

real-world setting, patients may not receive as much coaching and adherence is usually lower. Thus, real-world effectiveness studies may be needed to assess the comparative clinical effectiveness of inhalers outside of the clinical trial setting. In this review, we used high-quality observational studies to supplement data from randomized controlled trials with particular attention to longer-term outcomes, adherence, and low-frequency harms.

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In conclusion, patient-important outcomes that are relevant for clinical efficacy include COPD exacerbations, COPD symptoms, health-related quality of life, and mortality. Safety outcomes such as serious AEs, pneumonia, and cardiovascular outcomes are also important. Finally, real-world effectiveness could be used for adherence but should be interpreted cautiously.

3. Comparative Clinical Evidence

3.1. Interventions and Therapeutic Alternatives

To estimate the comparative therapeutic impact of Trelegy Ellipta and Breo Ellipta in patients with at least moderate COPD (defined in Supplement Section A1),[3] we compared each drug to their generic comparators.

Trelegy Ellipta

For Trelegy Ellipta, we first performed a network meta-analysis of randomized trials of triple therapy to assess comparative efficacy and safety, independent of adherence. We then assessed additional data from clinical trials comparing Trelegy Ellipta with generically available triple therapies. Finally, we sought evidence from observational studies on adherence and the impact of adherence on outcomes to supplement the randomized trial data.

Breo Ellipta

For Breo Ellipta, we reviewed findings from clinical trials comparing it with generically available dual therapies. Data related to adherence and long-term harms were sought from observational studies.

3.2 Trelegy Ellipta

Methods Overview

Detailed methods for the systematic literature review assessing the evidence on Trelegy Ellipta for the treatment of patients with at least moderate COPD are available in Supplement Section D1.

Evidence Base

We reviewed the comparative efficacy of all available triple therapies in patients with at least moderate COPD. Our search identified five systematic reviews and network meta-analyses (NMAs) comparing triple therapy combinations. The most recent was published in July 2022.[20,22,23,37,51] The conclusions of the NMAs differed due to differences in inclusion criteria and statistical methods. We updated the NMA with new evidence and included only randomized controlled trials (RCTs) that ensured participants in all arms of the trial were prescribed the same number of inhalers with the same dosing schedule to assess the efficacy of different triple therapy regimens independent of treatment adherence. Additional details about the prior NMAs and our methods can be found in the Supplement Section D1.

Evidence on Trelegy Ellipta included one Phase III RCT and two Phase IV RCTs.[52-56] The Phase III trial was deemed low risk of bias, but the two replicated Phase IV trials raised some concerns for bias for the COPD exacerbation outcome because it was only available from the manufacturer's clinical study report and the data analysis plan for this outcome was not reported.

Our search did not identify any observational studies directly comparing Trelegy Ellipta with generic alternatives. To estimate the effectiveness of Trelegy Ellipta versus any single inhaler triple therapies (SITTs) or multiple inhaler triple therapies (MITTs), we included one single-arm observational study[57] and ten claims-based observational studies: three compared two SITTs (FF/UMEC/VI vs BUD/FOR/GLY)[24,58,59]; two compared single-inhaler Trelegy Ellipta with MITTs [49,60]; three compared single-inhaler Trelegy Ellipta with both SITT and MITTs[61-63]; and two used a pre-post cohort study design with MITTs followed by Trelegy Ellipta[64,65]. See Supplement Table D3.1. for additional details about these studies. These observational studies were deemed to be at risk of bias due to confounding, selection bias, and lack of a protocol describing prespecified analyses.

Clinical Trial Evidence for Trelegy Ellipta versus Listed Comparators

Our search identified one Phase III RCT comparing single-inhaler Trelegy Ellipta with multiple inhaler FF/VI plus UMEC (i.e., components of Trelegy Ellipta) and two Phase IV RCTs comparing single-inhaler Trelegy Ellipta with multiple inhaler BUD/FOR plus TIO. All trials administered Trelegy Ellipta along with dummy inhalers to ensure that the number of inhalers used in all arms of the trials was identical. These three non-inferiority trials enrolled participants 40 years of age and above with a current diagnosis of COPD and a CAT score ≥10. Participants with a current diagnosis of asthma were excluded. Baseline characteristics were comparable between the treatment arms in all trials.[52,54] Additional details about these studies can be found in Supplement Section D2.1.

Observational Studies for Trelegy Ellipta

Our search identified 11 observational studies. Six of these 11 studies utilized databases from the US,[24,49,58-60,64] two from England,[61,65], two from Germany[57,62], and one from Japan [63]. The sample size of these studies ranged from 906 to 32,312 participants. The study populations were comparable to trial populations with respect to mean age (60-75 years), sex at birth (female 21-56%), and current smoker status (23-68%). A key difference between the clinical trials above and these observational studies was the inclusion of COPD patients with a prior asthma diagnosis. Three studies excluded patients with a concurrent asthma diagnosis at baseline.[58,59,64] Eight studies included those with a prior asthma diagnosis, totaling 8% to 80% of the study samples.[24,49,57,60-63,65] Additional details on study design and baseline characteristics of these observational studies are reported in Supplement Section D2.1 and Supplement Tables D3.1, D3.3-D3.5.

Evaluation of Clinical Trial Diversity

We rated the demographic diversity (race/ethnicity, sex, age) of the participants in the trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[66] The three Trelegy Ellipta trials achieved "fair" diversity for race/ethnicity and age, driven mostly by the underrepresentation of those who identify as Black or African American and those over 65 years of age with COPD. Two trials trial achieved "good" diversity on sex and one trial received a "poor" diversity rating as females were underrepresented. See Supplement D1 for full details of CDR methods and results.

Results

Clinical Benefits

NMA Evidence from Trials Comparing All Available Triple Therapies

The NMA found no significant differences in the annualized rate of moderate to severe exacerbations between single-inhaler FF/UMEC/VI and any of the included triple therapy combinations in patients with at least moderate COPD. Both single-inhaler FF/UMEC/VI and multiple inhaler BUD/FOR plus TIO had lower point estimates compared to other available triple therapy combinations, but these differences were not statistically significant. See Table 3.1 and Supplement Table D3.17.

The NMA also showed no significant differences in quality of life as assessed by the SGRQ total score across the triple therapies. See Supplement Tables D2.4 and D3.19.

Table 3.1. NMA Results: Relative Rates of Moderate to Severe Exacerbations with Triple Therapies for COPD

FF/UMEC/VI								
0.61 (0.24, 1.59)	BDP/FOR/GLY							
0.78 (0.29, 2.05)	1.27 (0.32, 4.87)	BUD/FOR/GLY						
0.81 (0.33, 2.11)	1.31 (0.37, 5.06)	1.03 (0.29, 4.12)	FF/VI + UMEC HD					
0.95 (0.53, 1.94)	1.55 (0.53, 5.17)	1.22 (0.41, 4.25)	1.09 (0.53, 2.72)	FF/VI + UMEC LD				
0.62 (0.23, 1.7)	1.01 (0.48, 2.13)	0.8 (0.20, 3.27)	0.77 (0.19, 2.88)	0.64 (0.19, 2.01)	BDP/FOR + TIO			
1.08 (0.63, 1.86)	1.76 (0.68, 4.50)	1.39 (0.46, 4.26)	1.34 (0.44, 3.76)	1.13 (0.46, 2.46)	1.74 (0.64, 4.73)	BUD/FOR + TIO		
0.57 (0.22, 1.50)	0.93 (0.42, 2.04)	0.73 (0.19, 2.90)	0.71 (0.18, 2.57)	0.60 (0.18, 1.79)	0.92 (0.36, 2.37)	0.53 (0.20, 1.38)	FP/SAL HD + TIO	
0.57 (0.18, 1.84)	0.92 (0.29, 2.99)	0.73 (0.16, 3.37)	0.70 (0.15, 3.04)	0.59 (0.15, 2.15)	0.92 (0.27, 3.09)	0.52 (0.16, 1.70)	1 (0.30, 3.23)	FP/SAL LD + TIO

Each box represents the estimated relative risk and 95% credible interval. The shaded column represents the comparisons for Trelegy Ellipta versus other triple therapies: all credible intervals include 1 indicating no statistically significant differences. Individual trial data can be found in Supplement Table D3.17.

BDP: beclomethasone dipropionate, BUD: budesonide, FF: fluticasone furoate, FOR: formoterol fumarate, FP: fluticasone propionate, GLY: glycopyrronium, HD: high dose, LD: low dose, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Direct Evidence from Trials Comparing Trelegy Ellipta with Listed Comparators

Moderate to Severe COPD Exacerbations

Results from key clinical trials of Trelegy Ellipta for annualized rates of moderate to severe exacerbations were generally consistent with the NMA findings. The efficacy of single-inhaler FF/UMEC/VI was compared with multiple inhaler FF/VI plus UMEC in the Phase III trial. After 24 weeks, the annualized rates of moderate to severe exacerbations were similar (0.85 vs 0.70, p=NS).[53] Similarly, in the two trials that compared single-inhaler FF/UMEC/VI with multiple inhaler BUD/FOR plus TIO over 12 weeks, there were no treatment differences.[55,56] See Table 3.2 and Supplement Table D3.6.

Table. 3.2. Key Outcomes of Trelegy Ellipta Trials

Trial	Bremner 2018[52,53]		Ferguson 2020[54,55] NCT03478683		Ferguson 2020[54,56] NCT03478696	
Treatment Arm	**FF/UMEC/ VI**	**FF/VI + UMEC**	**FF/UMEC/ VI**	**BUD/FOR + TIO**	**FF/UMEC /VI**	**BUD/FOR + TIO**
N	**527**	**528**	**363**	**365**	**366**	**366**
Moderate / Severe COPD Exacerbations						
≥ 1 Exacerbation, n (%)	129 (24)	142 (27)	33 (9)	35 (10)	47 (13)	42 (11)
Exacerbation Rate	0.70	0.85	0.46	0.50	0.62	0.58
Rate Ratio, (95% CI)	0.83 (0.67, 1.02)		0.91 (0.59, 1.41)		1.07 (0.72, 1.59)	
Transitional Dyspnea Index (TDI) Focal Score						
n evaluated	482	481	NR			
LS Mean change from baseline, (95% CI)	2.0 (1.8, 2.3)	1.9 (1.6, 2.1)				
Treatment difference, (95% CI)	0.1 (-0.2, 0.5)					
COPD Assessment Test (CAT) Score						
n evaluated	NR		348	344	344	347
LS Mean change from baseline, (95% CI)			-0.8 (-1.4, -0.3)	-0.2 (-0.8, 0.3)	-0.2 (-0.7, 0.3)	-0.1 (-0.6, 0.4)
Treatment difference, (95% CI)			-0.6 (-1.4, 0.2); p=0.141		-0.1 (-0.8, 0.6); p=0.746	
St. George's Respiratory Questionnaire (SGRQ) Score						
n evaluated	489	483	344	342	343	342
LS Mean change from baseline, (95% CI)	-5.8 (-7.0, -4.7)	-4.9 (-6.1, -3.8)	-1.2 (-2.2, -0.2)	-1.3 (-2.3, -0.3)	-1.5 (-2.6, -0.4)	-1.5 (-2.6, -0.4)
Treatment difference, (95% CI)	-0.9 (-2.5, 0.7)		0.1 (-1.3, 1.5); p=0.926		0.0 (-1.5, 1.6); p=0.609	

95% CI: 95 percent confidence interval, BUD: budesonide, FF: fluticasone furoate, FOR: formoterol fumarate, LS: least-squares, n: number, N: total number, NR: not reported, p: p-value, SD: standard deviation, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

COPD Symptoms and Health-Related Quality of Life (HRQoL) Measures

In the trials that measured changes from baseline in Transitional Dyspnea Index (TDI), COPD Assessment Test (CAT), or St George's Respiratory Questionnaire (SGRQ) total scores, there were no clinically or statistically significant differences between the arms of the studies.[52,54] See Table 3.2.

Lung Function

Lung function assessed using the percentage predicted FEV_1 was the primary endpoint in all three trials. Single inhaler FF/UMEC/VI was non-inferior to both multiple inhaler FF/VI plus UMEC and BUD/FOR plus TIO in the trials.[52,54] See Supplement Section D2.1.

Harms

NMA Evidence from Trials Comparing All Available Triple Therapies

We also conducted an NMA for discontinuations due to adverse events. There were no significant differences in discontinuation rates among the triple therapy combinations. See Supplement Section D1 and Supplemental Tables D2.5 and D3.18 for details.

Direct Evidence from Trials Comparing Trelegy Ellipta with Therapeutic Alternatives

Harms were higher in the Phase III trial compared to the two Phase IV trials because of a longer follow-up period, but the between-group differences were minimal in all three trials (Table 3.3). There are concerns about the risk of pneumonia among COPD patients receiving triple therapy combinations because of the inhaled corticosteroid. However, the incidence rates were low and comparable between the triple therapy arms across three trials.

In the Phase III trial, the discontinuation rate due to adverse events was higher in the single-inhaler FF/UMEC/VI arm compared to the multiple inhaler FF/VI plus UMEC arm.[52] However, pooled analysis of the two additional trials reported discontinuations due to adverse events occurring more frequently in the multiple inhaler BUD/FOR plus TIO arm compared to the single-inhaler FF/UMEC/VI arm.[54] Additional details are available in Table 3.3 and Supplemental Table D3.11.

Table. 3.3. Key Harms of Trelegy Ellipta Trials

Trial	Bremner 2018[52] NCT02729051		Ferguson 2020[54] NCT03478683		Ferguson 2020[54] NCT03478696	
Treatment Arm	**FF/UMEC/ VI**	**FF/VI + UMEC**	**FF/UMEC/ VI**	**BUD/FOR + TIO**	**FF/UMEC/ VI**	**BUD/FOR + TIO**
N	**527**	**528**	**363**	**365**	**366**	**366**
Follow-Up Period	**24 Weeks**		**12 Weeks**			
Any Adverse Events	255 (48)	253 (48)	131 (36)	121 (33)	92 (25)	109 (30)
Serious Adverse Events	52 (10)	57 (11)	25 (7)	14 (4)	12 (3)	17 (5)
Adverse Events Leading to Discontinuations	20 (4)	11 (2)	8 (2)	8 (2)	2 (<1)	6 (2)
Death	4 (<1)	4 (<1)	0	0	0	1 (<1)
Pneumonia	14 (3)	21 (4)	5 (1)	6 (2)	2 (<1)	3 (1)
Cardiovascular Events	30 (6)	28 (5)	10 (3)	8 (2)	11 (3)	8 (2)
Lower Respiratory Tract Infection	16 (3)	11 (2)	9 (2)	1 (<1)	1 (<1)	1 (<1)

Data are presented as number (%)

BUD: budesonide, FF: fluticasone furoate, FOR: formoterol fumarate, N: total number, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Observational Studies

We evaluated the adherence and persistence of Trelegy Ellipta compared with other triple therapies in 11 observational studies of patients with COPD. There were no high-quality comparative cohort studies or open-label randomized trials available to assess the impact of adherence or persistence with inhaler therapy on exacerbation rates, dyspnea, or quality of life.

Adherence

Six out of 11 observational studies reported data on treatment adherence using the proportion of days covered (PDC).[49,59-63] In all cases, adherence rates were low. The mean PDC for single-inhaler FF/UMEC/VI ranged from 0.51 to 0.61 while the mean PDC for MITTs ranged from 0.36 to 0.40, suggesting somewhat better adherence with single-inhaler FF/UMEC/VI. Additionally, a higher proportion of patients using single-inhaler FF/UMEC/VI (0.07 to 0.55) were at or above 80% adherence compared to the MITTs (0.04 to 0.30, Table 3.4).

Persistence

Four observational studies reported data on treatment non-persistence defined by the number of days between refills of medication.[49,59,61,62] However, definitions of this outcome varied across studies (gaps of ≥30, ≥45, or ≥60 days for non-persistence). Overall, more patients using single-inhaler FF/UMEC/VI achieved persistence than those with MITTs (23%-38% vs. 4%-14%) and single-inhaler BUD/FOR/GLY(44% vs. 38%). Despite its advantages, persistence for Trelegy Ellipta was low (<45% in all studies). See Table 3.4.

Table. 3.4. Treatment Adherence and Persistence at 12 Months from Observational Studies

Trial	Treatment	N	Proportion of Days Covered (PDC)		Proportion of Persistent Patients*
			Mean (SD)	PDC ≥0.8, %	%
Bogart 2024[60] (MAPD only)	**FF/UMEC/VI**	4,659	0.51 (0.3)	26	NR
	MITT	9,845	0.38 (0.3)	13	
Halpin 2022[61]	**FF/UMEC/VI**	622	0.61	33.6	38.1
	MITT	3,169	0.39	14.9	14.4
Mannino 2022[49]	**FF/UMEC/VI**	1,337	0.60 (0.34)	43.2	35.7
	MITT	3,442	0.40 (0.32)	17.4	13.9
Vogelmeier 2024[62]	**FF/UMEC/VI**	675	0.54 (0.11)	54.7	23.0
	MITT	4,079	0.36 (0.07)	29.9	4.4
Jokšaitė 2024[63]	**FF/UMEC/VI**	1,401	NR	6.6	NR
	MITT	1,909		3.8	
Young 2024[59]	**FF/UMEC/VI**	5,367	0.57	35.1	43.9
	BUD/FOR/GLY	1,268	0.50	24.8	38.2

*Variably defined non-persistence as a gap between refills of medication of longer than 30, 45, or 60 days
BUD: budesonide, FF: fluticasone furoate, FOR: formoterol, GLY: glycopyrronium, MAPD: Medicare Advantage with Part D, MITT: multiple inhaler triple therapy, n: number, N: total number, PDC: proportion of days covered, SD: standard deviation, UMEC: umeclidinium, VI: vilanterol

Moderate to Severe COPD Exacerbations

Four out of 11 observational studies reported data on moderate to severe COPD exacerbations.[24,58,64,65] Two claims-based US studies reported 6-12% lower risk of moderate to severe COPD exacerbations among participants initiating single-inhaler, once-daily FF/UMEC/VI compared those initiating single-inhaler, twice-daily BUD/FOR/GLY.[24,58] Two additional pre-post studies reported that 45-56% of patients experienced ≥1 moderate to severe exacerbations after 12 months post-initiation of FF/UMEC/VI compared to 51-62% in the pre-index period.[64,65] Study details are available in Supplement Section D2.1 and Supplement Tables D3.7-D3.8.

Long-Term Harms

Data on long-term harms of Trelegy Ellipta were reported in three observational studies.[24,57,58] In one study comparing once-daily FF/UMEC/VI and twice-daily BUD/FOR/GLY, there were no differences in rates of hospitalizations due to pneumonia or all-cause mortality between the two therapies.[24] Another claims-based study, funded by the manufacturer of Trelegy (GSK), compared the same two single inhalers and reported an 11% lower risk of all-cause mortality among Medicare fee-for-service patients initiating FF/UMEC/VI compared to those initiating BUD/FOR/GLY (5.6% vs. 6.4%; HR 0.89, 95% CI 0.80, 0.98, p=0.020) despite no statistically significant differences in the rate of severe COPD exacerbations (0.13 vs. 0.13). In addition, there were no statistically significant differences in mortality by inhaler type for COPD patients with Medicare Advantage, Medicaid, or

commercial insurance plans.[58] Additional harms data from the single-arm study are described in Supplement Section D2.

Summary of Findings

In summary, our NMA found no differences in moderate to severe COPD exacerbation rates between Trelegy Ellipta and other available triple therapy combinations. Clinical trials also found no differences between Trelegy Ellipta and generically available alternatives in moderate to severe COPD exacerbations and quality of life measures. Adverse events were comparable across all arms in the included trials and observational studies. Observational studies reported better adherence and persistence with single-inhaler Trelegy Ellipta than with multiple inhaler triple therapy combinations but both adherence and persistence rates were low.

Uncertainty and Controversies

The most important uncertainty in the clinical evidence is how modestly better adherence and persistence with once-daily therapy translates into clinical benefits that matter to patients: moderate to severe COPD exacerbations, shortness of breath, fatigue, and HRQoL. This is particularly challenging in observational studies because of the problem of reverse causality: patients with worse disease and more exacerbations may receive more coaching about using their inhalers and be more motivated to continue to use them. Thus, it is possible to observe that patients who are more adherent have more exacerbations and lower quality of life. In addition, patients with more severe disease are more likely to have trouble generating enough inspiratory force to trigger dry powder inhalers and thus suffer from inadvertent non-adherence. The proportion of days (PDC) covered by prescriptions was low with both Trelegy Ellipta and multiple inhaler triple therapy, but consistently favored Trelegy Ellipta by about 20% (~60% for Trelegy Ellipta and ~40% for multiple inhaler triple therapy) (Table 3.4). However, we have no clear data linking PDC to exacerbation rates or quality of life for patients with COPD. Persistence rates were very low (<40%) for all therapies, but generally 15% to 20% higher with Trelegy Ellipta. Again, we have no data quantifying the relationship between inhaler persistence and outcomes.

The existing clinical trials are of short duration (12-24 weeks) and so provide indirect evidence when evaluating inhaler impact on a life-long, progressive disorder like COPD. In addition, the primary outcomes in the trials were measures of lung function, not the outcomes important to patients (moderate to severe exacerbations, requirement for oxygen therapy, functional outcomes, quality of life, and mortality).

While HRQoL is an important outcome, patient groups raised the concern that existing HRQoL measures focus only on physical symptoms and limitations caused by COPD, and that they do not adequately address the psychosocial burden of a disease that may affect a patient's ability to engage in meaningful life activities (e.g., work, travel, playing with grandchildren, participation in community events). Thus, current measures may underestimate the impact of COPD symptoms on a person's quality of life.[67]

Data on the effectiveness of triple therapies has only indirect measures of both discontinuation of therapy and adherence using estimates based on medication refills. In addition, the definitions of adherence and persistence varied across the studies. Finally, none of the observational studies directly compared Trelegy Ellipta to generic triple therapy.

3.3 Breo Ellipta

Methods Overview

Detailed methods for the systematic literature review assessing the evidence on Breo Ellipta for the treatment of patients with at least moderate COPD are described in Supplement Section D1.

Evidence Base

The evidence for Breo Ellipta compared with generically available dual therapies was derived from four Phase III randomized controlled trials (RCTs) and one observational study.[68-74] The risk of bias was considered low for three trials (i.e., NCT01323621, NCT01323634, and NCT01342913) for the moderate to severe COPD exacerbation outcome. However, there were concerns about the NCT01706328 trial because of inconsistent reporting and inadequate analysis plan. The observational study from Stanford et al. was considered to be high risk of bias due to confounding, limited monitoring of intervention delivery (e.g., frequency and timing of dose), and lack of protocol to determine prespecified analyses.

Clinical Trials

Our search identified four clinical trials. Dransfield et al. 2014 reported data on 1,858 patients from three RCTs, all designed and conducted using a similar approach.[68] These Phase III trials included a two-week, single-blind, placebo run-in period and a 12-week, double-blind, randomized treatment period of either FF/VI 100/25 mcg once daily plus twice daily placebo or FP/SAL 250/50 mcg twice daily plus once daily placebo. Patients with COPD were eligible to participate if they were ≥40 years old, had a post-bronchodilator FEV_1/FVC ratio of ≤0.70, and had a smoking history of at least 10 pack-years. Baseline characteristics were similar in all arms and trials.

The fourth trial from Agustí et al. 2014 compared FF/VI 100/25 mcg once daily plus placebo with FP/SAL 500/50 mcg twice daily plus placebo.[72] Although a lower corticosteroid dose (250 mcg) was approved as a maintenance treatment for COPD and this higher FP dose was approved for the treatment of asthma, this trial was specifically designed to include the COPD population only. Additional details about design and baseline characteristics are available in Supplement Tables D3.13-D3.14.

Observational Studies

Our search identified one observational study. Stanford et al. 2019 conducted an observational study in which patients with COPD were selected from commercial and Medicare Advantage Prescription Drug (MAPD) health plans using the Optum Research Database.[74] This retrospective, new-user cohort study included patients aged ≥40, with at least one COPD diagnosis code and one pharmacy claim for either once-daily FF/VI 100/25 mcg or twice-daily BUD/FOR 160/4.5 mcg. Additional requirements were 12 months of continuous enrollment prior to the index date (i.e., started FF/VI or BUD/FOR) and another three to twelve months of continuous enrollment as a follow-up period. COPD exacerbation was assessed as a key secondary outcome in this study. See Supplement Table D2.6. This study reported data on a propensity score-matched cohort of 4,513 patients in each treatment group. The mean age of the matched cohort was 69, with more than half of the patients being female. Around 28% of the cohort were diagnosed with asthma and more than 40% of the included patients had a moderate to high comorbidity burden.

Evaluation of Clinical Trial Diversity

We rated the demographic diversity (race/ethnicity, sex, age) of the participants in the trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[66] Three of the four Breo Ellipta trials were given a "poor" diversity rating on race/ethnicity as they underrepresented Black/African American, Asian, and Hispanic individuals with COPD, recruiting 94%-98% White individuals. The fourth trial was rated as "fair" as this trial adequately represented Asian and White individuals. The trials also underrepresented females and thus received a "fair" diversity rating for sex. Diversity in age was not examined due to lack of reporting. See Supplement D1 for full details of CDR methods and results.

Results

Clinical Benefits

Moderate to Severe COPD Exacerbations

In a pooled analysis of three Phase III trials, Dransfield et al. 2014 reported that a similar proportion of participants receiving FF/VI 100/25 mcg and FP/SAL 250/50 mcg experienced moderate to severe COPD exacerbations during the 12-week randomized treatment period (4% vs. 3%) .[68] Data from Agustí et al. 2014 also found that similar proportions of participants experienced moderate to severe COPD exacerbations in both the FF/VI 100/25 mcg and the FP/SAL 500/50 mcg treatment groups (2-3%).[72] There were no differences in the proportions of participants using steroids, being hospitalized, or taking antibiotics between the two arms in all trials.[69-71,73] See Supplement Table D3.15.

Health-Related Quality of Life (HRQoL)

The three trials included in Dransfield et al. 2014 did not measure SGRQ. In Agustí et al. 2014 the SGRQ total scores decreased in both groups after 12 weeks with no statistically significant differences between the two treatment groups (FF/VI vs. FP/SAL -1.3, 95% CI -3.5 to 0.8; p=0.22).[72] See Supplement Table D3.15.

The EuroQol Questionnaire which includes five dimensions of the descriptive system section (EQ-5D) and a visual analog score (VAS) was only measured in Agustí et al. 2014 at baseline and end of the 12-week randomized treatment period.[73] There were no statistically significant differences between the two treatment groups for any of the five dimensions of the descriptive system section or EQ-5D VAS after 12 weeks. See Supplement Table D3.15. None of these trials reported data on TDI focal score, CAT score, and functional capacity.

Lung Function

Lung function assessed using the percentage predicted FEV_1 was the primary endpoint in all four clinical trials of Breo Ellipta. There were no statistically significant differences between FF/VI and FP/SAL in changes from baseline in weighted mean FEV_1 after 12 weeks of follow-up.

Harms

All three trials comparing FF/VI 100/25 mcg with FP/SAL 250/50 mcg reported similar proportions of participants experiencing any adverse events (28%), serious adverse events (3%), treatment discontinuations (9%), and discontinuations due to adverse events (3%) across both arms in the pooled analysis. Two participants (<1%) died due to adverse events in the FF/VI 100/25 mcg arm compared to four (<1%) in the FP/SAL 250/50 mcg arm. Eight participants (<1%) had pneumonia in the FF/VI 100/25 mcg arm compared to four (<1%) in the FP/SAL 250/50 mcg arm during the treatment period. The pooled analysis found that 2% of the participants experienced cardiovascular events in each arm.[68] See Supplement Table D3.16 for additional information.

Agustí et al. 2014 reported data on participants receiving FF/VI 100/25 mcg or FP/SAL 500/50 mcg.[72] There were no differences in the proportions of participants experiencing any adverse events in this trial (27% in the FF/VI 100/25 mcg group vs 26% in the FP/SAL 500/50 mcg group). There were nine non-fatal serious adverse events in total, affecting more participants in the FF/VI 100/25 mcg group (2%) compared to the FP/SAL 500/50 mcg group (1%). Six participants (2%) receiving FF/VI 100/25 mcg died compared to three participants (1%) receiving FP/SAL 500/50 mcg. Three participants had pneumonia during the treatment period: one in the FF/VI 100/25 mcg group and two in the FP/SAL 500/50 mcg group.[73] See Supplement Table D3.16 for additional information.

Observational Study

Adherence and Persistence

Findings from the Stanford et al. 2019 observational study suggest better adherence with once-daily FF/VI compared to twice-daily BUD/FOR as measured by mean proportion of days covered (PDC) (0.46 vs 0.41, p<0.001) and higher proportion of patients achieving 80% cut-off point for PDC in FF/VI compared to BUD/FOR (25% vs 18%).[74]

COPD Exacerbations

Stanford et al. 2019 reported a 9% reduced risk of having a moderate to severe COPD exacerbation in participants initiating FF/VI compared to those initiating BUD/FOR (adjusted HR: 0.91; 95% CI 0.85, 0.96; p<0.001).[74]

Long-Term Harms

Data on long-term harms were not available in Stanford et al. 2019.

Summary of Findings

A Cochrane review found that all ICS/LABA inhalers were equivalent to each other.[4] The Breo Ellipta clinical trials found no differences in moderate to severe COPD exacerbations and HRQoL measures (SGRQ and EQ-5D). However, in one observational study, there was a small reduction in moderate to severe exacerbations among participants initiating Breo Ellipta compared to those initiating BUD/FOR.[74] Adherence was marginally better in the once-daily Breo Ellipta than in generic twice-daily dual therapy combinations. Harms were comparable across treatment groups in all studies.

Uncertainty and Controversies

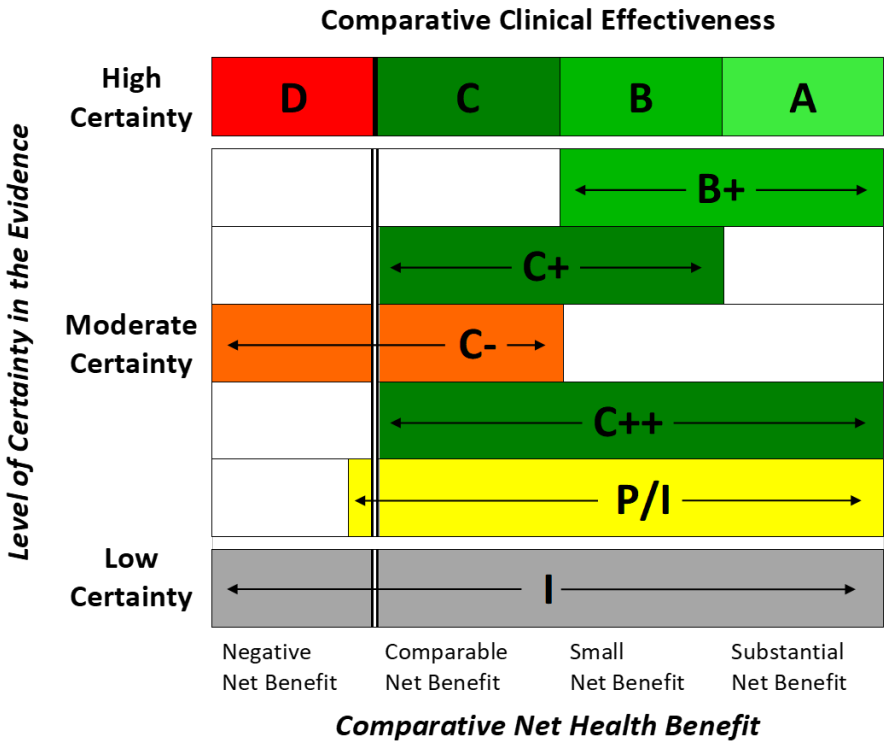
The most important uncertainty in the clinical evidence is how modestly better adherence and persistence with once-daily therapy translates into clinical benefits that matter to patients: moderate to severe COPD exacerbations, shortness of breath, fatigue, HRQoL. This is particularly challenging in observational studies because of the problem of reverse causality: patients with worse disease and more exacerbations may receive more coaching about using their inhalers and be more motivated to continue to use them. Thus, it is possible to observe that patients who are more adherent have more exacerbations and lower quality of life. In addition, patients with more severe disease are more likely to have trouble generating enough inspiratory force to trigger dry powder inhalers and thus suffer from inadvertent non-adherence. Adherence and persistence were higher with the once-daily inhaler Breo Ellipta than with twice-daily dual therapies, but the link to clinical benefits is uncertain.

In addition, none of the major guidelines (GOLD, American Thoracic Society, NICE) recommend the use of dual therapy with ICS/LABA, such as Breo Ellipta, for the treatment of COPD. The recommended dual therapy is a LAMA/LABA and if an ICS is required, then triple therapy is recommended.

3.4. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" *- Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Trelegy Ellipta

Our NMA and all prior NMAs, other than one published by the manufacturer of Trelegy Ellipta, found that all triple therapies have equivalent outcomes when used as prescribed. Efficacy of these therapies are best assessed in blinded and double dummy-controlled trials in which all participants share the same schedule of inhaled medications. However, Trelegy Ellipta offers the advantage of requiring only one puff once a day, while the comparators require multiple inhalers administered usually twice daily. Observational data suggests that patients are poorly adherent to all therapies but modestly more adherent to once-daily therapy, and this may lead to fewer COPD exacerbations, though the results have at best moderate certainty. Patients also prefer once-daily therapy. There are no important differences in harms between the triple therapies. Thus, we conclude that Trelegy Ellipta has comparable or incremental net health benefits compared with other generic triple therapies requiring multiple inhalers (C+).

Breo Ellipta

Current guidelines do not recommend using ICS/LABA therapy, like Breo Ellipta, for the management of COPD. However, they have been commonly used in the past and Breo Ellipta has an FDA indication for COPD. A Cochrane review found that the combination of a LAMA/LABA was superior to other dual combination therapies for COPD and that the other combinations, including ICS/LABA were equivalent to each other.[4] Breo Ellipta offers the advantage of requiring only one puff once a day, while the comparators with similar components require twice daily use. Observational data suggests that patients are slightly more adherent to once-daily therapy and that this may lead to fewer COPD exacerbations, though the results have at best moderate certainty. Patients also prefer once-daily therapy. There are no important differences in harms between dual therapies. Thus, we conclude that Breo Ellipta has comparable or incremental net health benefit compared with generic ICS/LABA dual therapies (C+).

4. Specific Populations and Patient Experience

4.1 Comparative Clinical Effectiveness – Subgroup Analyses and Heterogeneity

We did not find evidence of major differences in the balance of risks and benefits for patients with ESRD, the elderly, or those with terminal illness (e.g., cancer). There is currently no reported evidence that examined differences in risk and benefits for children or those with disabilities.

4.2 Patient Experience

This report was developed with input from multiple stakeholders, including patients, clinicians, researchers, payers, and the manufacturer of the Trelegy and Breo Ellipta. We updated ICER's prior assessment of the patient perspective by interviewing five people living with COPD, specifically about their use of inhalers and the impact of different inhaler schedules on their quality of life.

Treatment for COPD can be complex. Inhaled medications are a mainstay of therapy; however, patient groups, clinicians, and payers all brought up the concern that patients often have difficulty with proper inhaler technique, which may decrease the effectiveness of the treatments. They expressed frustration that clinicians do not take the time to demonstrate proper inhaler technique, particularly when prescribing a new inhaler. They also encouraged regular re-assessment of inhaler technique. Side effects of inhaled therapies include dry mouth, thrush, dental caries, and pneumonia.

Patients also reported how their comorbidities add to the challenges in proper use of their inhalers. Patients with arthritis have a hard time activating the inhalers. Patients with tremors have a hard time with proper positioning of the inhalers. Weaker patients may have trouble generating sufficient inspiratory force to trigger certain inhalers. Finally, patients with cognitive impairment have challenges remembering to take their inhalers and how to properly use the inhalers.

Patients consistently reported that once daily regimens were much easier than twice-daily regimens, particularly those that encourage dosing every 12 hours. Once-daily regimens were also much easier when traveling, particularly when changing multiple time zones. Taking one or more puffs at a time was not particularly bothersome, particularly when compared with inhalations that have to be taken twice a day. Finally, patients reported that it was easier to use inhalation devices that did not require the use of a spacer.

Patients expressed that prevention and management of exacerbations is an important part of disease management. Exacerbations are particularly common after respiratory infections, so patients described strategies to try to avoid respiratory infections whenever possible. They also expressed that it can take a long time to recover from a more severe exacerbation and that one may not completely recover to one's prior baseline. Some people with COPD formed a written plan with their doctor to understand what their respiratory status was and potential interventions when they have increased symptoms (e.g., American Lung Association COPD Action Plan).

4.3 Health Equity Considerations

COPD affects approximately 11.7 million (4.6%) of adults in the United States (US), with higher rates among non-Hispanic White individuals, American Indian/Alaska Native individuals, women, and adults older than 65.[5,6,75]

Women with COPD have been observed to be younger, smoke less, and have more dyspnea than men; women also account for a higher proportion of hospitalizations.[14,15] Lower socioeconomic status has been linked with greater disease progression.[16]

5. Comparative Effectiveness and Cost

5.1 Unmet Need

5.1.1 Qualitative Discussion

CMS defines unmet need as "treating a disease or condition in cases where no other treatment options exist, or existing treatments do not adequately address the disease or condition." Current dual and triple pharmacological treatments generally offer symptom management and reduced exacerbations compared to single therapy, with escalation of therapy for patients who are not adequately controlled. Some dual or triple therapies require multiple inhalations every day, sometimes with different inhalers, which can lead to poor adherence among patients with COPD. Even though single-use triple therapies may address issues of adherence, patients remain at risk of disease progression, as all currently-available treatments address symptoms only, and do not impact the course or trajectory of the disease.

5.1.2 Quantitative Discussion

Decision-analytic models, often used to support estimates of value-based drug pricing, can also produce quantitative assessments of unmet need. Calculations of proportional and absolute health "shortfall" are two different ways of representing society's considerations for severity or burden of illness. They are complementary measures that estimate the reduction in lifetime health due to a condition compared with health in the age- and sex-matched general US population. Using the decision-analytic model described in Section 5.2, we calculated proportional and absolute shortfalls in health using the equal-value of life year (evLY) measure.

We attest that all measures of health used throughout this report, most prominently the evLY, do *not* treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. The evLY treats the value of extended life of all individuals in exactly the same way, with each year of life gained from treatment valued identically. The evLY has served for many years as a bedrock of ICER's drug price benchmarks that are used by the Veterans Administration, Medicaid programs, and private insurers. In our public comments on the CMS draft guidance, we provided further rationale for why the evLY is consistent with the IRA and will be helpful to CMS in its deliberations. A detailed description of the evLY calculation can be found in the Supplement Section E1.

To quantify unmet need for patients with at least moderate COPD, we present evLY shortfall calculations assuming that patients have reached the maximal inhaled therapy recommended by the GOLD guidelines. We chose FF/UMEC/VI to represent the maximal inhaled therapy because it meets or exceeds the standard of care for patients with at least moderate COPD. To calculate the

absolute evLY shortfall, we subtracted the lifetime undiscounted evLYs with FF/UMEC/VI from the evLYs expected for the general population (calculated using age- and sex-adjusted estimates for mortality and a constant utility of 0.851 for quality of life). To calculate the proportional evLY shortfall, we divided the absolute evLY shortfall by the evLY life expectancy for the general population with the same age and sex distribution at baseline. Results are presented in Section 5.2.

The undiscounted absolute shortfall for Medicare patients with at least moderate COPD who have reached the maximal inhaled therapy recommended by the GOLD guidelines (e.g., FF/UMEC/VI) was 6.77 evLYs versus the general age- and sex-adjusted US population. The undiscounted proportional shortfall was 6.77/15.09=44.8%. For context, as shown in Table 5.1, the absolute evLY shortfall for Medicare patients with at least moderate COPD treated with triple therapy is similar to that observed with ulcerative colitis, but substantially less than observed for beta thalassemia. The proportional shortfall was similar to that for patients living with prostate cancer, but substantially less than for patients with multiple myeloma. The shortfalls were calculated assuming that patients are treated with triple therapy, and as such, represent the continued unmet need for patients with COPD despite existing therapies.

Table 5.1. Absolute and Proportional evLY Shortfalls for COPD

	Absolute evLY Shortfall	Proportional evLY Shortfall
Beta Thalassemia	25.5	52.5%
Multiple Myeloma	18.7	95.7%
Alzheimer's Disease	9.4	71.3%
Ulcerative Colitis	6.6	19.3%
Prostate Cancer	3.6	35.6%
High Cholesterol	1.7	10.9%
Chronic Obstructive Pulmonary Disease	6.8	44.8%

evLY: equal value life year

5.2 Overview and Model Structure

Trelegy Ellipta

We developed a decision analytic model and evaluated the lifetime clinical and economic outcomes of triple therapies for COPD. Specifically, we compared fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI), the fixed-dose combination found in the single-inhaler Trelegy Ellipta, to alternative triple therapies budesonide/formoterol (BUD/FOR) and tiotropium (TIO), fluticasone propionate/salmeterol (FP/SAL) and TIO, and FF/VI and TIO. Outcomes assessed included total costs, total evLYs, and incremental cost per evLY gained. The use of evLYs provide a standardized approach to assessing treatment value, accounting for both survival and overall health impact, while adhering to statutory requirements under the IRA set by CMS. Costs and outcomes were discounted at 3% annually.

The hypothetical cohort consisted of Medicare-aged patients with at least moderate COPD. Model cycles occurred monthly, aligning with clinical and adherence data, and patients were followed over a lifetime horizon. COPD progression was modeled across four health states: moderate COPD, severe COPD, very severe COPD, and death. Within each health state, exacerbations (moderate to severe) were tracked. A moderate exacerbation was defined as requiring corticosteroids/antibiotics without hospitalization, while a severe exacerbation required hospitalization. Exacerbations impacted mortality, costs, and quality of life and are detailed in the supplement. Rates of exacerbation were impacted by treatment persistence, as patients who remained on therapy experienced sustained benefits compared to those who discontinued or switched to reduced treatment regimens.

Treatment persistence was a critical component of the model, reflecting real-world challenges with discontinuation in COPD management. The model compared Trelegy Ellipta to other triple therapies, while also incorporating treatment transitions following discontinuation to reflect clinical practice. Patients discontinuing triple therapy due to adverse events (AEs) transitioned to LAMA/LABA therapy, and those on LAMA/LABA therapy transitioned to tiotropium; discontinuations for other reasons assumed no further treatment. Discontinuation rates due to AEs were assumed to be consistent across all triple and LAMA/LABA therapies and were derived from FF/UMEC/VI clinical trials, aggregated and adjusted for trial durations. Discontinuation for reasons other than AEs was calculated by subtracting AE-related discontinuation rates from all-cause rates. All-cause discontinuation rates were derived from Kaplan-Meier (KM) persistence curves digitized from claims-based real-world studies of single, dual, and triple therapies. These studies defined discontinuation as an interruption in prescription drug claims of ≥30 days for triple and dual therapies and ≥60 days for single therapies.

Additional key model inputs included quality of life values, COPD health state costs, and COPD-specific future unrelated health care costs. Productivity changes and other non-intervention indirect costs were included in a modified societal perspective analysis. Treatment effectiveness was estimated using findings from the clinical review, informed by a network meta-analysis.

Detailed methods and results are presented in the Supplement.

We attest that all measures of health used throughout this report, most prominently the evLY, do *not* treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. The evLY treats the value of extended life of all individuals in exactly the same way, with each year of life gained from treatment valued identically. The evLY has served for many years as a bedrock of ICER's drug price benchmarks that are used by the Veterans Administration, Medicaid programs, and private insurers. In our public comments on the CMS draft guidance, we provided further rationale for why the evLY is consistent with the IRA and will be helpful to CMS in its deliberations. A detailed description of the evLY calculation can be found in the Supplement Section E1.

Breo Ellipta

We developed a decision analytic model and evaluated the lifetime clinical and economic outcomes of dual therapies for COPD. Specifically, we compared fluticasone furoate/vilanterol (FF/VI), the fixed-dose combination found in the single-inhaler Breo Ellipta, to alternative dual therapies budesonide/formoterol (BUD/FOR) and fluticasone propionate/salmeterol (FP/SAL). Costs and outcomes were discounted at 3% annually.

The hypothetical cohort consisted of Medicare-aged patients with at least moderate COPD. Model cycles occurred monthly, aligning with clinical and adherence data, and patients were followed over a lifetime horizon. COPD progression was modeled across four health states: moderate COPD, severe COPD, very severe COPD, and death. Within each health state, exacerbations (moderate to severe) were tracked. A moderate exacerbation was defined as requiring corticosteroids/antibiotics without hospitalization, while a severe exacerbation required hospitalization. Exacerbations impacted mortality, costs, and quality of life and are detailed in the supplement. Rates of exacerbation were impacted by treatment persistence, as patients who remained on therapy experienced sustained benefits compared to those who discontinued or switched to reduced treatment regimens.

Treatment persistence was a critical component of the model, reflecting real-world challenges with discontinuation in COPD management. Patients discontinuing dual therapy due to adverse events (AEs) transitioned to tiotropium; discontinuations for other reasons assumed no further treatment. Discontinuation rates due to AEs were assumed to be consistent across all dual therapies and were derived from FF/VI clinical trials, aggregated and adjusted for trial durations. Discontinuation for reasons other than AEs was calculated by subtracting AE-related discontinuation rates from all-cause rates. All-cause discontinuation rates were derived from Kaplan-Meier (KM) persistence curves digitized from claims-based real-world studies of dual and single therapies. These studies defined discontinuation as an interruption in prescription drug claims of ≥30 days for dual therapies and ≥60 days for single therapies.

Additional key model inputs included quality of life values, COPD health state costs, and COPD-specific future unrelated healthcare costs. Productivity changes and other non-intervention indirect costs were included in a modified societal perspective analysis. Treatment effectiveness was estimated using findings from the clinical review, informed by a network meta-analysis.

Detailed methods and results are presented in the Supplement.

We attest that all measures of health used throughout this report, most prominently the evLY, do *not* treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. The evLY treats the value of extended life of all individuals in exactly the same way, with each year of

life gained from treatment valued identically. The evLY has served for many years as a bedrock of ICER's drug price benchmarks that are used by the Veterans Administration, Medicaid programs, and private insurers. In our public comments on the CMS draft guidance, we provided further rationale for why the evLY is consistent with the IRA and will be helpful to CMS in its deliberations. A detailed description of the evLY calculation can be found in the Supplement Section E1.

Results

Trelegy Ellipta

Projected Discounted Lifetime Health Outcomes and Non-Intervention Health Care Sector Costs for FF/UMEC/VI versus BUD/FOR + TIO and FP/SAL + TIO and FF/VI + TIO

Total lifetime discounted health outcomes for the intervention and each comparator are shown in Table 5.1. Total lifetime discounted non-intervention costs (inclusive of exacerbations and chronic condition costs) for the intervention and each comparator are shown in Table 5.2.

FF/UMEC/VI versus BUD/FOR + TIO

Compared to BUD/FOR + TIO, FF/UMEC/VI resulted in fewer exacerbations, increased life years, and increased evLYs gained, along with higher non-intervention health care sector costs (Table 5.3).

FF/UMEC/VI versus FP/SAL + TIO

Compared to FP/SAL + TIO, FF/UMEC/VI resulted in fewer exacerbations, increased life years, and increased evLYs gained, along with higher non-intervention health care sector costs (Table 5.3).

FF/UMEC/VI versus FF/VI + TIO

Compared to FF/VI + TIO, FF/UMEC/VI resulted in fewer exacerbations, increased life years, and increased evLYs gained, along with higher non-intervention health care sector costs (Table 5.3).

Table 5.2. Lifetime Health Outcomes by Triple Therapy Treatment Strategy

Treatment	Exacerbations	Life Years (Discounted)	evLYs (Discounted)
FF/UMEC/VI	11.29	8.45	6.82
BUD/FOR + TIO	11.61	8.39	6.77
FP/SAL + TIO	11.61	8.39	6.77
FF/VI + TIO	11.61	8.39	6.77

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, LY: Life year, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table 5.3. Lifetime Average Non-Intervention Health Care Sector Costs by Triple Therapy Treatment Strategy

Treatment	Subsequent COPD Drug Costs (Discounted)	Health State Costs (Discounted)	Exacerbation Costs (Discounted)	Future Unrelated Health State Costs (Discounted)	Total Non-Intervention Health Care Sector Costs (Discounted)
FF/UMEC/VI	$10,600	$19,900	$63,800	$163,000	$257,000
BUD/FOR + TIO	$9,000	$19,700	$65,600	$161,000	$256,000
FP/SAL + TIO	$9,000	$19,700	$65,600	$161,000	$256,000
FF/VI + TIO	$9,000	$19,700	$65,600	$161,000	$256,000

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, LY: Life year, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table 5.4. Incremental Lifetime Results for FF/UMEC/VI versus BUD/FOR + TIO and FP/SAL + TIO and FF/VI + TIO

Treatment	Exacerbations	Life Years (Discounted)	evLYs (Discounted)	Non-Intervention Health Care Sector Costs (Discounted)
FF/UMEC/VI vs. BUD/FOR + TIO	-0.32	0.06	0.05	$1,200
FF/UMEC/VI vs. FP/SAL + TIO	-0.32	0.06	0.05	$1,200
FF/UMEC/VI vs. FF/VI + TIO	-0.32	0.06	0.05	$1,200

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, LY: Life year, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

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Projected Discounted Lifetime Health Outcomes and Non-Intervention Health Care Sector Costs for FF/VI versus BUD/FOR and FP/SAL

Total lifetime discounted health outcomes for the intervention and each comparator are shown in Table 5.5. Total lifetime discounted non-intervention costs (inclusive of exacerbations and chronic condition costs) for the intervention and each comparator are shown in Table 5.6.

FF/VI versus BUD/FOR

Compared to BUD/FOR, FF/VI resulted in fewer exacerbations, increased life years, and increased evLYs gained, along with higher non-intervention health care sector costs (Table 5.6).

FF/VI versus FP/SAL

Compared to FP/SAL, FF/VI resulted in fewer exacerbations, increased life years, and increased evLYs gained, along with higher non-intervention health care sector costs (Table 5.6).

Table 5.5. Lifetime Health Outcomes by Dual Therapy Treatment Strategy

Treatment	Exacerbations	Life Years (Discounted)	evLYs (Discounted)
FF/VI	12.58	8.22	6.63
BUD/FOR	12.67	8.20	6.61
FP/SAL	12.67	8.20	6.61

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propioinate, LY: Life year, SAL: salmeterol, VI: vilanterol

Table 5.6. Lifetime Average Non-Intervention Health Care Sector Costs by Dual Therapy Treatment Strategy

Treatment	Subsequent COPD Drug Costs (Discounted)	Health State Costs (Discounted)	Exacerbation Costs (Discounted)	Future Unrelated Health State Costs (Discounted)	Total Non-Intervention Health Care Sector Costs (Discounted)
FF/VI	$8,500	$19,300	$71,100	$158,000	$257,000
BUD/FOR	$7,600	$19,200	$71,600	$158,000	$256,000
FP/SAL	$7,600	$19,200	$71,600	$158,000	$256,000

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propioinate, LY: Life year, SAL: salmeterol, VI: vilanterol

Table 5.7. Incremental Lifetime Results for FF/VI versus BUD/FOR and FP/SAL

Treatment	Exacerbations	Life Years (Discounted)	evLYs (Discounted)	Non-Intervention Health Care Sector Costs (Discounted)
FF/VI vs. BUD/FOR	-0.09	0.02	0.01	$800
FF/VI vs. FP/SAL	-0.09	0.02	0.01	$800

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propioinate, LY: Life year, SAL: salmeterol, VI: vilanterol

Estimated Annual Threshold Prices for FF/UMEC/VI Across a Range of Comparator Prices and Cost-Effectiveness Benchmarks

We framed our price threshold calculations as estimated annual prices that CMS should pay based on the comparator price (Table 5.8). In these calculations, the comparator represents any potential treatment alternative, including low cost generics, authorized generics, and heavily discounted branded triple therapies. Considering a range of cost-effectiveness thresholds is recommended, and the most commonly suggested thresholds in the US are $100,000 and $150,000 per additional year of health benefit. We used these same thresholds when using the evLYG, which would have the effect of increasing the premium prices at each threshold. We have included a wider range of thresholds to provide CMS with additional pricing points for consideration. Thirty-day estimated prices for FF/UMEC/VI can be calculated by dividing the annualized price by 12.175. Since the total evLYs were the same for all three comparators (BUD/FOR + TIO, FP/SAL + TIO, FF/VI + TIO), the incremental evLYs compared to FF/UMEC/VI were also the same. Consequently, the annual price for the comparator, as presented in Table 5.8, applies uniformly to all three comparator treatment regimens.

Table 5.8. Estimated Annual Threshold Prices for FF/UMEC/VI across a Range of Comparator Prices and Cost-Effectiveness Benchmarks

	Annual Threshold Prices for FF/UMEC/VI			
Annual Price for Comparator	**$50,000/evLY**	**$100,000/evLY**	**$150,000/evLY**	**$200,000/evLY**
$500	$750	$1,370	$2,000	$2,600
$1,000	$1,200	$1,800	$2,400	$3,000
$1,500	$1,600	$2,200	$2,800	$3,500
$2,000	$2,000	$2,600	$3,300	$3,900
$2,500	$2,400	$3,100	$3,700	$4,300
$3,000	$2,900	$3,500	$4,100	$4,700
$3,500	$3,300	$3,900	$4,500	$5,100
$4,000	$3,700	$4,300	$5,000	$5,600
$4,500	$4,100	$4,800	$5,400	$6,000
$5,000	$4,600	$5,200	$5,800	$6,400
$5,500	$5,000	$5,600	$6,200	$6,800
$6,000	$5,400	$6,000	$6,600	$7,300
$6,500	$5,800	$6,500	$7,100	$7,700
$7,000	$6,300	$6,900	$7,500	$8,100
$7,500	$6,700	$7,300	$7,900	$8,500
$8,000	$7,100	$7,700	$8,300	$9,000
$8,500	$7,500	$8,200	$8,800	$9,400
$9,000	$8,000	$8,600	$9,200	$9,800
$9,500	$8,400	$9,000	$9,600	$10,200
$10,000	$8,800	$9,400	$10,000	$10,700

evLYs: equal-value life years, FF: fluticasone furoate, UMEC: umeclidinium, VI: vilanterol

Note: Annual prices for FF/UMEC/VI are rounded to the nearest $100

Estimated Annual Threshold Prices for FF/VI Across a Range of Comparator Prices and Cost-Effectiveness Benchmarks

We framed our price threshold calculations as estimated annual prices that CMS should pay based on the comparator price (Table 5.9). In these calculations, the comparator represents any potential treatment alternative, including low cost generics, authorized generics, and heavily discounted branded dual therapies. Considering a range of cost-effectiveness thresholds is recommended, and the most commonly suggested thresholds in the US are $100,000 and $150,000 per additional year of health benefit. We have included a wider range of thresholds to provide CMS with additional pricing points for consideration. Thirty-day estimated prices for FF/VI can be calculated by dividing the annualized price by 12.175. Since the total evLYs were the same for both comparators (BUD/FOR, FP/SAL), the incremental evLYs compared to FF/VI were also the same. Consequently, the annual price for the comparator, as presented in Table 5.9, applies uniformly to both comparator treatment regimens.

Table 5.9. Estimated annual threshold prices for FF/VI across a range of comparator prices and cost-effectiveness benchmarks

	Annual Threshold Prices for FF/VI			
Annual Price for Comparator	**$50,000/evLY**	**$100,000/evLY**	**$150,000/evLY**	**$200,000/evLY**
$500	$400	$600	$800	$1,000
$1,000	$800	$1,000	$1,300	$1,500
$1,500	$1,300	$1,500	$1,700	$1,900
$2,000	$1,700	$2,000	$2,200	$2,400
$2,500	$2,200	$2,400	$2,600	$2,800
$3,000	$2,600	$2,900	$3,100	$3,300
$3,500	$3,100	$3,300	$3,500	$3,700
$4,000	$3,500	$3,700	$4,000	$4,200
$4,500	$4,000	$4,200	$4,400	$4,600
$5,000	$4,400	$4,600	$4,900	$5,000
$5,500	$4,900	$5,100	$5,300	$5,500
$6,000	$5,300	$5,500	$5,800	$6,000
$6,500	$5,800	$6,000	$6,200	$6,400
$7,000	$6,200	$6,400	$6,700	$6,900
$7,500	$6,700	$6,900	$7,100	$7,300
$8,000	$7,100	$7,300	$7,500	$7,800
$8,500	$7,600	$7,800	$8,000	$8,200
$9,000	$8,000	$8,200	$8,400	$8,700
$9,500	$8,500	$8,700	$8,900	$9,100
$10,000	$8,900	$9,100	$9,300	$9,500

evLYs: equal-value life years, FF: fluticasone furoate, VI: vilanterol

Note: Annual prices for FF/VI are rounded to the nearest $100.

Sensitivity Analyses

Trelegy Ellipta

One-way sensitivity analysis was conducted to identify the model parameters that had the greatest impact on the results, primarily the incremental cost-effectiveness ratio. Probabilistic sensitivity analysis was performed to assess the reliability of the model by accounting for uncertainty in input values for the model and evaluating the range of possible cost-effectiveness outcomes. In the Supplement, we present independent tornado diagrams for the incremental cost per additional evLYG for FF/UMEC/VI versus each triple therapy (BUD/FOR + TIO, FP/SAL + TIO, FF/VI + TIO). Based on probabilistic analyses, model findings did not meaningfully change when accounting for uncertainty in the model inputs.

Breo Ellipta

One-way sensitivity analysis was conducted to identify the model parameters that had the greatest impact on the results, primarily the incremental cost-effectiveness ratio. Probabilistic sensitivity analysis was performed to assess the reliability of the model by accounting for uncertainty in input values for the model and evaluating the range of possible cost-effectiveness outcomes. In the Supplement, we present independent tornado diagrams for the incremental cost per additional evLYG for FF/VI versus each dual therapy (BUD/FOR, FP/SAL). Based on probabilistic analyses, model findings did not meaningfully change when accounting for uncertainty in the model inputs.

Scenario Analyses

Trelegy Ellipta

We conducted a scenario analysis from a modified societal perspective which included lost productivity due to exacerbations and caregiver productivity loss. The societal perspective analysis is considered "modified" because it does not include broader societal impacts such as effects on education, tax payments or benefits, or environmental impact. The modified societal perspective analysis resulted in similar conclusions as the base-case analysis.

Detailed results from all scenario analyses can be found in the Supplement.

Breo Ellipta

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Detailed results from all scenario analyses can be found in the Supplement.

Model Validation

Trelegy Ellipta

Details related to model validation can be found in the Supplement.

Breo Ellipta

Details related to model validation can be found in the Supplement.

Uncertainty and Controversies

Trelegy Ellipta

No measure of health gain, including individual exacerbations or summary measures such as the evLY, captures all information important to value considerations. Additional considerations such as unmet need are relevant in discussion on value and pricing negotiations.

We recognize that quality of life associated with COPD exacerbations and their longer-term sequelae vary across individual patients. Our modeling approach aggregates these impacts to find an average projected lifetime benefit to inform threshold pricing estimates. Given that CMS is seeking a single price for consideration as an initial offer, it is reasonable for an aggregated population-based approach to be used.

In our review of COPD, we found that both adherence and persistence to treatments were suboptimal and generally low. While we successfully incorporated persistence into our model using real-world pharmacy claims data, we did not account for the impact of adherence on exacerbations while on treatment due to the substantial challenges with the available data. Relying solely on RCT data risked overestimating the association between adherence and exacerbations, as participants in RCTs typically adhere better to treatments due to close monitoring. Observational studies also presented two key issues: (1) measuring adherence and exacerbations within the same timeframe introduced potential temporal bias, where early exacerbations following treatment initiation might negatively affect adherence, making it unclear whether exacerbations caused poor adherence or

vice versa; and (2) healthy adherer bias, where patients with better adherence often engage in healthier behaviors independent of medication effects, potentially influencing exacerbation outcomes. Notably, studies addressing temporality found that higher adherence was associated with a greater risk of exacerbations, leading authors to suggest that reverse causality (exacerbations driving adherence) may underlie this relationship.

No publicly available net prices for FF/UMEC/VI specific to the Medicare population were available for our analysis; therefore we are unable to compare our results to current Medicare prices for these agents.

Breo Ellipta

No measure of health gain, including individual exacerbations or summary measures such as the evLYG, captures all information important to value considerations. Additional considerations such as unmet need are relevant in discussion on value and pricing negotiations.

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In our one-way sensitivity analysis, the treatment effect of dual therapy (ICS/LABA) compared to single therapy as a rate ratio on exacerbations was found to be highly influential on model results. In the base-case analysis, we used an estimate of 0.96 that slightly favored ICS/LABA compared to single therapy for exacerbations. However, the credible interval used to inform the upper bound of

the range suggested a less favorable rate ratio for dual therapy compared to single therapy. This uncertainty is reflected in current clinical practice guidelines, which do not endorse ICS/LABA combinations for the management of COPD.

No publicly available net prices for FF/VI for the Medicare population were available for our analysis; therefore we are unable to compare our results to current Medicare prices for these agents.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Chronic Obstructive Lung Disease (COPD): A lung condition caused by abnormalities of the airway and/or alveoli that cause persistent, often progressive, airflow obstruction. The presence of a post-bronchodilator FEV_1/FVC ratio of less than 0.7 on spirometry testing is required for the diagnosis of COPD. The severity of airflow obstruction in COPD is determined by post-bronchodilator FEV_1 values and classified into four "GOLD Grades", see Table A1.1.[3] Subtypes include emphysema and chronic bronchitis. The most common symptoms include dyspnea, cough, and sputum production.[76]

Table A1.1. GOLD Grade for Severity of Airflow Obstruction in COPD (FEV_1/FVC < 0.7)[3]

GOLD Grade	Severity	Post-Bronchodilator FEV_1 (% Predicted)
GOLD 1	Mild	≥80
GOLD 2	Moderate	50-79
GOLD 3	Severe	30-49
GOLD 4	Very Severe	<30

FEV: Forced expiratory volume in one second, FVC: forced vital capacity, GOLD: Global Initiative for Chronic Obstructive Lung Disease

Long-acting muscarinic antagonists (LAMA): A bronchodilator treatment that works by blocking the bronchoconstriction effects of acetylcholine. This prevents the neurotransmitter from causing the muscles surrounding the lungs' airways to constrict, reducing symptoms of COPD.[77]

Long-acting beta agonists (LABA): A bronchodilator treatment option that induces smooth muscle relaxation by stimulating beta-adrenergic receptors.[77]

Inhaled corticosteroids (ICS): An anti-inflammatory therapeutic option for COPD. Targeting lung inflammation with an ICS can have clinical benefits in selected patients on lung function, symptoms, and exacerbation risk, but it can also be associated with adverse effects, including an increased risk of pneumonia.[78]

Dual bronchodilator therapy (dual therapy): A combination of LAMA and LABA therapies. These can either be delivered separately or as a fixed dose combination.

Triple therapy: A combination of LAMA, LABA, and ICS therapies. These can either be delivered separately or as a fixed dose combination.

Dry Powder Inhaler (DPI): A DPI is a breath-actuated inhaler that releases medicine in a dry powdered form into the airways when a deep breath is taken.[79]

Metered-Dose Inhaler (MDI): An MDI is a type of inhaler that uses a chemical propellant to spray the medicine into the airways.[80]

Soft-Mist Inhaler (SMI): An SMI is a type of inhaler that uses a mechanical spring (as opposed to a chemical propellant) to spray fine particles of medicine at a slow velocity into the airways.[81]

Outcome-Related Terms

Forced expiratory volume in one second (FEV_1): The volume of air (in liters) exhaled in the first second during forced exhalation after maximal inspiration. The ratio of FEV_1 to forced vital capacity (FVC) or the maximum amount of exhaled after maximal inspiration is used to detect airflow obstruction. An FEV_1/FVC ratio of <0.7 post-bronchodilation indicates the presence of airflow obstruction and is typically used to establish a diagnosis of COPD.[76,82]

COPD exacerbations: Defined as worsening of COPD.[83]

- Moderate exacerbation: Worsening of COPD symptoms for >2 days requiring a minimum of three days of therapy with oral or systemic corticosteroids +/- antibiotics.
- Severe exacerbation: Worsening of COPD symptoms requiring inpatient hospitalization.

See Table A1.2. for definitions of moderate to severe exacerbations used across included trials.

St. George's Respiratory Questionnaire (SGRQ): An instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. The self-reported questionnaire consists of 50 items evaluating symptom components (frequency & severity) and impact components (social functioning, psychological disturbances resulting from airways disease).[84] Scores range from 0 to 100, with higher scores indicating more health limitations. A mean change score of four units is associated with slightly efficacious treatment, eight units for moderately efficacious change and 12 units for very efficacious treatment in COPD and asthma.[43] However, a recent thesis reported that for those with moderate to very severe COPD, the MCID should be at least seven points.[84]

Healthcare resource utilization (HCRU): All unscheduled visits to a physician office, visits to urgent care, visits to emergency department, and hospitalizations for any cause and/or related to COPD and visits/contact due to COPD exacerbation.[83]

Transitional Dyspnea Index (TDI): Interviewer-administered rating used to measure change in dyspnea in three categories (functional impairment, magnitude of task, and magnitude of effort). Scores range from −3 (major deterioration) to +3 (major improvement) for each domain. The sum of all domains yields the TDI focal score (−9 to +9). A negative score indicates more severity in dyspnea whereas a positive score shows positive gains. A one-unit change has been determined to be MCID for those with a COPD diagnosis.[39]

COPD Assessment Test (CAT): A simple 8-item patient-completed questionnaire covering a broad range of effects of COPD on health-related quality of life, including factors such as cough, chest tightness, breathlessness, daily activities, quality of sleep, and energy levels. Scores range from 0-40 with a higher score indicating a higher impact of COPD on a patient's life with a decrease of two units suggesting a meaningful difference.[85,86]

Proportion Of Days Covered (PDC): A method of estimating medication adherence from administrative data on the proportion of days a person has access to a medication (coverage) over a given period of time.[87] For trials included in our assessment, PDC was defined as the number of overlapping days for which medications were available divided by the number of days between the index date through the end of the follow-up period. "Good" adherence to triple therapy among patients with COPD is defined as having a PDC of ≥0.8.[25] See Table A1.3. for definitions of adherence used across relevant trials.

Persistence: Persistence is calculated using the duration of time from initiation to discontinuation of a therapy. The definition of discontinuation differs across studies. It is variously defined as a gap between refills of a medication that are longer than 14, 30, 45, or 60 days.[88] See Table A1.3. for definitions of persistence used across relevant trials.

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[89] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[90,91] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4%=2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above 1.0 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDIs for all racial and ethnic groups were less than 1.0.

Table A1.2. Definitions of Moderate to Severe Exacerbations in Relevant Trials

Trial (Author & Year)	Definitions of Moderate Exacerbations	Definitions of Severe Exacerbations
Rabe 2020[92]	Exacerbations leading to treatment with systemic glucocorticoids, antibiotics, or both for at least 3 days	Exacerbations resulting in hospitalization or death
Lipson 2017[93]**; Bansal 2021**[94]	Exacerbations requiring treatment with oral/systemic corticosteroids +/- antibiotics, without hospitalization	Exacerbations requiring in-patient hospitalization
Lipson 2018[95]	Exacerbations leading to treatment with antibiotics or systemic glucocorticoids	Exacerbations leading to hospitalization or death
Ferguson 2018[96]	Exacerbations leading to treatment with systemic corticosteroids, antibiotics, or both for ≥3 days, or ≥1 depot injectable dose of corticosteroids)	Exacerbations leading to hospital admission or a visit to a healthcare facility, e.g. emergency department, that lasted ≥24 hours, or COPD-related death)
Bremner 2018[52]**; Siler 2015**[97]**; Ferguson 2020**[54]	Exacerbations requiring oral/systemic corticosteroids +/- antibiotics	Exacerbations requiring hospitalization
Papi 2018[98]**; Singh 2016**[99]**; Vestbo 2017**[100]	Exacerbations that require treatment with systemic corticosteroids +/- antibiotics	Exacerbations requiring hospital admission or resulting in death
Welte 2009[101]	Not defined, however, the definition of severe exacerbations captures common definitions of moderate exacerbations	Exacerbations defined as worsening of COPD leading to treatment with systemic corticosteroids [oral or parenteral] and/or hospitalization/emergency room visits)

Trial (Author & Year)	Definitions of Moderate Exacerbations	Definitions of Severe Exacerbations
Aaron 2017[102]	A sustained worsening of the patient's respiratory condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD. An acute change in regular COPD medications was defined as physician-directed, short-term use of oral or intravenous steroids, oral or intravenous antibiotics, or both therapies	
Hanania 2012[103]	Exacerbations requiring the use of systemic corticosteroids and/or antibiotics, unscheduled or urgent care physician/clinic office visits, hospitalizations and/or emergency room visits	
Siler 2016[99]	An acute worsening of symptoms of COPD requiring the use of any treatment beyond study medication or rescue albuterol/salbutamol. This includes using antibiotics, systemic corticosteroids and/or emergency treatment or hospitalization	

Table A1.3. Definitions of Adherence and Persistence in Relevant Observational Studies

Study (Author & Year)	Definitions
Adherence	
Bogart 2024[60]	Adherence was evaluated using proportion of days covered (PDC), defined as the number of overlapping days on which medication was available divided by 365 (the number of days between the index date through the end of 12-month follow-up period)
Halpin 2022[61]	Adherence was evaluated using PDC (calculated by dividing the number of days covered by a fixed time interval: 6, 12, or 18 months). Patients were considered 'covered' for days on which they had a valid prescription for all three components of triple therapy. For patients with a subsequent prescription dated before the duration of their existing prescription run out (an overlap in the cover of prescriptions), the subsequent prescription date was shifted to the end of the previous prescription days of supply, for the PDC calculation
Mannino 2022[49]	Adherence was evaluated using PDC (calculated for each patient as the total number of days on therapy for all three triple therapy components: ICS, LAMA, and LABA) starting from the index date divided by a fixed time interval (i.e., 180 days for the main analysis and 365 days for the subgroup analysis).
Vogelmeier 2024[62]	Adherence was evaluated using PDC (defined as the number of days "covered"/number of days in the period). Days covered by a prescription were calculated based on the quantity of the medication dispensed and the defined daily dosage as formulated by the World Health Organization and the Wissenschaftliches Institut der Ortskrankenkassen (WIdO, Scientific Institute of the General Local Health Insurance Fund, AOK), which serves as a proxy for the prescribed daily dosage
Beeh 2024[57]	Adherence was evaluated using the Test of Adherence to Inhalers (TAI) questionnaire consisting of 10 questions to identify aspects of daily use of inhalers. Scored range from 10 to 50, with 50 representing good adherence, 46-49 points intermediate adherence, and ≤45 points poor adherence.
Stanford 2019[74]	Adherence was evaluated using PDC (calculated by dividing the total number of days which medication was available, based on filled prescriptions, by the length of each subject's observation time). The cohort's mean PDC as a continuous measure was compared, as well as, the proportion of patients with PDC above pre-specified cut-points of 0.5 and 0.8.
Young 2024[59]	Adherence was evaluated using PDC (calculated by dividing the total number of days "covered" for each patient (i.e., days with medication on hand) for their treatment in a given time interval by the duration of the time interval (i.e., 180, 270, or 365 days).
Jokšaitė et al. 2024[63]	Adherence was evaluated using PDC (calculated for each patient by dividing the total number of days 'covered' for triple therapy by a fixed time interval).

Persistence	
Halpin 2022[61]	Non-persistence was defined as a gap of A) 45 or B) 60 days between the end of a prescription duration and the following refill. For MITT users, non-persistence was defined as a gap of A) 45 or B) 60 days between prescriptions in any of the three components of MITT.
Mannino 2022[49]	Non-persistence (discontinuation) was defined as a gap of >30 days (>60 days was also evaluated as a sensitivity analysis) between the end of a dispensing and the following fill, or the end of the last dispensing and the end of follow up. For MITT users, non-persistence was defined as noted above, but for any of the three components of the triple therapy.
Vogelmeier 2024[62]	Medication non-persistence (discontinuation) was defined as a gap of >30 days between the end of a SITT prescription and the following refill, or for MITT users, a gap of >30 days between prescriptions in any of the three MITT components.
Young 2024[59]	Persistence was assessed as time to discontinuation of index therapy. Discontinuation was defined as a gap in therapy between two subsequent prescription fills > 30 days between the end of the days of supply of a dispensing and the start date of the next fill, or between the end of the days of supply of the last dispensing and the end of the follow-up period.
Jokšaitė et al. 2024[63]	Persistence was defined as the time from treatment initiation at the index date to treatment discontinuation where discontinuation was defined as a gap of ≥14, 30, 45, and 60 days between the end of the SITT prescription and the next fill or between periods of MITT use.

ICS: inhaled corticosteroid steroids, LABA: long-acting beta agonist, LAMA: long-acting muscarinic antagonist, MITT: multiple inhaler triple therapy, PDC: proportion of days covered, SITT: single inhaler triple therapy

A2. Potential Cost-Saving Measures in COPD

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for COPD (e.g., hospitalizations for pneumonia from ICS therapy), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of COPD beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with COPD that could be reduced, eliminated, or made more efficient. One clinical expert mentioned that routine repeat spirometry tests to monitor lung function after diagnosis are not necessary, as clinical practice guidelines recommend that therapy choices are driven by symptoms and exacerbations.

A3. Patient Input on Clinical Trial Design

We solicited this information from the manufacturer of Trelegy Ellipta and Breo Ellipta and did not receive any feedback on this topic.

B. Patient Perspectives: Supplemental Information

B1. Methods

This report was developed with input from multiple stakeholders, including patients, clinicians, researchers, payers, and the manufacturer of the Trelegy and Breo Ellipta. We updated ICER's prior assessment of the patient perspective by interviewing five people living with COPD, specifically about their use of inhalers and the impact of different inhaler schedules on their quality of life, which is described in detail in the main report.

B2. Supplemental Patient Input

There may be less variability in drug delivery using nebulized devices compared with inhalers; however, nebulized treatments can be time-consuming and are less portable than inhalers. Patients who require systemic steroids, such as prednisone, can have significant side effects such as diabetes, weight gain, and osteoporosis, which then require separate management, adding to the complexity of care. Furthermore, treatments for COPD can be expensive, and one in six US adults with COPD have reported cost-related non-adherence, including missing doses, taking lower than prescribed doses, and delaying filling prescriptions,[104] which could affect disease control. Finally, pulmonary rehabilitation and regular exercise play important roles in helping individuals with COPD maintain quality of life. However, pulmonary rehabilitation programs may be difficult to access, particularly in more rural areas, and maintenance of improvement after the program ends is challenging.

Patient groups pointed out that the demographics of COPD are changing, and that there are now more women living with COPD than men. We heard concerns that women are less likely to be diagnosed, potentially because doctors are less likely to recognize COPD symptoms in women, often leading to delays in diagnosis and treatment. Additionally, there is concern that a diagnosis of COPD carries a stigma because of its link with cigarette smoking and thus leads people to underreport their smoking habits and blame themselves for their symptoms.

Individuals living with COPD described limitations in their daily activities, often due to shortness of breath and fatigue. For example, many tasks take more energy and time than usual to complete. Some chores that require bending and lifting, such as making the bed, filling the dishwasher, or doing laundry, are very difficult or impossible. Since symptoms can vary from day to day, there is a need to plan ahead and for patients to pace themselves – e.g., learning to sit and rest between activities, not going out when it's too hot or humid, and learning proper breathing techniques to

help with shortness of breath. With more severe disease, equipment such as shower chairs and wheelchairs may become necessary to help them complete activities of daily living. Additionally, traveling outside of the house can pose significant logistical challenges if wheelchairs and oxygen tanks are required.

Pulmonary rehabilitation is a key component in high quality care for patients with COPD. Unfortunately, these programs tend to be concentrated in urban areas so many patients have limited access. In addition, insurance often limits access to these programs. Potential solutions include community based rehabilitation programs and telehealth pulmonary rehabilitation.

In people with severe COPD, oxygen therapy may become necessary, and eventually some people need around-the-clock oxygen supplementation. Individuals who use oxygen regularly described numerous challenges to being oxygen-dependent. For example, the tubing delivering the oxygen often gets tangled when doing activities, and the oxygen itself can cause secondary nasal and sinus issues. The weight of oxygen tanks may limit mobility; patients may also need to limit their activities so that they do not run out of oxygen before returning home. Portable oxygen concentrators can help with mobility, but patients may still be limited by battery life or having oxygen requirements that are too high for concentrators. Finally, access to liquid oxygen is extremely limited but people who used liquid oxygen described how it improved their mobility and quality of life, as it is lighter, lasts longer, and is less drying than other types of oxygen supplementation.

The caregiving burden for COPD falls mainly to unpaid caregivers. For patients with less severe disease, caregiving for COPD primarily involves helping patients primarily with symptoms and medication management. This is particularly relevant for older patients and those with comorbidities, as they may have additional challenges with medication adherence. Such patients may require careful monitoring or adaptations to treatment due to the possibility that the effects of COPD medications may exacerbate other conditions.[105,106] As the disease progresses, caregivers may need to take on more physical chores such as shopping, cooking, housekeeping, and hygiene needs. Anxiety and depression are more common in individuals with COPD, and caregivers may need to help patients with emotional and psychological support.

When asked about considerations for future treatments, people with COPD we interviewed cited the need for treatments with new mechanisms of action, particularly those that are disease-modifying and could decrease the need for supplemental oxygen, and those that could decrease mucus production, as current treatments do not adequately address this symptom. We also heard that treatments with fewer side effects could improve quality of life for people with COPD.

Patient groups raised the concern that existing COPD quality of life measures focus only on physical symptoms and limitations caused by COPD. However, they do not adequately address the psychosocial burden of disease that may affect a patient's ability to engage in meaningful life

activities (e.g., work, travel, playing with grandchildren, participation in community events) and thus may underestimate the impact of COPD symptoms on a person's quality of life.

C. Clinical Guidelines

American Thoracic Society (ATS) 2020 Clinical Practice Guideline for the Pharmacologic Management of COPD[28]

ATS guidelines focus on therapy choices for specific clinical situations. For those with COPD who experience dyspnea or exercise intolerance, ATS recommends LABA + LAMA over monotherapy. If patients continue to experience symptoms despite LABA + LAMA therapy, ATS recommends use of the triple therapy (LABA + LABA + ICS) in those with a history of one or more exacerbations in the past year requiring antibiotics, oral steroids, or hospitalization. In those receiving triple therapy, ICS can be withdrawn if the patient has had no exacerbations in the past year. ATS notes that they do not recommend for or against ICS as an additive therapy to long-acting bronchodilators in those with COPD and eosinophilia, except if they have had a history of one or more exacerbations in the past year where they recommend ICS as an additive therapy. In patients with COPD and a history of severe and frequent exacerbations, ATS advises against maintenance oral corticosteroid therapy. For those with COPD who experience advanced refractory dyspnea, ATS suggests opioid-based therapy be considered in a personalized shared decision-making approach.[28]

The National Institute for Health and Care Excellence (NICE) 2019[29]

For those with a confirmed diagnosis of COPD, the fundamentals of care include: 1) treatment and support to stop smoking, 2) pneumococcal and influenza vaccinations; 3) pulmonary rehabilitation if indicated, co-developing a personalized self-management plan, and optimizing treatment for comorbidities. Inhaled therapies should be started if all the above interventions have been offered. If the patient is limited by symptoms or has exacerbations despite short-acting bronchodilators treatment, they should be offered long-acting bronchodilators. If the patient has no asthmatic features or features suggesting steroid responsiveness (e.g., any previous diagnosis of asthma or atopy, a higher blood eosinophil count, substantial variation in FEV_1 over time [at least 400 ml] or substantial diurnal variation in peak expiratory flow [at least 20%]), they should be offered LABA + LAMA. If the patient has symptoms that impact quality of life or has one severe or two moderate exacerbations in one year, the clinician could consider triple therapy with awareness of risk of pneumonia in those who take ICS. If there is no improvement after three months of ICS use, then the patient should revert to LABA + LAMA.[29]

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2025[3]

Pharmacological treatment for patients with COPD is based upon which group they would be best placed in. Patients with COPD in "group A" should be offered either a short- or long-acting bronchodilator, with a preference for one that is long-acting. Patients in "group B" should be offered LABA + LAMA, preferably as a single inhaler. Patients in "group E" should be offered LABA + LAMA and consider offering triple therapy if eosinophils count is ≥300 cells/mcL. The guidelines note that LABA + ICS is no longer recommended, since LABA + LAMA + ICS has been shown to be superior to LABA + ICS if there is an indication for ICS.

For follow-up therapy, treatment should be based upon two traits: 1) dyspnea and 2) occurrence of exacerbations. For those with dyspnea on monotherapy (e.g., LABA or LAMA), they should be offered LABA + LAMA. If there is no improvement, clinicians should consider switching inhaler devices, adding ensifentrine, or treating other causes of dyspnea. Those with exacerbations on monotherapy should also receive LABA + LAMA, except those with eosinophils count is ≥300 cells/mcL, who should be offered LABA + LAMA + ICS, preferably as a single inhaler. For patients on LABA + LAMA and persistent exacerbations, they should be offered LABA + LAMA + ICS if their eosinophil count is ≥100 cells/mcL. For patients who continue to have exacerbations on triple therapy, the addition of roflumilast or a macrolide antibiotic such as azithromycin may be considered; those with eosinophil counts ≥300 cells/mcL should consider the addition of dupilumab. ICS should not be used when: 1) there are repeated pneumonia events; 2) eosinophil count is <100 cells/mcL; or 3) there is a history of mycobacterial infection.[3]

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

We were interested in understanding whether there are differences in efficacy and safety among triple therapy combinations when they are taken consistently as directed.

Research Question #1: What is the comparative efficacy of triple therapy inhalers in patients with at least moderate COPD when delivered with comparable treatment adherence?

For the remainder of the clinical evidence review, we answered two additional questions in which better adherence could affect outcomes:

- **Research Question #2**: What is the net health benefit of Breo Ellipta versus generically available dual (ICS/LABA) therapy inhalers in patients with at least moderate COPD?
- **Research Question #3**: What is the net health benefit of Trelegy Ellipta versus generically available triple therapy inhalers in patients with at least moderate COPD?

PICOTS

In line with the three research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

D1.1 Populations, Interventions, and Comparators

Research Questions	Populations	Intervention	Comparators (generically available drugs based on CMS Guidelines)
Research Question #1	Patients with at least moderate COPD	All available fixed dose and open combinations of ICS/LABA/LAMA	
Research Question #2	Patients with at least moderate COPD	Trelegy Ellipta (Fixed-dose combination of fluticasone furoate, ICS; vilanterol, LABA; and umeclidinium, anticholinergic)	• Budesonide/formoterol fumarate + tiotropium [open combination of ICS/LABA + LAMA] • Fluticasone propionate/salmeterol xinafoate + tiotropium [open combination of ICS/LABA + LAMA] • Fluticasone furoate/vilanterol trifenatate + tiotropium [open combination of ICS/LABA and LAMA]
Research Question #3	Patients with at least moderate COPD	Breo Ellipta (Fixed-dose combination of fluticasone furoate ICS; and vilanterol trifenatate, LABA)	• Budesonide/formoterol fumarate [Fixed-dose ICS/LABA] • Fluticasone propionate/salmeterol xinafoate [Fixed-dose ICS/LABA]

CMS: Centers for Medicare and Medicaid; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids, LABA: long-acting beta-agonists, LAMA: long-acting muscarinic antagonists

Outcomes

The outcomes of interest for research question #1 are the following:

- Number of moderate to severe exacerbations
- Discontinuations due to AEs
- Health-related quality of life
- Mortality

The outcomes of interest for research questions #2 and #3 are the following:

- Patient-Important Outcomes
    - Changes in dyspnea (e.g., transitional dyspnea index [TDI], Modified Medical Research Council Dyspnea Scale [mMRC])
    - Changes in functional capacity (e.g., 6-minute walk distance)
    - COPD-related hospitalization or emergency room visit
    - Use of rescue medication
    - Requirement for long-term continuous or intermittent oxygen use
    - Health-related quality of life (e.g., St. George's Respiratory Questionnaire [SGRQ])
    - Number of exacerbations (e.g., annual rate of moderate and severe exacerbations)
- Changes in lung function (e.g., changes in average or peak forced expiratory volume [FEV_1])
- Adverse events (AEs) including, but not limited to:

    - Serious AEs
    - Discontinuation due to AEs
    - Other AEs including, but not limited to:
        - Mortality
        - Pneumonia
        - Cardiovascular outcomes (e.g., myocardial infarction, ischemic heart disease, stroke, hypertension)
        - Urinary tract risks, including urinary retention
- Adherence (e.g., Proportion of Days with full dose, proportion of doses received)
- Total discontinuation rate

Timing

Evidence on intervention effectiveness and harms was derived from studies of any duration.

Settings

All relevant settings were considered, with a focus on all settings in the United States.

Study Design

For research question #1, evidence was abstracted from randomized, double-blinded, placebo-controlled trials only. For research questions #2 and #3, evidence was abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality, observational studies were included to inform evidence on adherence, discontinuation rates, long-term outcomes, low-frequency harms, and to validate our network meta-analysis results.

Table D1.2 PRISMA 2020 Checklist

Section and Topic	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.

Section and Topic	#	Checklist Item
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.

Section and Topic	#	Checklist Item
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for COPD followed established best research methods.[107,108] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[109] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To ensure we had identified all relevant, high-quality observational studies in our searches, we also conducted a targeted search for data on dose frequency, adherence, long-term outcomes, and low-frequency adverse events for inhaler use in patients with COPD. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews.

Table D1.3. Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials – Triple Therapy NMA (Research Question #1)

COPD	exp Pulmonary Disease, Chronic Obstructive/ or ("Airflow Obstruction, Chronic" or "Airflow Obstructions, Chronic" or "chronic airflow obstruction" or "chronic airway obstruction" or "chronic obstructive bronchopulmonary disease" or "chronic obstructive lung disease" or "chronic obstructive pulmonary disease" or "chronic obstructive respiratory disease" or "chronic pulmonary obstructive disease" or "chronic pulmonary obstructive disorder" or "Chronic Airflow Obstruction" or "Chronic Airflow Obstructions" or "Chronic Obstructive Airway Disease" or "Chronic Obstructive Lung Disease" or "Chronic Obstructive Pulmonary Disease" or "Chronic Obstructive Pulmonary Diseases" or "COAD" or "COPD" or "lung chronic obstructive disease" or "lung disease, chronic obstructive" or "obstructive chronic lung disease" or "obstructive chronic pulmonary disease" or "obstructive lung disease, chronic" or "pulmonary disease, chronic obstructive" or "pulmonary disorder, chronic obstructive").ti,ab.
LABA (General)	exp "adrenergic beta-2 receptor agonists"/ or ("long-acting OR long acting OR ultra-long acting OR ultra-long-acting" and ("B agonist*" or "B-agonist*" or "B2 agonist*" or "B2-agonist*" or "B-2 agonist*" or "B(2) agonist*" or "B(2)-agonist*" or "B adrenergic agonist*" or "B-adrenergic agonist*" or "B2 adrenergic agonist*" or "B2-adrenergic agonist*" or "B-2 adrenergic agonist*" or "B-2-adrenergic agonist*" or "B2 adrenergic agonist*" or "B2-adrenergic agonist*" or "B-2 adrenergic agonist*" or "B-2-adrenergic agonist*" or "B(2) adrenergic agonist*" or "B(2)-adrenergic agonist*" or "B adrenoceptor agonist*" or "B-adrenoceptor agonist*" or "B2 adrenoceptor agonist*" or "B2-adrenoceptor agonist*" or "B-2 adrenoceptor agonist*" or "B-2-adrenoceptor agonist*" or "B2 adrenoceptor agonist*" or "B2-adrenoceptor agonist*" or "B-2

	adrenoceptor agonist*" or "B-2-adrenoceptor agonist*" or "B(2) adrenoceptor agonist*" or "B(2)-adrenoceptor agonist*" or "beta agonist*" or "beta-agonist*" or "beta2 agonist*" or "beta2-agonist*" or "beta-2 agonist*" or "beta-2-agonist*" or "beta(2) agonist*" or "beta(2)-agonist*" or "beta adrenergic agonist*" or "beta-adrenergic agonist*" or "beta2 adrenergic agonist*" or "beta2-adrenergic agonist*" or "beta-2 adrenergic agonist*" or "beta-2-adrenergic agonist*" or "beta(2) adrenergic agonist*" or "beta(2)-adrenergic agonist*" or "beta adrenoceptor agonist*" or "beta-adrenoceptor agonist*" or "beta2 adrenoceptor agonist*" or "beta2-adrenoceptor agonist*" or "beta-2 adrenoceptor agonist*" or "beta-2-adrenoceptor agonist*" or "beta(2) adrenoceptor agonist*" or "beta(2)-adrenoceptor agonist*")).ti,ab. or ("LABA" or "LABAs" or "ultra-LABA" or "ultra-LABAs").ti,ab.
LABA (Individual drugs)	exp "Formoterol Fumarate"/ or exp "Salmeterol Xinafoate"/ or ("formoterol" or "formoterol-fumarate" or "eformoterol" or "Atimos" or "EFO" or "Fluir" or "Foradil" or "Foradile" or "Formoair" or "Oxis" or "Perforomist" or "Tempus" or "indacaterol" or "indacaterol" or "Indacaterol-maleate" or "arcapta" or "hirobriz" or "onbrez" or "onbrize" or "oslif" or "olodaterol" or "olodaterol" or "Striverdi" or "Salmeterol" or "Salmeterolum" or "Salmeterol-xinafoate" or "Aeromax" or "Astmerole" or "Arial" or "Neovent" or "Qitai" or "Serevent" or "Vertine" or "vilanterol" or "Vilanterol-trifenatate" or "vilanterol").ti,ab.
LAMA (General)	exp "Muscarinic Antagonists"/ or exp "Cholinergic Antagonists"/ or ((("long-acting" or "long acting" or "ultra-long acting" or "ultra-long-acting") and (muscarinic antagonist* or muscarinic receptor antagonist* or antimuscarinic agent* or anti-muscarinic agent* or muscarinic blocker* or muscarinic receptor blocker* or Cholinergic antagonist* or Cholinergic receptor antagonist* or anticholinergic agent* or anti-cholinergic agent* or cholinergic blocker* or cholinergic receptor blocker* or cholinolytic agent*)) or "LAMA" or "LAMAs" or "ultra-LAMA" or "ultra-LAMAs").ti,ab.
LAMA (Individual drugs)	exp "Glycopyrrolate"/ or exp "tiotropium bromide"/ or ("aclidinium bromide" or "aclidinium" or "aclidinium-bromide" or "Tudorza" or "Eklira" or "Bretaris" or "Glycopyrrolate" or "glycopyrronium" or "Glycopyrronium-bromide" or "Seebri" or "tiotropium" or "Tiotropium-bromide" or "Spiriva" or "Tiova" or "Umeclidinium" or "Umeclidinium-bromide" or "Incruse").ti,ab.
ICS (General)	(Inhal*.ti,ab. and ((exp Steroids/ or exp "Adrenal Cortex Hormones"/) and (exp "Bronchodilator Agents"/ or exp "Anti-Asthmatic Agents"/))) or (corticosteroid* or cortico-steroid* or glucocorticoid* or steroid* or ICS).ti,ab.
ICS (Individual drugs)	exp "Beclomethasone"/ or exp "Budesonide"/ or exp "Fluticasone"/ or exp "Mometasone Furoate"/ or exp "Triamcinolone"/ or exp "Triamcinolone Acetonide"/ or ("beclomethasone 17-monopropionate" or "beclomethasone" or "beclometasone" or "Beclomethasone-17-monopropionate" or "Beclometasone-17-monopropionate" or "Beclomethasone-dipropionate" or "Beclometasone-dipropionate" or "Beclomethasone-dipropionate-monohydrate" or "AeroBec" or "Aerovent" or "Asmabec" or "Beclate" or "Beclazone" or "Becloforte" or "Beclomet" or "Beclovent" or "Beconase" or "Becotide" or "Bekotid" or "Clenil" or "Qvar" or "Respocort" or "Vanceril" or "Vancenase" or "Ventolair" or "Budesonide" or "Aeronide" or "Aerovent" or "B Cort" or "Benita" or "Budecort" or "Budeson" or "Budiair" or "Giona" or "Horacort" or "Miflonide" or "Noex" or "Novopulmon" or "Numark" or "Pulmicort" or "Rhinocort" or "ciclesonide" or "ciclesonide M1" or "ciclesonide" or "Alvesco" or "Flunisolide" or "Flunisolide" or "Aerobid" or "Aerospan" or "Pulmilide" or "fluticasone propionate-17-carboxylic acid" or "fluticasone furoate" or "Fluticason" or "Fluticasone" or "Fluticasone-propionate" or "Fluticasone-furoate" or "Allegro" or "Arnuity" or "Dalman" or "Flixotide" or "Flutica" or "Flutide" or "Flutivate" or "Flovent" or "Mometason" or "Mometasone" or "Mometasone-furoate" or "Mometasone-furoate-monohydrate" or "Asmanex" or "Elocom" or "Elocon" or "Ecural" or "Mometasona" or "Novasone" or "Triamcinolone" or "Aristocort" or "Azmacort" or "Kenacort" or "Kenalog" or "Tricort" or "Trilone" or "Volon").ti,ab.
ICS/LABA/	(Trimbow or "Trelegy" or "FF/UMEC/VI" or "Triohale" or "fluticasone furoate/umeclidinium/vilanterol" or "Closed Triple" or "Elebrato Ellipta" or "Temybric Ellipta" or

LAMA (Mixed Drugs)	"triple therapy" or "BGF" or "BGF MDI" or "budesonide + formoterol fumarate + glycopyrronium" or "budesonide/formoterol fumarate/glycopyrronium" or "BUD/GLY/FOR" or "BUD/FOR/GLY" or "Trixeo Aerosphere" or "Riltrava Aerosphere").ti,ab.
Combination	1 and (((2 or 7) and (3 or 4) and (5 or 6)) or 8)
No Animals	9 NOT ((animals not (humans and animals)).sh.)
English	limit 10 to english language
Publication Type	11 not ("clinical trial, veterinary" or "collected work " or "comment" or "congress " or "consensus development conference " or "consensus development conference, nih " or "video-audio media " or "webcast" or "technical report " or "corrected and republished article OR dataset OR dictionary OR directory OR duplicate publication OR editorial OR electronic supplementary materials OR evaluation study OR lecture OR legal case OR legislation OR letter OR meta analysis OR expression of concern " or "festschrift " or "government publication " or "guideline " or "historical article " or "interactive tutorial " or "interview " or "introductory journal article " or "patient education handout " or "news " or "retracted publication " or "newspaper article " or "observational study, veterinary " or "retraction of publication OR review " or "scientific integrity review OR systematic review " or "randomized controlled trial, veterinary " or "periodical index " or "personal narrative " or "portrait " or "practice guideline " or "pragmatic clinical trial " or "preprint " or "published erratum ").pt.
RCT	12 and ((groups or trial or randomly).ti,ab. or drug therapy.sh. or placebo.ti,ab. or randomized.ti,ab. or controlled clinical trial.pt. or randomized controlled trial.pt.)
Date Limit	limit 13 to yr="2020 -Current"
Duplicates	Remove duplicates from 14

Date of last search: January 10, 2025

Table D1.4. EMBASE Search Strategy – Triple Therapy NMA (Research Question #1)

COPD	'chronic obstructive lung disease'/exp OR 'airflow obstruction, chronic':ti,ab OR 'airflow obstructions, chronic':ti,ab OR 'chronic airway obstruction':ti,ab OR 'chronic obstructive bronchopulmonary disease':ti,ab OR 'chronic obstructive respiratory disease':ti,ab OR 'chronic pulmonary obstructive disease':ti,ab OR 'chronic pulmonary obstructive disorder':ti,ab OR 'chronic airflow obstruction':ti,ab OR 'chronic airflow obstructions':ti,ab OR 'chronic obstructive airway disease':ti,ab OR 'chronic obstructive lung disease':ti,ab OR 'chronic obstructive pulmonary disease':ti,ab OR 'chronic obstructive pulmonary diseases':ti,ab OR 'coad':ti,ab OR 'copd':ti,ab OR 'lung chronic obstructive disease':ti,ab OR 'lung disease, chronic obstructive':ti,ab OR 'obstructive chronic lung disease':ti,ab OR 'obstructive chronic pulmonary disease':ti,ab OR 'obstructive lung disease, chronic':ti,ab OR 'pulmonary disease, chronic obstructive':ti,ab OR 'pulmonary disorder, chronic obstructive':ti,ab
LABA (General)	'beta 2 adrenergic receptor stimulating agent'/exp OR (('long-acting':ab,ti OR 'long acting':ab,ti OR 'ultra-long acting':ab,ti OR 'ultra-long-acting':ab,ti) AND ('β agonist*':ab,ti OR 'β-agonist*':ab,ti OR 'β2 agonist*':ab,ti OR 'β2-agonist*':ab,ti OR 'β-2 agonist*':ab,ti OR 'β-2-agonist*':ab,ti OR 'b2 agonist*':ab,ti OR 'b2-agonist*':ab,ti OR 'b-2 agonist*':ab,ti OR 'b-2-agonist*':ab,ti OR 'β(2) agonist*':ab,ti OR 'β(2)-agonist*':ab,ti OR 'β adrenergic agonist*':ab,ti OR 'β-adrenergic agonist*':ab,ti OR 'β2 adrenergic agonist*':ab,ti OR 'β2-adrenergic agonist*':ab,ti OR 'β-2 adrenergic agonist*':ab,ti OR 'β-2-adrenergic agonist*':ab,ti OR 'b2 adrenergic agonist*':ab,ti OR 'b2-adrenergic agonist*':ab,ti OR 'b-2 adrenergic agonist*':ab,ti OR 'b-2-adrenergic agonist*':ab,ti OR 'β(2) adrenergic agonist*':ab,ti OR 'β(2)-adrenergic agonist*':ab,ti OR 'β adrenoceptor agonist*':ab,ti OR 'β-adrenoceptor agonist*':ab,ti OR 'β2 adrenoceptor agonist*':ab,ti OR 'β2-adrenoceptor agonist*':ab,ti OR 'β-2 adrenoceptor agonist*':ab,ti OR 'β-2-adrenoceptor agonist*':ab,ti OR 'b2 adrenoceptor agonist*':ab,ti OR 'b2-adrenoceptor agonist*':ab,ti OR 'b-2 adrenoceptor agonist*':ab,ti OR 'b-2-adrenoceptor agonist*':ab,ti OR 'β(2) adrenoceptor agonist*':ab,ti OR 'β(2)-adrenoceptor agonist*':ab,ti OR 'beta agonist*':ab,ti OR 'beta-agonist*':ab,ti OR 'beta2 agonist*':ab,ti OR 'beta2-agonist*':ab,ti

	OR 'beta-2 agonist*':ab,ti OR 'beta-2-agonist*':ab,ti OR 'beta(2) agonist*':ab,ti OR 'beta(2)-agonist*':ab,ti OR 'beta adrenergic agonist*':ab,ti OR 'beta-adrenergic agonist*':ab,ti OR 'beta2 adrenergic agonist*':ab,ti OR 'beta2-adrenergic agonist*':ab,ti OR 'beta-2 adrenergic agonist*':ab,ti OR 'beta-2-adrenergic agonist*':ab,ti OR 'beta(2) adrenergic agonist*':ab,ti OR 'beta(2)-adrenergic agonist*':ab,ti OR 'beta adrenoceptor agonist*':ab,ti OR 'beta-adrenoceptor agonist*':ab,ti OR 'beta2 adrenoceptor agonist*':ab,ti OR 'beta2-adrenoceptor agonist*':ab,ti OR 'beta-2 adrenoceptor agonist*':ab,ti OR 'beta-2-adrenoceptor agonist*':ab,ti OR 'beta(2) adrenoceptor agonist*':ab,ti OR 'beta(2)-adrenoceptor agonist*':ab,ti)) OR 'laba':ab,ti OR 'labas':ab,ti OR 'ultra-laba':ab,ti OR 'ultra-labas':ab,ti
LABA (Individual Drugs)	'formoterol fumarate'/exp OR 'formoterol':ab,ti OR 'formoterol-fumarate':ab,ti OR 'eformoterol':ab,ti OR 'atimos':ab,ti OR 'efo':ab,ti OR 'fluir':ab,ti OR 'foradil':ab,ti OR 'foradile':ab,ti OR 'formoair':ab,ti OR 'oxis':ab,ti OR 'perforomist':ab,ti OR 'tempus':ab,ti OR 'indacaterol'/exp OR 'indacaterol':ab,ti OR 'indacaterol-maleate':ab,ti OR 'arcapta':ab,ti OR 'hirobriz':ab,ti OR 'onbrez':ab,ti OR 'onbrize':ab,ti OR 'oslif':ab,ti OR 'olodaterol'/exp OR 'olodaterol':ab,ti OR 'striverdi':ab,ti OR 'salmeterol xinafoate'/exp OR 'salmeterol':ab,ti OR 'salmeterolum':ab,ti OR 'salmeterol-xinafoate':ab,ti OR 'aeromax':ab,ti OR 'astmerole':ab,ti OR 'arial':ab,ti OR 'neovent':ab,ti OR 'qitai':ab,ti OR 'serevent':ab,ti OR 'vertine':ab,ti OR 'vilanterol'/exp OR 'vilanterol-trifenatate':ab,ti OR 'vilanterol':ab,ti
LAMA (General)	'cholinergic receptor blocking agent'/exp OR 'muscarinic receptor blocking agent'/exp OR (('long-acting':ab,ti OR 'long acting':ab,ti OR 'ultra-long acting':ab,ti OR 'ultra-long-acting':ab,ti) AND ('muscarinic antagonist*':ab,ti OR 'muscarinic receptor antagonist*':ab,ti OR 'antimuscarinic agent*':ab,ti OR 'anti-muscarinic agent*':ab,ti OR 'muscarinic blocker*':ab,ti OR 'muscarinic receptor blocker*':ab,ti OR 'cholinergic antagonist*':ab,ti OR 'cholinergic receptor antagonist*':ab,ti OR 'anticholinergic agent*':ab,ti OR 'anti-cholinergic agent*':ab,ti OR 'cholinergic blocker*':ab,ti OR 'cholinergic receptor blocker*':ab,ti OR 'cholinolytic agent*':ab,ti)) OR 'lama':ab,ti OR 'lamas':ab,ti OR 'ultra-lama':ab,ti OR 'ultra-lamas':ab,ti
LAMA (Individual Drugs)	'aclidinium bromide'/exp OR 'aclidinium':ab,ti OR 'aclidinium-bromide':ab,ti OR 'tudorza':ab,ti OR 'eklira':ab,ti OR 'bretaris':ab,ti OR 'glycopyrrolate'/exp OR 'glycopyrronium'/exp OR 'glycopyrrolate':ab,ti OR 'glycopyrronium':ab,ti OR 'glycopyrronium-bromide':ab,ti OR 'seebri':ab,ti OR 'tiotropium bromide'/exp OR 'tiotropium':ab,ti OR 'tiotropium-bromide':ab,ti OR 'spiriva':ab,ti OR 'tiova':ab,ti OR 'umeclidinium':ab,ti OR 'umeclidinium-bromide':ab,ti OR 'incruse':ab,ti
ICS (General)	'inhal*':ab,ti AND ('glucocorticoid'/exp OR 'corticosteroid':ab,ti OR 'cortico-steroid':ab,ti OR 'glucocorticoid*':ab,ti OR 'steroid*':ab,ti) OR 'ics':ab,ti
ICS (Individual Drugs)	'beclomethasone'/exp OR 'beclometasone'/exp OR 'beclometasone dipropionate'/exp OR 'beclomethasone':ab,ti OR 'beclometasone':ab,ti OR 'beclomethasone-17-monopropionate':ab,ti OR 'beclometasone-17-monopropionate':ab,ti OR 'beclomethasone-dipropionate':ab,ti OR 'beclometasone-dipropionate':ab,ti OR 'beclomethasone-dipropionate-monohydrate':ab,ti OR 'aerobec':ab,ti OR 'asmabec':ab,ti OR 'beclate':ab,ti OR 'beclazone':ab,ti OR 'becloforte':ab,ti OR 'beclomet':ab,ti OR 'beclovent':ab,ti OR 'beconase':ab,ti OR 'becotide':ab,ti OR 'bekotid':ab,ti OR 'clenil':ab,ti OR 'qvar':ab,ti OR 'respocort':ab,ti OR 'vanceril':ab,ti OR 'vancenase':ab,ti OR 'ventolair':ab,ti OR 'budesonide'/exp OR 'budesonide':ab,ti OR 'aeronide':ab,ti OR 'aerovent':ab,ti OR 'b cort':ab,ti OR 'benita':ab,ti OR 'budecort':ab,ti OR 'budeson':ab,ti OR 'budiair':ab,ti OR 'giona':ab,ti OR 'horacort':ab,ti OR 'miflonide':ab,ti OR 'noex':ab,ti OR 'novopulmon':ab,ti OR 'numark':ab,ti OR 'pulmicort':ab,ti OR 'rhinocort':ab,ti OR 'ciclesonide'/exp OR 'ciclesonide':ab,ti OR 'alvesco':ab,ti OR 'flunisolide':ab,ti OR 'flunisolide'/exp OR 'aerobid':ab,ti OR 'aerospan':ab,ti OR 'pulmilide':ab,ti OR 'fluticasone'/exp OR 'fluticasone furoate'/exp OR 'fluticason':ab,ti OR 'fluticasone':ab,ti OR 'fluticasone-propionate':ab,ti OR 'fluticasone-furoate':ab,ti OR 'allegro':ab,ti OR 'arnuity':ab,ti OR 'dalman':ab,ti OR 'flixotide':ab,ti OR 'flutica':ab,ti OR 'flutide':ab,ti OR 'flutivate':ab,ti OR 'flovent':ab,ti OR 'mometasone furoate'/exp OR 'mometason':ab,ti OR 'mometasone':ab,ti OR 'mometasone-furoate':ab,ti OR 'mometasone-furoate-monohydrate':ab,ti OR 'asmanex':ab,ti OR

	'elocom':ab,ti OR 'elocon':ab,ti OR 'ecural':ab,ti OR 'mometasona':ab,ti OR 'novasone':ab,ti OR 'triamcinolone'/exp OR 'triamcinolone acetonide'/exp OR 'triamcinolone':ab,ti OR 'aristocort':ab,ti OR 'azmacort':ab,ti OR 'kenacort':ab,ti OR 'kenalog':ab,ti OR 'tricort':ab,ti OR 'trilone':ab,ti OR 'volon':ab,ti
ICS/LABA/ LAMA (Mixed Drugs)	trimbow:ti,ab OR 'trelegy':ti,ab OR 'ff/umec/vi':ti,ab OR 'triohale':ti,ab OR 'fluticasone furoate/umeclidinium/vilanterol':ti,ab OR 'closed triple':ti,ab OR 'elebrato ellipta':ti,ab OR 'temybric ellipta':ti,ab OR 'triple therapy':ti,ab OR 'bgf':ti,ab OR 'bgf mdi':ti,ab OR 'budesonide + formoterol fumarate + glycopyrronium':ti,ab OR 'budesonide/formoterol fumarate/glycopyrronium':ti,ab OR 'bud/gly/for':ti,ab OR 'bud/for/gly':ti,ab OR 'trixeo aerosphere':ti,ab OR 'riltrava aerosphere':ti,ab
Combination	#1 AND ((#2 or #3) and (#4 or #5) and (#6 or #7) or #8)
No Animals	#9 NOT 'animal'/exp NOT ('human'/exp AND 'animal'/exp)
English	#10 AND [english]/lim
Publication Type	#11 NOT ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)
RCT	#12 AND ('double blind procedure'/exp OR 'double blind procedure':ab,ti OR 'randomized controlled trial'/exp OR 'randomized controlled trial':ab,ti OR 'single blind procedure'/exp OR 'single blind procedure':ab,ti OR 'random*':ab,ti OR 'factorial*':ab,ti OR 'placebo*':ab,ti OR ('doubl*':ab,ti AND 'blind*':ab,ti) OR ('singl*':ab,ti AND 'blind*':ab,ti) OR 'assign*':ab,ti OR 'allocat*':ab,ti OR 'volunteer*':ab,ti)
Date Limit	#12 AND [31-12-2019]/sd NOT [10-01-2025]/sd

Date of last search: January 10, 2025

Table D1.5. Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews – Trelegy Ellipta (Research Question #2)

COPD	exp Pulmonary Disease, Chronic Obstructive/ OR ("Airflow Obstruction, Chronic" OR "Airflow Obstructions, Chronic" OR "chronic airflow obstruction" OR "chronic airway obstruction" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "chronic obstructive respiratory disease" OR "chronic pulmonary obstructive disease" OR "chronic pulmonary obstructive disorder" OR "Chronic Airflow Obstruction" OR "Chronic Airflow Obstructions" OR "Chronic Obstructive Airway Disease" OR "Chronic Obstructive Lung Disease" OR "Chronic Obstructive Pulmonary Disease" OR "Chronic Obstructive Pulmonary Diseases" OR "COAD" OR "COPD" OR "lung chronic obstructive disease" OR "lung disease, chronic obstructive" OR "obstructive chronic lung disease" OR "obstructive chronic pulmonary disease" OR "obstructive lung disease, chronic" OR "pulmonary disease, chronic obstructive" OR "pulmonary disorder, chronic obstructive").ti,ab.
Trelegy Ellipta	("elebrato ellipta" OR "fluticasone furoate plus umeclidinium bromide plus vilanterol trifenatate" OR "fluticasone furoate plus vilanterol plus umeclidinium" OR "fluticasone furoate plus vilanterol trifenatate plus umeclidinium bromide" OR "fluticasone furoate/umeclidinium bromide/vilanterol trifenatate" OR "fluticasone furoate/umeclidinium/vilanterol" OR "fluticasone furoate/vilanterol trifenatate/umeclidinium bromide" OR "fluticasone furoate/vilanterol/umeclidinium" OR "gsk 2834425" OR "gsk2834425" OR "temybric ellipta" OR "trelegy ellipta" OR "umeclidinium bromide plus fluticasone furoate plus vilanterol trifenatate" OR "umeclidinium bromide plus vilanterol trifenatate plus fluticasone furoate" OR "umeclidinium bromide/fluticasone furoate/vilanterol trifenatate" OR "umeclidinium bromide/vilanterol trifenatate/fluticasone furoate" OR "umeclidinium plus fluticasone furoate plus vilanterol" OR "umeclidinium plus vilanterol plus fluticasone furoate" OR "umeclidinium/fluticasone furoate/vilanterol" OR "umeclidinium/vilanterol/fluticasone furoate"

	OR "vilanterol plus fluticasone furoate plus umeclidinium" OR "vilanterol plus umeclidinium plus fluticasone furoate" OR "vilanterol trifenatate plus fluticasone furoate plus umeclidinium bromide" OR "vilanterol trifenatate plus umeclidinium bromide plus fluticasone furoate" OR "vilanterol trifenatate/fluticasone furoate/umeclidinium bromide" OR "vilanterol trifenatate/umeclidinium bromide/fluticasone furoate" OR "vilanterol/fluticasone furoate/umeclidinium" OR "vilanterol/umeclidinium/fluticasone furoate" OR "fluticasone furoate plus umeclidinium plus vilanterol").ti,ab.
Generic Triple Therapy	((tiotropium or "tiotropium bromide" or Spiriva*) and ((budesonide and (formoterol or "formoterol fumarate" or eformoterol or arformoterol)) or ("adoair" or "Advair*" or "Aerivio*" or "Airduo*" or "Airexar*" or "Airflusal*" or anasma or "apc 5000" or apc5000 or atmadisc or "bropair spiromax" or campona* or "Combination, Fluticasone-Salmeterol" or "Drug Combination, Fluticasone-Salmeterol" or "Fluticasone - Salmeterol" or "Fluticasone Propionate-Salmeterol*" or "fluticasone propionate plus salmeterol*" or "Fluticasone Propionate Salmeterol*" or "Fluticasone Propionate, Salmeterol*" or "fluticasone propionate/salmeterol xinafoate" or "Fluticasone Salmeterol*" or inaladuo or plusvent or "salmeterol xinafoate plus fluticasone propionate" or "salmeterol xinafoate/fluticasone propionate" or "sas 40023" or sas40023 or "seffalair spiromax" or "sereflo*" or "Seretide*" or serflu or "seroflo*" or sirdupla or viani or "wixela inhub") or (("fluticasone" or "fluticasone propionate") and ("salmeterol" or "salmeterol xinafoate")) or ("airbufo forspiro" or "alenia" or "assieme*" or "biresp spiromax" or "breyna" or "budamate" or "budased f" or "budelite f" or "buderap f" or "Budesonide Formoterol Drug Combination" or "Budesonide Formoterol Fumarate Drug Combination" or "budesonide plus formoterol*" or "budesonide, formoterol fumarate*" or "budesonide/formoterol*" or "budesonide-formoterol*" or "budevin f" or "budsocare f" or "bufar*" or "bufoler*" or "bufomix*" or "bufori easyhaler" or "Combination, Budesonide-Formoterol Drug" or "Drug Combination, Budesonide-Formoterol" or "duoresp spiromax" or "duori*" or "fixbufo easyhaler" or "flamboyant (drug)" or "fobuler" or "fobumix easyhaler" or "foracort*" or "foradil*" or "forarite" or "forb" or "formonide" or "formoterol fumarate dihydrate plus budesonide" or "formoterol fumarate dihydrate/budesonide" or "formoterol fumarate plus budesonide" or "formoterol fumarate/budesonide" or "formoterol plus budesonide" or "formoterol/budesonide" or "formoterol-budesonide" or "gardette*" or "gibiter*" or "ludonaze bf" or "orbufox*" or "orest*" or "pt 009" or "pt009" or "pulentia" or "pulmalio" or "pulmelia" or "pulmoresp" or "pulmoton" or "respimix easyhaler" or "rilast*" or "sinestic" or "Symbicort*" or "syn 010" or "syn010" or "vannair" or "vyaler spiromax" or "vylaer spiromax" or "weldinide f") or ((fluticasone or "fluticasone furoate") and (vilanterol or "vilanterol trifenatate")) or ("breo" or "breo ellipta" or "fluticasone furoate plus vilanterol trifenatate" or "fluticasone furoate/vilanterol" or "fluticasone furoate/vilanterol trifenatate" or "relovair" or "relvar" or "relvar ellipta" or "revinty ellipta" or "vilanterol plus fluticasone furoate" or "vilanterol trifenatate plus fluticasone furoate" or "vilanterol trifenatate/fluticasone furoate" or "vilanterol/fluticasone furoate" or "fluticasone furoate plus vilanterol"))).ti,ab.
Combination	1 AND (2 OR 3)
No Animals	6 NOT (animals not (humans and animals)).sh.
Publication Type	5 not (address or autobiography or bibliography or biography or comment or case report or congress or clinical trial, veterinary or collected work or consensus development conference or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or encyclopedia or "expression of concern" or festschrift or guideline or government publication or guideline or historical article or interactive tutorial or interview or lecture or legal case or legislation or letter or news or newspaper article or observational study, veterinary or patient education handout or periodical index or personal narrative or portrait or practice guideline or published erratum randomized controlled trial, veterinary or "retraction of publication" or video-audio media or webcast).pt.
English	limit 8 to English language
Duplicates	Remove duplicates from 9

Date of last search: January 10, 2025

Table D1.6. EMBASE Search Strategy – Trelegy Ellipta (Research Question #2)

COPD	'chronic obstructive lung disease'/exp OR ('Airflow Obstruction, Chronic' OR 'Airflow Obstructions, Chronic' OR 'chronic airflow obstruction' OR 'chronic airway obstruction' OR 'chronic obstructive bronchopulmonary disease' OR 'chronic obstructive lung disease' OR 'chronic obstructive pulmonary disease' OR 'chronic obstructive respiratory disease' OR 'chronic pulmonary obstructive disease' OR 'chronic pulmonary obstructive disorder' OR 'Chronic Airflow Obstruction' OR 'Chronic Airflow Obstructions' OR 'Chronic Obstructive Airway Disease' OR 'Chronic Obstructive Lung Disease' OR 'Chronic Obstructive Pulmonary Disease' OR 'Chronic Obstructive Pulmonary Diseases' OR 'COAD' OR 'COPD' OR 'lung chronic obstructive disease' OR 'lung disease, chronic obstructive' OR 'obstructive chronic lung disease' OR 'obstructive chronic pulmonary disease' OR 'obstructive lung disease, chronic' OR 'pulmonary disease, chronic obstructive' OR 'pulmonary disorder, chronic obstructive'):ti,ab
Trelegy Ellipta	('elebrato ellipta' OR 'fluticasone furoate plus umeclidinium bromide plus vilanterol trifenatate' OR 'fluticasone furoate plus vilanterol plus umeclidinium' OR 'fluticasone furoate plus vilanterol trifenatate plus umeclidinium bromide' OR 'fluticasone furoate/umeclidinium bromide/vilanterol trifenatate' OR 'fluticasone furoate/umeclidinium/vilanterol' OR 'fluticasone furoate/vilanterol trifenatate/umeclidinium bromide' OR 'fluticasone furoate/vilanterol/umeclidinium' OR 'gsk 2834425' OR 'gsk2834425' OR 'temybric ellipta' OR 'trelegy ellipta' OR 'umeclidinium bromide plus fluticasone furoate plus vilanterol trifenatate' OR 'umeclidinium bromide plus vilanterol trifenatate plus fluticasone furoate' OR 'umeclidinium bromide/fluticasone furoate/vilanterol trifenatate' OR 'umeclidinium bromide/vilanterol trifenatate/fluticasone furoate' OR 'umeclidinium plus fluticasone furoate plus vilanterol' OR 'umeclidinium plus vilanterol plus fluticasone furoate' OR 'umeclidinium/fluticasone furoate/vilanterol' OR 'umeclidinium/vilanterol/fluticasone furoate' OR 'vilanterol plus fluticasone furoate plus umeclidinium' OR 'vilanterol plus umeclidinium plus fluticasone furoate' OR 'vilanterol trifenatate plus fluticasone furoate plus umeclidinium bromide' OR 'vilanterol trifenatate plus umeclidinium bromide plus fluticasone furoate' OR 'vilanterol trifenatate/fluticasone furoate/umeclidinium bromide' OR 'vilanterol trifenatate/umeclidinium bromide/fluticasone furoate' OR 'vilanterol/fluticasone furoate/umeclidinium' OR 'vilanterol/umeclidinium/fluticasone furoate' OR 'fluticasone furoate plus umeclidinium plus vilanterol'):ti,ab
Generic Triple Therapy	(tiotropium:ti,ab OR 'tiotropium bromide':ti,ab OR spiriva*:ti,ab) AND (budesonide:ti,ab AND (formoterol:ti,ab OR 'formoterol fumarate':ti,ab OR eformoterol:ti,ab OR arformoterol:ti,ab) OR 'adoair':ti,ab OR 'advair*':ti,ab OR 'aerivio*':ti,ab OR 'airduo*':ti,ab OR 'airexar*':ti,ab OR 'airflusal*':ti,ab OR anasma:ti,ab OR 'apc 5000':ti,ab OR apc5000:ti,ab OR atmadisc:ti,ab OR 'bropair spiromax':ti,ab OR campona*:ti,ab OR 'fluticasone - salmeterol':ti,ab OR 'fluticasone propionate-salmeterol*':ti,ab OR 'fluticasone propionate plus salmeterol*':ti,ab OR 'fluticasone propionate/salmeterol xinafoate':ti,ab OR 'fluticasone salmeterol*':ti,ab OR inaladuo:ti,ab OR plusvent:ti,ab OR 'salmeterol xinafoate plus fluticasone propionate':ti,ab OR 'sas 40023':ti,ab OR sas40023:ti,ab OR 'seffalair spiromax':ti,ab OR 'sereflo*':ti,ab OR 'seretide*':ti,ab OR serflu:ti,ab OR 'seroflo*':ti,ab OR sirdupla:ti,ab OR viani:ti,ab OR 'wixela inhub':ti,ab OR ('fluticasone':ti,ab AND ('salmeterol':ti,ab OR 'salmeterol xinafoate':ti,ab)) OR 'airbufo forspiro':ti,ab OR 'alenia':ti,ab OR 'assieme*':ti,ab OR 'biresp spiromax':ti,ab OR 'breyna':ti,ab OR 'budamate':ti,ab OR 'budased f':ti,ab OR 'budelite f':ti,ab OR 'buderap f':ti,ab OR 'budesonide formoterol drug combination':ti,ab OR 'budesonide plus formoterol*':ti,ab OR 'budesonide/formoterol*':ti,ab OR 'budesonide-formoterol*':ti,ab OR 'bufomix*':ti,ab OR 'duoresp spiromax':ti,ab OR 'symbicort*':ti,ab OR 'vannair':ti,ab OR 'vyaler spiromax':ti,ab OR 'vylaer spiromax':ti,ab OR 'weldinide f':ti,ab OR ((fluticasone:ti,ab OR 'fluticasone furoate':ti,ab) AND (vilanterol:ti,ab OR

	'vilanterol trifenatate':ti,ab)) OR 'breo':ti,ab OR 'breo ellipta':ti,ab OR 'fluticasone furoate plus vilanterol trifenatate':ti,ab OR 'relvar ellipta':ti,ab OR 'vilanterol/fluticasone furoate':ti,ab)
Combination	#1 AND (#2 OR #3)
No Animals	#4 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)
Publication Type	#5 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'review'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)
English	#6 AND [english]/lim

Date of last search: January 10, 2025

Table D1.7. Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews – Breo Ellipta (Research Question #3)

COPD	exp Pulmonary Disease, Chronic Obstructive/ OR ("Airflow Obstruction, Chronic" OR "Airflow Obstructions, Chronic" OR "chronic airflow obstruction" OR "chronic airway obstruction" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "chronic obstructive respiratory disease" OR "chronic pulmonary obstructive disease" OR "chronic pulmonary obstructive disorder" OR "Chronic Airflow Obstruction" OR "Chronic Airflow Obstructions" OR "Chronic Obstructive Airway Disease" OR "Chronic Obstructive Lung Disease" OR "Chronic Obstructive Pulmonary Disease" OR "Chronic Obstructive Pulmonary Diseases" OR "COAD" OR "COPD" OR "lung chronic obstructive disease" OR "lung disease, chronic obstructive" OR "obstructive chronic lung disease" OR "obstructive chronic pulmonary disease" OR "obstructive lung disease, chronic" OR "pulmonary disease, chronic obstructive" OR "pulmonary disorder, chronic obstructive").ti,ab.
Breo Ellipta	("breo" OR "breo ellipta" OR "FF/VI" OR "fluticasone furoate plus vilanterol" OR "fluticasone furoate plus vilanterol trifenatate" OR "fluticasone furoate/vilanterol" OR "fluticasone furoate/vilanterol trifenatate" OR "GSK 2285997" OR "GSK 642444 (LABA)/GSK 685698 (ICS)" OR "GSK2285997" OR "GSK-2285997" OR "GSK642444 (LABA)/GSK685698 (ICS)" OR "GSK-642444 (LABA)/GSK-685698 (ICS)" OR "Horizon" OR "relovair" OR "relvar" OR "relvar ellipta" OR "revinty ellipta" OR "vilanterol plus fluticasone furoate" OR "vilanterol trifenatate plus fluticasone furoate" OR "vilanterol trifenatate/fluticasone furoate" OR "vilanterol/fluticasone furoate").ti,ab.
Generic ICS/LABA	("airbufo forspiro" or "alenia" or "assieme*" or "biresp spiromax" or "breyna" or "budamate" or "budased f" or "budelite f" or "buderap f" or "Budesonide Formoterol Drug Combination" or "Budesonide Formoterol Fumarate Drug Combination" or "budesonide plus formoterol*" or "budesonide, formoterol fumarate* " or "budesonide/formoterol*" or "budesonide-formoterol*" or "budevin f" or "budsocare f" or "bufar*" or "bufoler*" or "bufomix*" or "bufori easyhaler" or "Combination, Budesonide-Formoterol Drug" or "Drug Combination, Budesonide-Formoterol" or "duoresp spiromax" or "duori*" or "fixbufo easyhaler" or "flamboyant (drug)" or "fobuler" or "fobumix easyhaler" or "foracort*" or "foradil*" or "forarite" or "forb" or "formonide" or "formoterol fumarate dihydrate plus budesonide" or "formoterol fumarate dihydrate/budesonide" or "formoterol fumarate plus budesonide" or "formoterol fumarate/budesonide" or "formoterol plus budesonide" or "formoterol/budesonide" or "formoterol-budesonide" or "gardette*" or "gibiter*" or "ludonaze bf" or "orbufox*" or "orest*" or "pt 009" or "pt009" or "pulentia" or "pulmalio" or "pulmelia" or "pulmoresp" or "pulmoton" or "respimix easyhaler" or "rilast*" or "sinestic" or "Symbicort*" or "syn 010" or "syn010" or "vannair" or "vyaler spiromax" or "vylaer spiromax" or "weldinide f" or ("adoair" or "Advair* " or "Aerivio*" or "Airduo* " or "Airexar*" or "Airflusal*" or "anasma" or "apc 5000" or "apc5000" or "atmadisc" or "bropair spiromax" or "campona*" or "Combination, Fluticasone-Salmeterol" or "Drug Combination, Fluticasone-Salmeterol" or "Fluticasone - Salmeterol" or "Fluticasone Propionate-Salmeterol*" or "fluticasone propionate plus salmeterol* " or "Fluticasone Propionate Salmeterol*" or "Fluticasone Propionate, Salmeterol* " or "fluticasone

	propionate/salmeterol xinafoate" or "Fluticasone Salmeterol*" or "inaladuo" or "plusvent" or "salmeterol xinafoate plus fluticasone propionate" or "salmeterol xinafoate/fluticasone propionate" or "sas 40023" or "sas40023" or "seffalair spiromax" or "sereflo*" or "Seretide*" or "serflu" or "seroflo*" or "sirdupla" or "viani" or "wixela inhub")).ti,ab. OR ((budesonide and ("formoterol fumarate" or formoterol)) or ((fluticasone or "fluticasone propionate") and (salmeterol or "salmeterol xinafoate"))).ti,ab.
Combination	1 AND (2 OR 3)
No Animals	4 NOT (animals not (humans and animals)).sh.
Publication Type	5 not (address or autobiography or bibliography or biography or comment or case report or congress or clinical trial, veterinary or collected work or consensus development conference or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or encyclopedia or "expression of concern" or festschrift or guideline or government publication or guideline or historical article or interactive tutorial or interview or lecture or legal case or legislation or letter or news or newspaper article or observational study, veterinary or patient education handout or periodical index or personal narrative or portrait or practice guideline or published erratum randomized controlled trial, veterinary or "retraction of publication" or video-audio media or webcast).pt.
English	limit 6 to English language
Duplicates	Remove duplicates from 7

Date of last search: January 10, 2025

Table D1.8. EMBASE Search Strategy – Breo Ellipta (Research Question #3)

COPD	'chronic obstructive lung disease'/exp OR ('Airflow Obstruction, Chronic' OR 'Airflow Obstructions, Chronic' OR 'chronic airflow obstruction' OR 'chronic airway obstruction' OR 'chronic obstructive bronchopulmonary disease' OR 'chronic obstructive lung disease' OR 'chronic obstructive pulmonary disease' OR 'chronic obstructive respiratory disease' OR 'chronic pulmonary obstructive disease' OR 'chronic pulmonary obstructive disorder' OR 'Chronic Airflow Obstruction' OR 'Chronic Airflow Obstructions' OR 'Chronic Obstructive Airway Disease' OR 'Chronic Obstructive Lung Disease' OR 'Chronic Obstructive Pulmonary Disease' OR 'Chronic Obstructive Pulmonary Diseases' OR 'COAD' OR 'COPD' OR 'lung chronic obstructive disease' OR 'lung disease, chronic obstructive' OR 'obstructive chronic lung disease' OR 'obstructive chronic pulmonary disease' OR 'obstructive lung disease, chronic' OR 'pulmonary disease, chronic obstructive' OR 'pulmonary disorder, chronic obstructive'):ti,ab
Breo Ellipta	('breo' OR 'breo ellipta' OR 'FF/VI' OR 'fluticasone furoate plus vilanterol' OR 'fluticasone furoate plus vilanterol trifenatate' OR 'fluticasone furoate/vilanterol' OR 'fluticasone furoate/vilanterol trifenatate' OR 'GSK 2285997' OR 'GSK 642444 (LABA)/GSK 685698 (ICS)' OR 'GSK2285997' OR 'GSK-2285997' OR 'GSK642444 (LABA)/GSK685698 (ICS)' OR 'GSK-642444 (LABA)/GSK-685698 (ICS)' OR 'Horizon' OR 'relovair' OR 'relvar' OR 'relvar ellipta' OR 'revinty ellipta' OR 'vilanterol plus fluticasone furoate' OR 'vilanterol trifenatate plus fluticasone furoate' OR 'vilanterol trifenatate/fluticasone furoate' OR 'vilanterol/fluticasone furoate'):ti,ab
Generic ICS/LABA	('airbufo forspiro' OR 'alenia' OR 'assieme*' OR 'biresp spiromax' OR 'breyna' OR 'budamate' OR 'budased f' OR 'budelite f' OR 'buderap f' OR 'Budesonide Formoterol Drug Combination' OR 'Budesonide Formoterol Fumarate Drug Combination' OR 'budesonide plus formoterol*' OR 'budesonide, formoterol fumarate*' OR 'budesonide/formoterol*' OR 'budesonide-formoterol*' OR 'budevin f' OR 'budsocare f' OR 'bufar*' OR 'bufoler*' OR 'bufomix*' OR 'bufori easyhaler' OR 'Combination, Budesonide-Formoterol Drug' OR 'Drug Combination, Budesonide-Formoterol' OR 'duoresp spiromax' OR 'duori*' OR 'fixbufo easyhaler' OR 'flamboyant (drug)' OR 'fobuler' OR 'fobumix easyhaler' OR 'foracort*' OR 'foradil*' OR 'forarite' OR 'forb' OR 'formonide' OR 'formoterol fumarate dihydrate plus budesonide' OR 'formoterol fumarate dihydrate/budesonide' OR 'formoterol fumarate plus budesonide' OR 'formoterol fumarate/budesonide' OR 'formoterol plus budesonide' OR 'formoterol/budesonide' OR

	'formoterol-budesonide' OR 'gardette*' OR 'gibiter*' OR 'ludonaze bf' OR 'orbufox*' OR 'orest*' OR 'pt 009' OR 'pt009' OR 'pulentia' OR 'pulmalio' OR 'pulmelia' OR 'pulmoresp' OR 'pulmoton' OR 'respimix easyhaler' OR 'rilast*' OR 'sinestic' OR 'Symbicort*' OR 'syn 010' OR 'syn010' OR 'vannair' OR 'vyaler spiromax' OR 'vylaer spiromax' OR 'weldinide f' OR 'adoair' OR 'Advair*' OR 'Aerivio*' OR 'Airduo*' OR 'Airexar*' OR 'Airflusal*' OR 'anasma' OR 'apc 5000' OR 'apc5000' OR 'atmadisc' OR 'bropair spiromax' OR 'campona*' OR 'Combination, Fluticasone-Salmeterol' OR 'Drug Combination, Fluticasone-Salmeterol' OR 'Fluticasone - Salmeterol' OR 'Fluticasone Propionate-Salmeterol*' OR 'fluticasone propionate plus salmeterol*' OR 'Fluticasone Propionate Salmeterol*' OR 'Fluticasone Propionate, Salmeterol*' OR 'fluticasone propionate/salmeterol xinafoate' OR 'Fluticasone Salmeterol*' OR 'inaladuo' OR 'plusvent' OR 'salmeterol xinafoate plus fluticasone propionate' OR 'salmeterol xinafoate/fluticasone propionate' OR 'sas 40023' OR 'sas40023' OR 'seffalair spiromax' OR 'sereflo*' OR 'Seretide*' OR 'serflu' OR 'seroflo*' OR 'sirdupla' OR 'viani' OR 'wixela inhub'):ti,ab OR ((budesonide AND ('formoterol fumarate' OR formoterol)) OR ((fluticasone OR 'fluticasone propionate') AND (salmeterol OR 'salmeterol xinafoate'))):ti,ab
Combination	#1 AND (#2 OR #3)
No Animal	#4 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)
Publication Type	#5 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'review'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)
English	#6 AND [english]/lim

Date of last search: January 10, 2025

Figure D1.1. PRISMA flow Chart Showing Results of Literature Search for Triple Therapy NMA

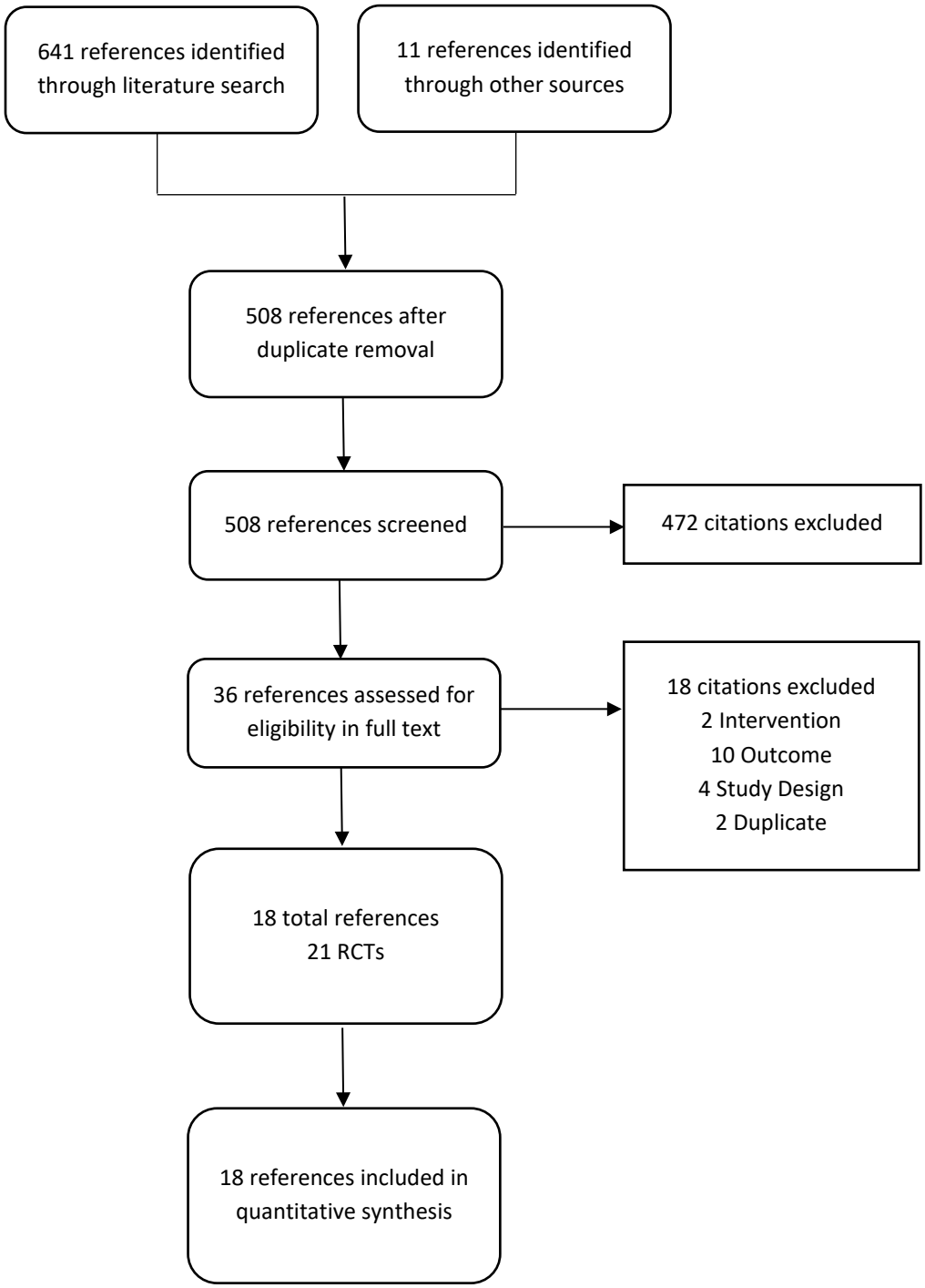


Figure D1.2. PRISMA flow Chart Showing Results of Literature Search for Trelegy Ellipta

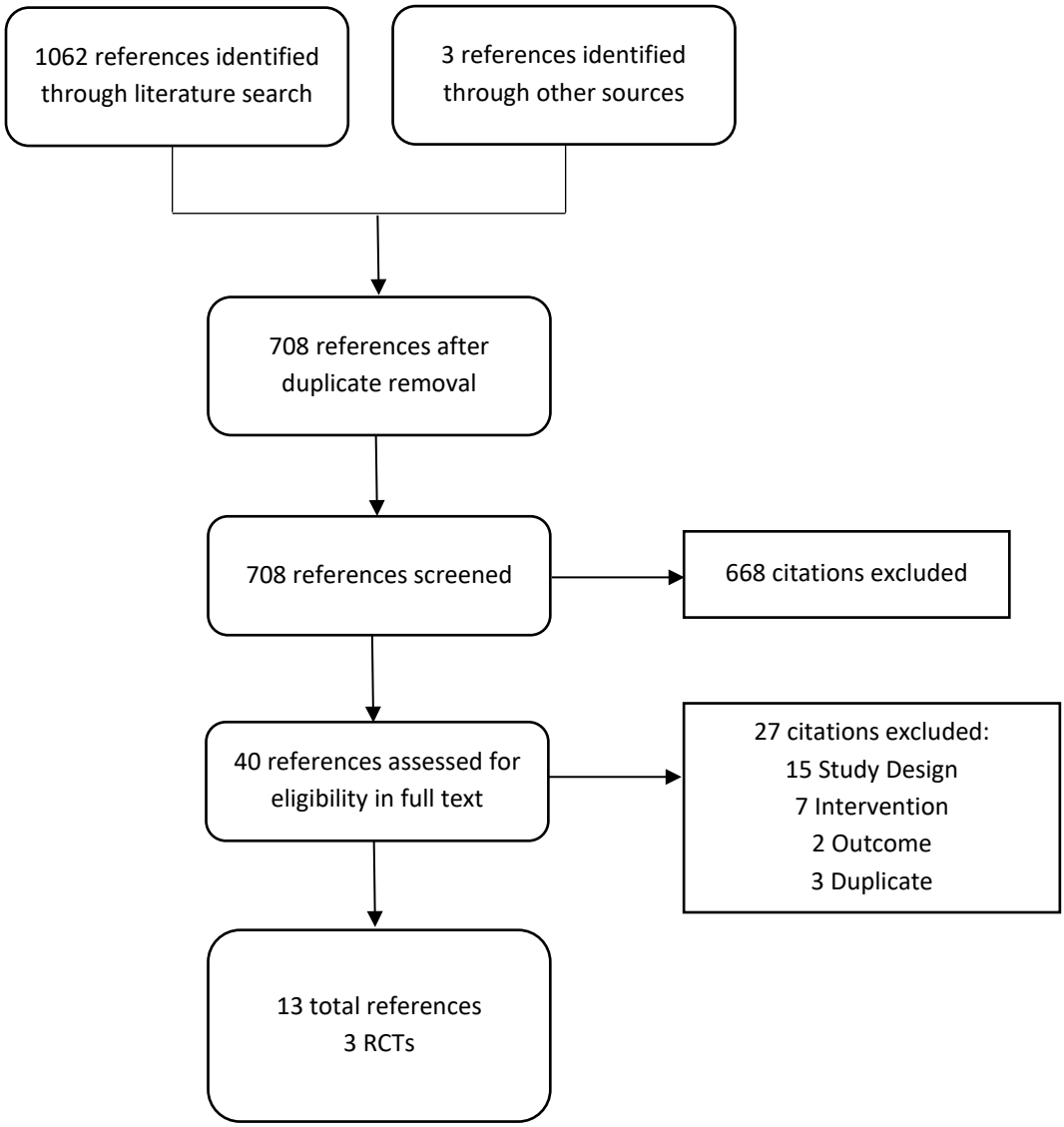
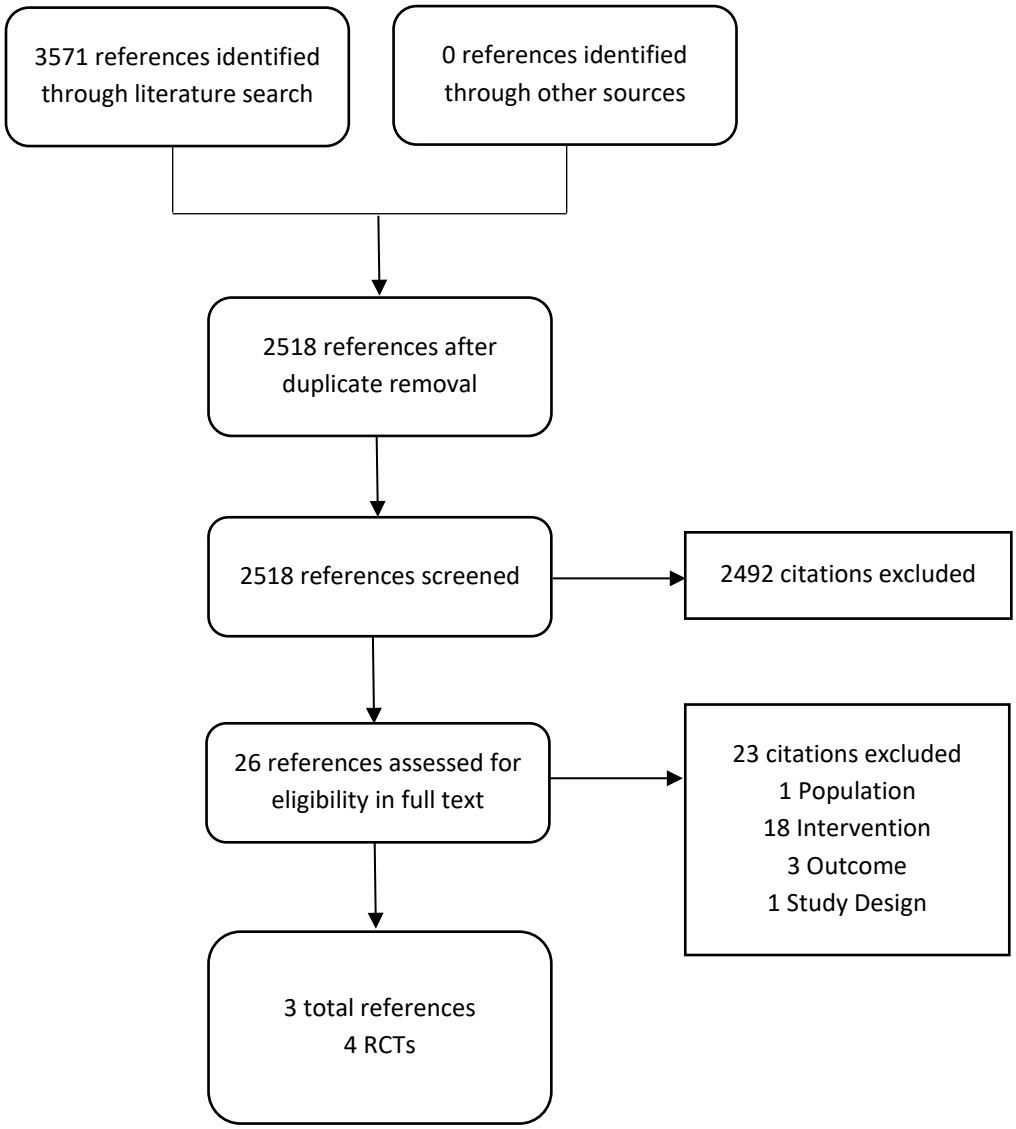


Figure D1.3. PRISMA flow Chart Showing Results of Literature Search for Breo Ellipta



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge; a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full-text appraisal. One investigator reviewed full papers and provided justification for the exclusion of each excluded study. All literature that did not undergo a formal peer review process is described separately.

Data Extraction

Data were extracted into Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[108,110] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the following outcomes: rate of moderate to severe exacerbations, SGRQ total score, and discontinuation due to adverse events for trials included in the NMA, and trials specifically examining the comparative efficacy and safety of Trelegy Ellipta or Breo Ellipta and their therapeutic alternatives. See Tables D1.3-5.

Table D1.9. Risk of Bias Assessment (Rate of Moderate to Severe Exacerbations)

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Outcome Measurement	Selection of the Reported Result	Overall Risk of Bias	Comment
Trials Included in NMA							
Aaron 2017	Low	Low	Low	Low	Low	Low	-
Bansal 2021	Low	Low	Low	Low	Low	Low	-
Bremner 2018	Low	Low	Low	Low	Low	Low	-
Chapman 2018	Low	Low	High	Low	Low	High	Imputation methods for missing data were not explained. Withdrawal or discontinuation due to lack of efficacy was higher in one group than the other.
Ferguson 2018	Low	Low	Low	Low	Low	Low	-
Ferguson 2020 Study 207608	Low	Low	Low	Low	Some concerns	Some concerns	Neither the manuscript nor the protocol reported analysis plan for the exacerbation data. Data was only reported in the study report.
Ferguson 2020 Study 207609	Low	Low	Low	Low	Some concerns	Some concerns	
Hanania 2012	Low	Low	Low	Low	Low	Low	-
Lipson 2017	Low	Low	Low	Low	Low	Low	-
Lipson 2018	Low	Low	Low	Low	Low	Low	-
Papi 2018	Low	Low	Low	Low	Low	Low	-
Rabe 2020	Low	Low	Low	Low	Low	Low	-
Singh 2016	Low	Low	Low	Low	Low	Low	-
Siler 2015 Study 200109	Low	Low	Low	Low	Low	Low	-
Siler 2015 Study 200110	Low	Low	Low	Low	Low	Low	-
Vestbo 2017	Low	Low	Low	Low	Low	Low	-
Welte 2009	Low	Low	Low	Low	Low	Low	-
Zheng 2021	Low	Low	High	Low	Low	High	Missing data without explanation of imputation methods. More participants discontinued due to COPD exacerbation in one group than the other.
Pepin 2014*	Low	Low	Low	Low	Low	Low	-
Covelli 2016*	Low	Low	Low	Low	Low	Low	-

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Outcome Measurement	Selection of the Reported Result	Overall Risk of Bias	Comment
Wedzicha 2008*	Low	Low	High	Low	Low	High	Missing data on exacerbations, with 6-8% of participants discontinuing the trial due COPD exacerbation which was higher in the tiotropium arm.
Trelegy Ellipta							
Bremner 2018	Low	Low	Low	Low	Low	Low	-
Ferguson 2020 Study 207608	Low	Low	Low	Low	Some concerns	Some concerns	Neither the manuscript nor the protocol reported analysis plan for the exacerbation data. Data was only reported in the study report.
Ferguson 2020 Study 207609	Low	Low	Low	Low	Some concerns	Some concerns	
Breo Ellipta							
Dransfield 2014 NCT01323634	Low	Low	Low	Low	Low	Low	-
Dransfield 2014 NCT01323621	Low	Low	Low	Low	Low	Low	-
Dransfield 2014 NCT01706328	Low	Low	Low	Low	Some concerns	Some concerns	Data was reported inconsistently, and the analysis plan was unclear.
Agustí 2014 NCT01342913	Low	Low	Low	Low	Low	Low	-

*These trials comparing ICS/LABA combinations to tiotropium were added to a separate NMA comparing all triple therapy to all ICS/LABA and to tiotropium to supplement assumptions in the economic model.

Table D1.10. Risk of Bias Assessment (SGRQ Total Score)

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Outcome Measurement	Selection of the Reported Result	Overall Risk of Bias	Comment
Trials Included in NMA							
Aaron 2017	Low	Low	Low	Low	Low	Low	-
Bremner 2018	Low	Low	Low	Low	Low	Low	-
Chapman 2018	Low	Low	High	Low	Low	High	Imputation methods for missing data were not explained. Withdrawal or discontinuation due to lack of efficacy was higher in one group than the other
Ferguson 2018	Low	Low	Low	Low	Low	Low	-
Ferguson 2020 Study 207608	Low	Low	Low	Low	Low	Low	-
Ferguson 2020 Study 207609	Low	Low	Low	Low	Low	Low	-
Frith 2015	Low	Low	High	Low	Low	High	Missing data due to high discontinuation and higher rate of discontinuation in the placebo group
Lipson 2017	Low	Low	High	Low	Low	High	More participants discontinued in BUD/FOR group due to lack of efficacy
Lipson 2018	Low	Low	Low	Low	Low	Low	-
Papi 2018	Low	Low	Low	Low	Low	Low	-
Rabe 2020	Low	Low	Low	Low	Low	Low	-
Singh 2016	Low	Low	Low	Low	Low	Low	-
Siler 2015 Study 200109	Low	Low	Low	Low	Low	Low	-
Siler 2015 Study 200110	Low	Low	Some concerns	Low	Low	Some concerns	Missing data in SGRQ and unclear how missing data was handled
Vestbo 2017	Low	Low	Low	Low	Low	Low	-
Welte 2009	Low	Low	Low	Low	Low	Low	-
Zheng 2021	Low	Low	Some concerns	Low	Low	Some concerns	-

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Outcome Measurement	Selection of the Reported Result	Overall Risk of Bias	Comment
Aaron 2017	Low	Low	High	Low	Low	High	Missing data without explanation of imputation methods. More participants discontinued due to COPD exacerbation in one group than the other and may also be related to SGRQ
Trelegy Ellipta							
Bremner 2018	Low	Low	Low	Low	Low	Low	-
Ferguson 2020 Study 207608	Low	Low	Low	Low	Low	Low	-
Ferguson 2020 Study 207609	Low	Low	Low	Low	Low	Low	-
Breo Ellipta							
Agustí 2014 NCT01342913	Low	Low	Some concern	Low	Low	Some concern	Missing data in SGRQ with no imputation for missing data.

Table D1.11. Risk of Bias Assessment (Discontinuation due to Adverse Events)

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Outcome Measurement	Selection of the Reported Result	Overall Risk of Bias	Comment
Trials Included in NMA							
Aaron 2017	Low	Low	Low	Low	Low	Low	-
Bansal 2021	Low	Low	Low	Low	Low	Low	-
Bremner 2018	Low	Low	Low	Low	Low	Low	-
Chapman 2018	Low	Low	Low	Low	Low	Low	-
Ferguson 2018	Low	Low	Low	Low	Low	Low	-
Ferguson 2020 Study 207608	Low	Low	Low	Low	Low	Low	-
Ferguson 2020 Study 207609	Low	Low	Low	Low	Low	Low	-
Frith 2015	Low	Low	Low	Low	Low	Low	-
Hanania 2012	Low	Low	Low	Low	Low	Low	-
Lipson 2017	Low	Low	Low	Low	Low	Low	-
Lipson 2018	Low	Low	Low	Low	Low	Low	-
Papi 2018	Low	Low	Low	Low	Low	Low	-
Rabe 2020	Low	Low	Low	Low	Low	Low	-
Singh 2016	Low	Low	Low	Low	Low	Low	-
Siler 2015 Study 200109	Low	Low	Low	Low	Low	Low	-
Siler 2015 Study 200110	Low	Low	Low	Low	Low	Low	-
Vestbo 2017	Low	Low	Low	Low	Low	Low	-
Welte 2009	Low	Low	Low	Low	Low	Low	-
Zheng 2021	Low	Low	Low	Low	Low	Low	-
Trelegy Ellipta							
Bremner 2018	Low	Low	Low	Low	Low	Low	-

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Outcome Measurement	Selection of the Reported Result	Overall Risk of Bias	Comment
Ferguson 2020 Study 207608	Low	Low	Low	Low	Low	Low	-
Ferguson 2020 Study 207609	Low	Low	Low	Low	Low	Low	-
Breo Ellipta							
Dransfield 2014 NCT01323634	Low	Low	Low	Low	Low	Low	-
Dransfield 2014 NCT01323621	Low	Low	Low	Low	Low	Low	-
Dransfield 2014 NCT01706328	Low	Low	Low	Low	Low	Low	-
Agustí 2014 NCT01342913	Low	Low	Low	Low	Low	Low	-

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[66] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.12. Representation for each demographic category was evaluated by quantitatively comparing clinical trial participants with disease-specific prevalence estimates, using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR).[6,111] Next, a representation score between zero to three was assigned based on the PDRR estimate (See Table D1.13. for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.14.

Table D1.12. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity*	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

*Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity

Table D1.13. Representation Score

Participant to Disease-Prevalence Representation Ratio (PDRR)	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

Table D1.14. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

Results

Table D1.15. presents the clinical trial diversity ratings on race and ethnicity, sex, and age (older adults) for three Trelegy Ellipta and four Breo Ellipta trials.

Table D1.15. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older Adults)
Trelegy Ellipta Trials			
Bremner et al. 2018	Fair	Poor	Fair
Ferguson et al. 2020 - Study 207608	Fair	Good	Fair
Ferguson et al. 2020 - Study 207609	Fair	Good	Fair
Breo Ellipta Trials			
Dransfield et al. 2014 - NCT01323634	Poor	Fair	NC
Dransfield et al. 2014 - NCT01323621	Poor	Fair	NC
Dransfield et al. 2014 - NCT01706328	Poor	Fair	NC
Agustí 2014 - NCT01342913	Fair	Fair	NC

NE: Not Estimated, NR: Not Reported, NC: Not Calculated.

Trelegy Ellipta

Race and Ethnicity: All three trials were international trials and we did not have access to US-specific demographic data from the manufacturer. All three trials were rated as "fair" as, while they adequately represented White and Asian individuals, they all underrepresented Black/African American individuals with COPD. Based on prevalence estimates, 12.9% of those with COPD identify as Black or African American)[6] but two trials only enrolled 9% of those who identify as Black or African American and one trial did not report the number of Black or African American individuals who were enrolled. See Table D1.16.

Sex: Two of the three trials adequately represented males and females. However, Bremner et al. (2018) underrepresented females (26% of trial participants vs. 53% of patients with COPD)[111] and this study was rated as "poor". See Table D1.15.

Age: All three trials underrepresented older adults (53-60% of trial participants vs. 80% of patients with COPD[111]) and were rated as "fair". See Table D1.15.

Breo Ellipta

Race and Ethnicity: All four trials were international trials and we did not have access to US-specific demographic data. All trials underrepresented Black or African American individuals with COPD (enrolled only 0.2-6% vs. 12.9% of those with COPD who identify as Black or African American),[6] Hispanic individuals with COPD (enrolled only 0.4-1% vs. 10.7% of those with COPD who identify as Hispanic),[6] and three of the four trials enrolled zero Asian participants. Three trials were given a "poor" rating, and the one trial that adequately represented Asian individuals with COPD was given a "fair" rating. See Table D1.15.

Sex: All four trials underrepresented females (28-36% of trial participants vs. 53% of patients with COPD)[111] and were thus rated "fair". See Table D1.15.

Age: All four trials did not report those over the age of 65 years and thus we did not provide a rating.

Table D1.16. Race and Ethnicity

	White	Black/ African American	Asian	Hispanic/ Latino	Total Score	Diversity Rating	AIAN	NHPI
Prevalence[6]	61.7%	12.9%	1.3%	10.7%	-	-	1.3%	0.1%
Trials of Trelegy Ellipta								
Bremner et al. 2018	79.5%	0	13.5%	14%	-	-	3.1%	NR
PDRR	1.29	0	10.4	1.31	-	-	2.38	NC
Score	3	0	3	3	9	Fair	NC	NC
Ferguson et al. 2020 - Study 207608	90%	9%	1%	12%	-	-	NR	NR
PDRR	1.46	0.70	0.77	1.12	-	-	NC	NC
Score	3	2	2	3	10	Fair	NC	NC
Ferguson et al. 2020 - Study 207609	89.5%	9%	1%	15%	-	-	NR	NR
PDRR	1.45	0.70	0.77	1.40	-	-	NC	NC
Score	3	2	2	3	10	Fair	NC	NC
Dransfield et al. 2014 - NCT01323634	97%	3%	NR	1%	-	-	1%	NR
PDRR	1.57	0.23	NC	0.09	-	-	0.77	NC

	White	Black/ African American	Asian	Hispanic/ Latino	Total Score	Diversity Rating	AIAN	NHPI
Score	3	1	0	1	5	Poor	NC	NC
Dransfield et al. 2014 - NCT01323621	94%	6%	NR	1%	-	-	NR	NR
PDRR	1.52	0.47	NC	0.09	-	-	NC	NC
Score	3	1	0	1	5	Poor	NC	NC
Dransfield et al. 2014 - NCT01706328	98%	2%	NR	1%	-	-	1%	NR
PDRR	1.59	0.16	NC	0.09	-	-	0.77	NC
Score	3	1	0	1	5	Poor	NC	NC
Agustí 2014 - NCT01342913	81%	0.2%	19%	0.4%	-	-	NR	NR
PDRR	1.31	0.02	14.62	0.04	-	-	NC	NC
Score	3	1	3	1	8	Fair	NC	NC

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.17. Sex and Age

	Sex				Age		
	Male	**Female**	**Score**	**Rating**	**Older Adults (≥65 Years)**	**Score**	**Rating**
Prevalence[111]	49.9%	53.1%	-	-	81.5%	-	-
Trials of Trelegy Ellipta							
Bremner et al. 2018	74.5%	25.5%	-	-	60.1%	-	-
PDRR	1.59	0.48	-	-	0.74	-	-
Score	3	1	4	Poor	2	2	Fair
Ferguson et al. 2020 - Study 207608	52.5%	47.5%	-	-	54.7%	-	-
PDRR	1.12	0.89	-	-	0.67	-	-
Score	3	3	6	Good	2	2	Fair
Ferguson et al. 2020 - Study 207609	51%	49%	-	-	53%	-	-
PDRR	1.09	0.92	-	-	0.65	-	-
Score	3	3	6	Good	2	2	Fair
Trials of Breo Ellipta							
Dransfield et al. 2014 - NCT01323634	64%	36%	-	-	NR	-	-
PDRR	1.36	0.68	-	-	NC	-	-
Dransfield et al. 2014 - NCT01323621	68%	32%	-	-	NR	-	-
PDRR	1.46	0.60	-	-	NC	-	-
Score	3	2	5	Fair	NC	0	NC

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 Years)	Score	Rating
Dransfield et al. 2014 - NCT01706328	72%	28%	-	-	NR	-	-
PDRR	1.54	0.53	-	-	NC	-	-
Score	3	2	5	Fair	NC	0	NC
Agustí 2014 - NCT01342913	82%	28%	-	-	NR	-	-
PDRR	1.75	0.53	-	-	NC	-	-
Score	3	2	5	Fair	NC	0	NC

NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[112,113]

Assessment of Bias

Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include COPD, Trelegy Ellipta, Breo Ellipta, fluticasone furoate/umeclidinium/vilanterol, and fluticasone furoate/vilanterol. We selected studies which would have met our inclusion criteria, and for which no findings have been published.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in Tables D3.1-D3.19 and synthesized qualitatively below. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality were noted in the text of the report.

All data analyses were validated by an independent member of the research team. The validator reviewed and confirmed the data analysis methods, data format, and analysis code. The validator re-ran the analysis, validated the results, and confirmed the appropriateness of reported data.

Feasibility of Conducting Network Meta-Analysis (NMA)

Previous NMAs have reported inconsistent findings for evidence comparing Trelegy Ellipta with other triple therapies for the treatment of COPD.[20,22,23,37,51] Thus, we examined the feasibility of conducting NMAs with updated evidence for: 1) moderate to severe exacerbations, 2) SGRQ total score, 3), discontinuation due to AEs, and 4) mortality. The goal of our NMAs was to assess the

comparative efficacy and safety of triple therapies for COPD when taken as instructed independent of differences in treatment adherence. The results of the NMAs were used primarily to confirm the assumption in the economic model that all triple therapies are similarly effective in treating patients with at least moderate COPD. As the most recent of the five prior NMAs included data up to October 2020, we conducted a systematic literature search for new data on single-inhaler and multiple-inhaler triple therapy combinations published between January 2020 (to account for delays in indexing) and January 2025. We cross-referenced all trials included in the prior NMAs against our inclusion and exclusion criteria and examined whether there were notable differences in study design, PICOTS, and analytic methods as well as the quality of the studies.

While we initially aimed to conduct an NMA of all-cause mortality, this NMA was not feasible due to data limitations. The first issue was the presence of zero values in the data which the model was unable to handle properly, leading us to remove trials with zero values in all arms and use continuity correction in the remaining trials. Typically, a value of "0.5" is added as the continuity correction, but due to the inability of the model to use non-integer data, we resorted to adding "1.0". Even with these adjustments, some comparisons were associated with large credible intervals that were impossible to interpret and signaled uncertainty in the results due to limited evidence, as represented by a large right skew on the density plot for this outcome, variability in the number of deaths across the trials, and/or poor model convergence. Additional data on mortality is required to reliably conduct an NMA on this outcome.

NMA Methods

Trial Selection

We included blinded randomized controlled trials (RCTs) that ensured participants in all arms of the trial were prescribed the same number of inhalers with the same dosing schedule enrolling patients with at least moderate COPD treated with any triple therapy combination of ICS, LAMA, and LABA for 12 weeks or longer. Outcomes from trials with open-label arms are likely to be influenced by differences in adherence between once-daily inhalers and multiple inhalers taken more than once daily. We sought evidence on patient-important outcomes such as moderate to severe COPD exacerbation, SGRQ total scores, discontinuation rate due to adverse events, and mortality.

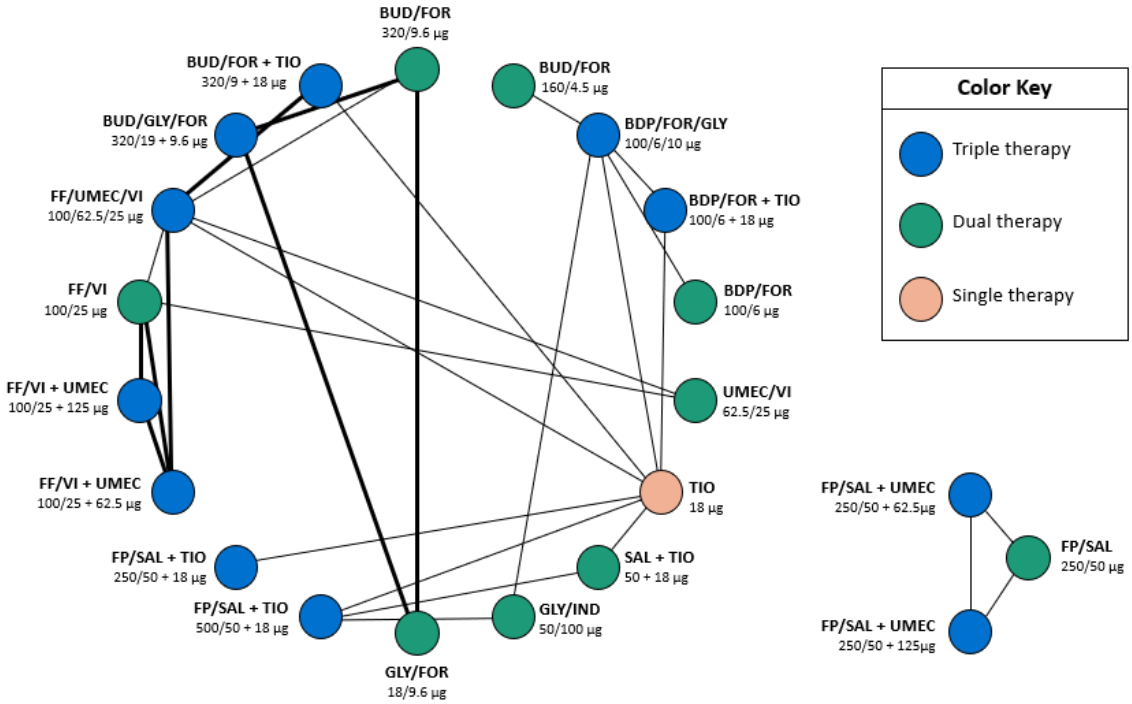
A total of 18 publications relating to 21 RCTs were included.[52,54,92-103,114-117] Of the 18 publications, 16 were identified from prior NMAs and two from the updated search. We examined and confirmed similarity across the trials in terms of population, design, intervention type, outcome definitions or measurements, and analytic methods. See Tables D1.2-D1.3 for the search strategies and Figure D1.1 for the PRISMA diagram.

Treatment Nodes and Networks

Within the 21 trials, we included triple therapy arms using Food and Drug Administration (FDA)/European Medicines Agency (EMA) approved doses or higher doses that were currently used in clinical practice but excluded doses lower than label recommendations (e.g., 160/4.8 mcg budesonide/formoterol twice daily). Trial arms administering the same triple therapy were grouped into a single node if their doses were considered equivalent (e.g. the "BDP/FOR/GLY 100/6/10 mcg" node included the following equivalent doses of beclomethasone dipropionate/formotorol fumerate dihydrate/glycopyrronium: a 100/6/10 mcg metered dose, a 100/6/12.5 mcg metered dose using glycopyrronium bromide, and an 87/9/5 mcg delivered dose). Distinct doses of the same therapy were maintained as separate nodes (e.g. BUD/GLY/FOR 320/18/9.6 mcg and BUD/GLY/FOR 160/18/9.6 mcg) as were open versus fixed-dose combinations of the same triple therapy components (e.g., FF/UMEC/VI and FF/VI + UMEC). Our approach identified 12 unique triple therapy nodes for the analysis.

The network for moderate to severe exacerbations included nine of 12 triple therapies. Two triple therapies could not be connected to any of the four networks (FP/SAL + UMEC 250/50 + 62.5 mcg and 250/50 + 125 mcg doses) and one triple therapy did not have data on exacerbations (FP/SAL + GLY 500/50 + 50 ug).[99,115] The network for SGRQ total score included nine of 12 triple therapies as one triple therapy (FP/SAL + TIO 250/50 + 50 ug) did not report data on this outcome.[103] The network for discontinuations due to adverse events included 10 of 12 triple therapies and all 21 trials reported data related to this outcome. See figures D1.4-D1.6 below.

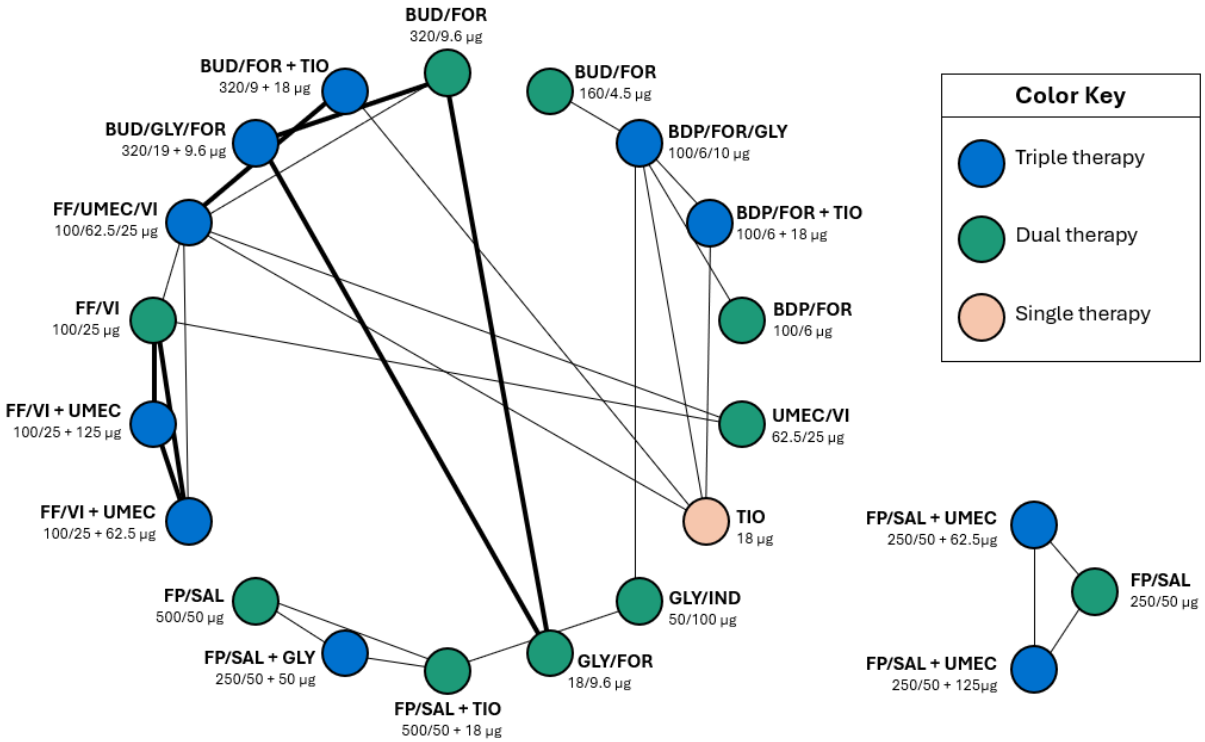
Figure D1.4 NMA Network Diagram: Rate of Moderate to Severe Exacerbations



Edge thickness corresponds with the number of trials for a given comparison

BDP: beclomethasone, BUD: budesonide, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, mcg: microgram, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

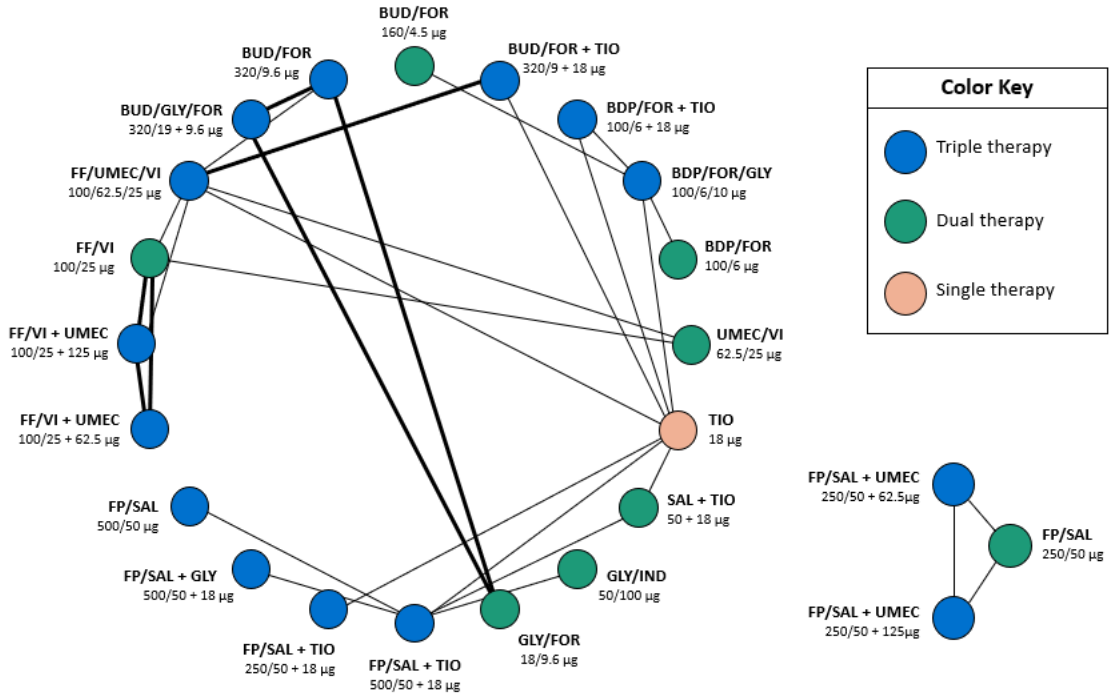
Figure D1.5 NMA Network Diagram: SGRQ Total Score



Edge thickness corresponds with the number of trials for a given comparison

BDP: beclomethasone, BUD: budesonide, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, mcg: microgram, SAL: salmeterol, SGRQ: St. George's Respiratory Questionnaire, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Figure D1.6 NMA Network Diagram: Rate of Discontinuation due to Adverse Events



Edge thickness corresponds with the number of trials for a given comparison
BDP: beclomethasone, BUD: budesonide, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, mcg: microgram, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Data Preparation

Moderate to Severe Exacerbations

We used the rate ratio with corresponding standard error (SE) from the included trials and then transformed them to the log scale as a primary input to the NMA. In total, 18 trials reported rates of moderate to severe exacerbations: ten reported adjusted rates from linear models adjusting for relevant covariates, five reported raw rates per patient-year, and three reported total number of exacerbations, sample size, and mean treatment exposure with which we could calculate raw rates of exacerbation and variance. We followed data preparation methods described in the supplemental section of Ismaila et al 2022.[22]

Data presented as adjusted rate ratios were directly available for ten out of 18 studies.[52,92,96,98,100-102,114,116,117] These studies presented 95% confidence intervals (CI) associated with study-level rate ratios. We converted the available 95% CI to SEs using equation 1.1 below:

$$SE(\ln(RR)) = \frac{\ln(\text{Upper}) - \ln(\text{Lower})}{3.92} \quad (Equation\ 1.1)$$

Five trials reported only treatment-specific moderate-to-severe exacerbation rates.[54,93-95] These rates were converted to rate ratios by using the ratio of the two corresponding rates. To obtain SEs associated with these calculated rate ratios, we abstracted the total number of exacerbations and person-years data for each treatment arm from either published studies or gray literature (i.e., clinicaltrials.gov, manufacturer documents) and ultimately converted them to study-level SEs using the equation 1.2 below.

$$SE(\ln(RR)) = \sqrt{\frac{1}{a} + \frac{1}{b}} \quad (Equation\ 1.2)$$

where a and b refer to the total number of exacerbations in intervention and control groups, respectively.

For the remaining three studies, we calculated treatment-specific rates (see equation 1.3) and study-level rate ratios using the total number of exacerbations and person-years data.[97,103] Additionally, we used the above equation 1.2 to calculate the SEs.

$$Rate = \frac{Total\ number\ of\ exacerbations}{Person - years} \quad (Equation\ 1.3)$$

In cases where the total number of exacerbations was not reported, we checked if the proportions of patients with 0, 1, or ≥2 exacerbations were reported. If person-year was not reported directly, we estimated it from sample size and mean treatment exposure days (see equation 1.4).

$$Person - years = \frac{Sample\ size \times Mean\ exposed\ days}{365} \quad (Equation\ 1.4)$$

St. George's Respiratory Questionnaire (SGRQ)

We used arm-level mean changes from baseline in SGRQ total scores for all trials except one trial that only reported a study-level mean difference.[101] 12 out of 18 trials reported standard errors directly and we calculated it for five trials using equation 1.5. For Aaron et al 2017, we assumed the value based upon the largest standard error value from the trials of the same type of therapy (e.g., triple, dual, single) as the most conservative estimate of standard error.

$$SE = \frac{Upper\ CI - Lower\ CI}{3.92} \quad (Equation\ 1.5)$$

Discontinuation Due to Adverse Events

Data for discontinuation due to adverse events were directly available from the trials.

NMA Models

We conducted Bayesian NMAs using random-effects models to estimate a treatment effect for our four outcomes. We performed both fixed- and random-effects models to confirm a priori assumption that random-effects would be more appropriate given the heterogeneity in study design, including different inclusion/exclusion criteria and differences in length of follow-up among the trials. Model fit in terms of the posterior distribution for the deviance (Dbar), the deviance information criterion (DIC), and heterogeneity (I^2) confirmed the use of the random-effects models. See Table D1.18 below.

Table D1.18. Model Fit Statistics for Random- versus Fixed-Effects Models

Outcome	Data Points	Random Effects Model			Fixed Effects Model		
		Dbar	DIC	I^2	Dbar	DIC	I^2
Moderate to Severe Exacerbations	25	29.03	51.50	17%	40.54	57.55	41%
Discontinuation due to AEs	46	48.22	89.59	7%	50.20	88.59	10%
SGRQ Score	43	41.80	79.29	0%	42.59	77.63	1%

AEs: adverse events, Dbar: posterior distribution for the deviance, DIC: deviance information criterion, I^2: heterogeneity statistics, SGRQ: St. George's Respiratory Questionnaire

The input for moderate to severe COPD exacerbations was log-transformed rate ratio and standard error, and the output was relative risk (RR) with 95% credible intervals generated using a normal likelihood with an identity link. The input for SGRQ was the change from baseline in mean total score and the output was the relative mean difference with 95% credible intervals using a normal likelihood and identity link. The inputs the binary outcome (i.e., discontinuation due to adverse events) was the number of patients with an event and the total number of patients. The output was the relative risk with 95% credible intervals generated with a binomial likelihood and a log link. Input data for each NMA are provided in Supplement Tables D3.17-19.

NMA Limitations

Our NMA has certain limitations. Firstly, our network consists mostly of comparisons from single trials; this may limit the robustness and precision of the results and meant that we were unable to conduct sensitivity analyses (e.g., comparing results when including or excluding high risk of bias studies, comparing results at different follow-up timepoints). The duration of follow-up ranged from 12 to 52 weeks for the included trials. Previous NMAs found no difference in the results for change from baseline in SGRQ total score reported 24 weeks and those reported 52 weeks.[20] To account for any differences based on follow-up timepoint, we used the annualized rate ratio as an input for moderate to severe exacerbations and relative risk as the outputs for moderate to severe exacerbations and discontinuation due to AEs which should correct the follow-up bias. Secondly, although trials were largely similar, some differences exist in terms of exacerbation history and

disease severity. Our random-effects models were able to account for much of the heterogeneity (ranging from 0-15% depending on the outcome assessed). Thirdly, there were instances of missing data. In the NMA of moderate to severe exacerbations, adjusted exacerbation rates were not available in six studies included. In this case, we used unadjusted rates with the assumption that randomization may have balanced the groups in terms of prognostic factors. In the NMA of change in SGRQ total score from baseline, standard error data was not available from one study (Aaron et al 2017). In this case and to take a conservative approach, we imputed the largest standard error reported from the dual therapies included in the same NMA.

D2. Additional Clinical Effectiveness Results

The main report includes primary sources of data and key evidence to inform our review of Trelegy Ellipta and Breo Ellipta for the treatment of patients with at least moderate COPD. In this supplement, we describe additional trial characteristics, baseline data, and relevant endpoints from the trials and observational studies that are not included in the main clinical section.

D2.1 Trelegy Ellipta

Additional Evidence Base

Clinical Trials

Phase III Trial (NCT02729051)

NCT02729051 was a Phase III, double-blind, non-inferiority trial in which patients were randomized to receive either once-daily Trelegy (FF/UMEC/VI 100/62.5/25 mcg) plus placebo or once-daily FF/VI 100/25 mcg plus UMEC 62.5 mcg.[52] The trial design included a two-week run-in period with existing COPD medications and a 24-week treatment period. The study enrolled participants aged 40 years and older who had a confirmed COPD diagnosis with a ≥10-pack-year smoking history and CAT score ≥10. Participants diagnosed with asthma were excluded from the trial. Additional inclusion and exclusion criteria are described in Supplement Table D3.1.

In total, 1,055 COPD patients (527 in the single ELLIPTA inhaler arm and 528 in the double ELLIPTA inhaler arm) who had at least one moderate to severe exacerbation in the past 12 months were randomized. At baseline, the mean age for participants was 66 years; 37% were using triple therapy combinations prior to the trial. More than half of the trial participants (56%) had experienced at least two moderate to severe exacerbations in the past 12 months and 18% had a history of pneumonia.[52] See additional baseline characteristics in Supplement Table D3.1.

Phase IV Trials (NCT03478683 and NCT03478696)

NCT03478683 and NCT03478696 were two identical Phase IV, double-blind, triple-dummy, non-inferiority trials in which patients were randomized to receive either once-daily Trelegy (FF/UMEC/VI 100/62.5/25 mcg) using a single ELLIPTA inhaler or BUD/FOR 200/6 mcg twice daily plus TIO 18 mcg once daily.[54] The trial design included a four-week run-in period with BUD/FOR 200/6 mcg twice daily plus TIO 18 mcg once daily and a 12-week treatment period followed by one week of additional safety follow-up. These studies enrolled participants aged 40 years old and above with COPD diagnosis who had been receiving daily COPD maintenance therapy for at least three months prior to screening. Participants were required to have a smoking history of ≥10-pack-years, a CAT score ≥10, and no current diagnosis of asthma. Additional inclusion and exclusion criteria are available in Table 3.1 and Supplement Table D3.1.

The investigators randomized a total of 1,460 patients 1:1 to receive single-inhaler FF/UMEC/VI or multi-inhaler BUD/FOR plus Tio in these two replicated trials. The mean age for all the trial participants was 65 years old, with around 30% having experience with triple therapy combinations.[54]

A key difference between the Phase III and Phase IV trials was the inclusion of participants with no moderate to severe exacerbation in the past 12 months. The Phase III trial excluded this patient group, whereas the two replicated trials had 46% participants with no moderate to severe exacerbation, with a substantial proportion of participants also experiencing ≥2 exacerbations in the last 12 months. See additional baseline characteristics in Supplement Tables D2.2 and D3.2.

Table. D2.1. Overview of Key Trelegy Ellipta Trials

Trial	Design and Treatments	N	Included Population	Primary Outcome
Bremner et al 2018[52] **NCT02729051**	Phase III, randomized, double-blind, non-inferiority FF/UMEC/VI vs FF/VI + UMEC	1,055	• Participants ≥40 years of age • COPD diagnosis with CAT score ≥10 • ≥10-pack-year smoking history • Post bronchodilator FEV1/FVC < 0.70 • Post bronchodilator FEV1 < 50% of predicted and ≥ 1 moderate/severe exacerbation in previous 12 months OR ≥ 50% to <80% of predicted and ≥2 moderate exacerbations or ≥1 severe exacerbations in the past 12 months	Change from baseline in trough FEV_1 at week 24
Ferguson et al 2020[54] **NCT03478683N CT03478696**	Phase IV, randomized, double-blind, non-inferiority FF/UMEC/VI vs BUD/FOR + TIO	1,460	• Participants ≥40 years of age • COPD diagnosis with CAT score ≥10 • ≥10-pack-year smoking history • Maintenance therapy for ≥3 months • Post bronchodilator FEV_1/FVC <0.70 • Post bronchodilator FEV_1 <50% of predicted and ≥1 moderate/severe exacerbation in previous 12 months OR ≥50% to <80% of predicted and ≥2 moderate exacerbations or ≥1 severe exacerbations in the past 12 months	Weighted mean change from baseline in 0-24 hour FEV_1 at week 12

BUD: budesonide, CAT: COPD Assessment Test, COPD: chronic obstructive pulmonary disease, FEV_1: forced expiratory volume in one second, FF: fluticasone furoate, FOR: formoterol fumarate, FVC: forced vital capacity, N: total number, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol, vs: versus

Table. D2.2. Key Baseline Characteristics of Trelegy Ellipta Trials

Trial		Bremner 2018[52]		Ferguson 2020[54] NCT03478683		Ferguson 2020[54] NCT03478696	
Treatment Arm		FF/UMEC/ VI	FF/VI + UMEC	FF/UMEC/ VI	BUD/FOR + TIO	FF/UMEC/ VI	BUD/FOR + TIO
N		527	528	363	365	366	366
Age	Mean (SD)	66.7 (8.5)	65.9 (8.8)	65.4 (7.9)	64.9 (8.1)	65.5 (8.2)	(65.1 (6.4)
	≥65 years	321 (60.9)	312 (59.2)	203 (55.9)	195 (53.4)	199 (54.4)	189 (51.6)
Sex, n (%)	Female	136 (26)	134 (25)	180 (50)	164 (45)	180 (49)	179 (49)
Race, n (%)	White	417 (79)	420 (80)	327 (90)	330 (90)	319 (87)	338 (92)
	Black	NR	NR	34 (9)	33 (9)	43 (12)	23 (6)
	Asian	72 (14)	68 (13)	1 (<1)	1 (<1)	3 (<1)	5 (1)
	Hispanic	71 (13)	77 (15)	39 (11)	46 (13)	50 (14)	58 (16)
Smoking Status, n (%)	Current	209 (40)	192 (36)	186 (51)	168 (46)	170 (46)	190 (52)
	Former	318 (60)	336 (64)	177 (49)	197 (54)	196 (54)	176 (48)
Moderate/ Severe Exacerbations in Prior Year	1, n (%)	236 (45)	227 (43)	60 (17)	69 (19)	69 (19)	75 (20)
	≥2, n (%)	291 (55)	301 (57)	130 (36)	128 (35)	131 (36)	123 (34)
GOLD stage	Moderate	174 (34)	189 (37)	76 (21)	82 (23)	71 (20)	84 (23)
	Severe	251 (49)	253 (49)	236 (65)	226 (62)	219 (60)	221 (60)
	Very severe	90 (17)	69 (13)	51 (14)	56 (15)	72 (20)	61 (17)
CAT Score, mean (SD)		19.6 (5.8)	20.1 (6.1)	21.6 (6.5)	22.0 (6.6)	22.2 (6.3)	22.3 (6.4)
Treatment History, ICS/LABA/LAMA, n (%)		198 (38)	193 (37)	113 (31)	96 (26)	118 (32)	116 (32)

BUD: budesonide, CAT: COPD Assessment Test, FF: fluticasone furoate, FOR: formoterol fumarate, FVC: forced vital capacity, GOLD: Global Initiative for Chronic Obstructive Lung Disease, ICS: inhaled corticosteroids, LABA: long-acting beta-agonist, LAMA: long-acting muscarinic antagonist, n: number, N: total number, SD: standard deviation, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Additional Clinical Trial Outside the Scope of This Review

Phase IV Trial (INTREPID)

One additional Phase IV, randomized, open-label, INTREPID trial comparing Trelegy Ellipta with MITTs was identified during the search but not described in the main clinical section or the supplemental tables as comparators included non-generic triple therapies.[118] This study was conducted in multiple centers outside the US and enrolled participants aged 40 years old or above with a physician-confirmed diagnosis of COPD who were on maintenance therapies for at least 16 weeks, had a CAT score of at least 10, and had a history of at least one COPD moderate to severe exacerbation. The primary endpoint was the proportion of responders based on the CAT score at week 24.

Observational Studies

As mentioned in our main report, we did not find any observational studies comparing Trelegy Ellipta with the generically available triple therapies listed in our PICOTS. Hence, a total of 11 observational studies comparing Trelegy Ellipta with any triple therapy combinations were included in our assessment of Trelegy Ellipta. Here, we provide brief descriptions of these eight studies.

Beeh et al. 2024 was a single-arm observational study conducted in Germany that included patients with COPD initiating FF/UMEC/VI.[57] Participants (N=927) were at least 18 years of age with moderate to severe COPD and at least one COPD exacerbation in the prior 12 months. Key outcomes included COPD Assessment Test (CAT) score, moderate and severe exacerbations, changes in FEV_1, treatment adherence as measured by the Test of Adherence to Inhalers (TAI) questionnaire, and safety compared between baseline and 12 months following initiation of FF/UMEC/VI.

Mannino et al. 2022 was a retrospective cohort study of patients with COPD initiating triple therapy of either FF/UMEC/VI (N=7282) or multiple inhaler triple therapy (MITT, N=7160) using the IQVIA PharMetrics Plus claims database.[49] Participants were 40 years of age or older with a diagnosis of COPD and at least 12 months of health insurance coverage prior to and six months following the index data, with no use of MITT at baseline. Adherence, as measured by the proportion of days covered (PDC), and persistence at six and 12 months were reported as key outcomes.

Bogart et al. 2024 was a retrospective cohort study of patients with COPD enrolled in Medicare Advantage program Part D or commercial enrollees who initiated either FF/UMEC/VI (N=4659) or MITT (N=9845).[60] Data came from the Optum Research Database. Participants were adults 40 years of age or older with a confirmed COPD diagnosis and no prior use of MITT at baseline. Key outcomes included COPD exacerbation rates, adherence as measured by proportion of days covered (PDC), and COPD-related HCRU reported up to 12 months of follow-up.

Hanania et al. 2023 study also used the Optum Research Database.[64] This retrospective, pre-post study compared patients 12 months pre and post initiation with FF/UMEC/VI. Participants (N=912) were adults 40 years of age or older with a confirmed COPD diagnosis, either Medicare Advantage with Part D or commercial enrollees, and at least 30 days of consecutive MITT during the 12 months prior to the index date. Patients with a diagnosis of asthma were excluded. A majority of participants were covered by Medicare (88%). Rates of COPD exacerbations and COPD-related healthcare resource utilizations were reported as key outcomes.

Rothnie et al. 2024 was a retrospective, pre-post study of participants with COPD initiating FF/UMEC/VI following MITT conducted in England. Data came from linked electronic health records and secondary administrative databases.[65] Participants were at least 35 years of age with a COPD diagnosis, receiving a prescription for MITT for 12 months prior to the index date, and had six months of follow-up after initiation of FF/UMEC/VI (N=2533). Rates of COPD exacerbations and COPD-related HCRU were compared 12 months before and 6 months after initiation with FF/UMEC/VI for those previously on MITT.

Halpin et al. 2022 was a retrospective cohort study of patients with COPD initiating either FF/UMEC/VI or MITT.[61] This new-user study used similar datasets as Rothnie et al 2024. Participants were at least 35 years of age with a COPD diagnosis, receiving a prescription of single inhaler triple therapy (SITT, either FF/UMEC/VI or BDP/FOR/GLY) or MITTs within the indexing period. Of relevance to this review, adherence as the proportion of days covered and persistence were compared between those initiating FF/UMEC/VI (N=1319) or MITT (N=4092) after six months.

Vogelmeier et al. 2024 was a retrospective cohort study that compared patients with COPD initiating triple therapy of SITT (FF/UMEC/VI or BDP/FOR/GLY) or MITTs.[62] This study used a claims database with longitudinal data from Germany. Participants were at least 35 years of age with a COPD diagnosis with a prescription of SITT or MITT within the indexing period. For those initiating FF/UMEC/VI (N=675), outcomes of adherence and persistence were compared to those initiating MITT (N=4079) were assessed.

Feldman et al. 2024 was a new-user, propensity score-matched, retrospective cohort study conducted using a US-based large claims database that includes both commercial and Medicare Advantage health plans.[24] All patients were ≥40 years old and had at least 365 days of continuous enrollment prior to cohort entry. A total of 20,388 matched pairs of COPD patients initiating either single-inhaler FF/UMEC/VI or single-inhaler BUD/FOR/GLY were identified. The median follow-up period was higher in the FF/UME/VI arm (135 days) than in the BUD/FOR/GLY arm (105 days). Key outcomes were the first moderate to severe COPD exacerbation and first pneumonia hospitalization.

Mannino et al. 2024 was a retrospective weighted cohort study comparing efficacy of FF/UMEC/VI or BUD/GLY/FOR in Medicare Fee-for-Service patients with COPD 12-months after initiation.[58] Data come from the Komodo Research Data (KRD) claims database. A total of 32,312 adults who switched from single inhaler triple therapy to FF/UMEC/VI and 12,230 who switched to BUD/GLY/FOR were included in the study. Key outcomes of interest were the rate of COPD exacerbations and all-cause mortality over a 12-month period.

Young et al. 2024 was a retrospective weighted cohort study comparing efficacy of FF/UMEC/VI or BUD/GLY/FOR in patients with COPD 12-months after initiation.[59] Claims data come from the IQVIA PharMetrics Plus Database. Adults ages 40 years or above with COPD who initiated FF/UMEC/VI (N=8912) or BUD/GLY/FOR (N=2685) were included in the study. Key outcomes were adherence to the triple therapies and median duration of persistence to treatment over 12 months.

Jokšaitė et al. 2024 was a retrospective weighted cohort study assess the efficacy of Overall SITT, FF/UMEC/VI, BUD/GLY/FOR or MITT in patients with COPD up to 18 months post-initiation.[63] Data come from the Medical Data Vison Co., Ltd hospital claims database. For the comparison of interest (FF/UMEC/VI vs. MITT) data from 1401 patients initiating FF/UMEC/VI and 1909 patients initiating MITT were used to compare adherence and persistence to the respective triple therapy treatments after 12 and 18 months.

Baseline characteristics are reported in Supplement Table D3.3-D3.5 for all observational studies.

Additional Clinical Benefit

NMA Results

Moderate to Severe COPD Exacerbation

We described in the main report that there were no statistically significant differences between single-inhaler FF/UMEC/VI and any of the included triple therapy combinations in patients with at least moderate COPD. Literature suggests no intraclass differences between ICS/LABA therapies.[4] As such, we indirectly compared combined triple therapies and combined ICS/LABAs to a single therapy (tiotropium) to be used as an input for cost-effectiveness model. Of note, tiotropium was used as the single therapy as it was the only single therapy available in the included studies. We included three additional clinical trials from a previous systematic review that compared only ICS/LABA with tiotropium.[4,119-121] There was no other RCT comparing ICS/LABA with Tiotropium after the publication of this systematic review. Hence, our analysis included a total of 24 RCTs, including 21 previously mentioned trials and three new ICS/LABA RCTs. Frith et al 2015 was excluded for not reporting moderate to severe exacerbations data and three additional trials were excluded due to their focus on comparisons of the triple versus triple therapies.[52,54,115]

Results of the NMA showed a statistically significant lower rate of moderate to severe COPD exacerbations with triple therapy compared to ICS/LABAs or tiotropium. There was no statistically significant difference between ICS/LABA and tiotropium in the rate of moderate to severe COPD exacerbations. See Table D2.3.

Table D2.3. NMA Results: Combined Triple Therapy and Combined ICS/LABAs Versus Tiotropium

Triple Therapy		
0.74 (0.62, 0.85)	ICS/LABA	
0.70 (0.56, 0.85)	0.95 (0.75, 1.18)	Tiotropium

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1.0.

SGRQ Total Score

Indirect comparison suggests that there were no statistically significant differences in changes from baseline SGRQ total score across all available triple therapy combinations. See Table D2.4.

Table D2.4. NMA Results: SGRQ for Triple Therapy for COPD

FF/UMEC/VI								
-0.43 (-2.54, 1.62)	BDP/FOR/ GLY							
-1.18 (-3.31, 0.82)	-0.75 (-3.71, 2.15)	BUD/FOR/ GLY						
-0.17 (-1.93, 1.61)	0.27 (-2.44, 3.04)	1.01 (-1.65, 3.79)	FF/VI + UMEC HD					
-0.99 (-2.41, 0.41)	-0.56 (-3.06, 1.97)	0.19 (-2.27, 2.74)	-0.83 (-2.41, 0.74)	FF/VI + UMEC LD				
0.76 (-1.52, 3.01)	1.2 (-0.72, 3.13)	1.95 (-1.09, 5.05)	0.94 (-1.97, 3.79)	1.76 (-0.92, 4.42)	BDP/FOR + TIO			
-0.26 (-1.39, 0.91)	0.16 (-1.68, 2.12)	0.92 (-1.39, 3.36)	-0.1 (-2.2, 2.04)	0.72 (-1.06, 2.58)	-1.03 (-3.08, 1.09)	BUD/FOR + TIO		
0.55 (-1.63, 2.75)	0.98 (-0.87, 2.88)	1.74 (-1.23, 4.81)	0.71 (-2.09, 3.52)	1.54 (-1.05, 4.18)	-0.22 (-2.54, 2.15)	0.81 (-1.22, 2.83)	FP/SAL HD + TIO*	
-0.55 (-3.63, 2.57)	-0.11 (-2.97, 2.79)	0.63 (-3.02, 4.42)	-0.38 (-3.98, 3.19)	0.46 (-2.94, 3.86)	-1.31 (-4.51, 1.95)	-0.28 (-3.26, 2.7)	-1.1 (-3.29, 1.1)	FP/SAL + GLY

Each box represents the estimated relative mean difference and 95% credible interval. The shaded column represents the comparisons for Trelegy Ellipta versus other triple therapies: all credible intervals include 1.0 indicating no statistically significant differences. Individual trial data can be found in Supplement Table D3.19.

BDP: beclomethasone dipropionate, BUD: budesonide, FF: fluticasone furoate, FOR: formoterol fumarate, FP: fluticasone propionate, GLY: glycopyrronium, HD: high dose, LD: low dose, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Clinical Benefits from Trials

COPD Exacerbations

In the Phase III study, both single-inhaler FF/UMEC/VI and multi-inhaler FF/VI plus UMEC had similar time to first on-treatment moderate to severe COPD exacerbation (adjusted HR 0.87; 95% CI 0.68, 1,12).[52]

Data from the INTREPID trial on moderate to severe COPD exacerbations were comparable to the results described in the main section. The annualized moderate to severe rates were similar for both single-inhaler FF/UMEC/VI and MITTs (1.2 vs 1.1) in the INTREPID trial. Around 28% of trial participants in the single-inhaler FF/UMEC/VI experienced at least one moderate to severe exacerbation during the 24-week treatment period compared to 30% in the MITT arm.[118]

Lung Function Outcomes

Lung function (i.e., percentage predicted FEV_1) was the key primary endpoint in all three trials described in the main clinical section. Higher values of FEV_1 indicate better lung capacity and airflow. The Phase III trial comparing single-inhaler FF/UMEC/VI and multi-inhaler FF/VI plus UMEC reported a treatment difference of 26 mL (95% CI -2 to 53 mL) in the mean change from baseline in trough FEV_1 at week 24. The trial met non-inferiority status as the lower bound of 95% CI was above the prespecified -50 mL margin for the primary endpoints.[52] The two replicated Phase IV trials compared single-inhaler FF/UMEC/VI and multi-inhaler BUD/FOR plus TIO. Both trials demonstrated non-inferiority with a similar prespecified margin where the treatment difference in the mean change from baseline in FEV_1 was 14 mL (95% CI -5 to 34 mL) in the pooled analysis.[54] However, the INTREPID trial showed a statistically significant treatment difference of 50 mL (95% CI 26 to 73 mL) in mean change from baseline in FEV_1, favoring single-inhaler FF/UMEC/VI over MITTs.[118] See Supplement Table D3.6.

Health-Related Quality of Life (HRQoL) Measure: COPD Assessment Test (CAT)

After 24 weeks of randomized treatment period, patients receiving single-inhaler FF/UMEC/VI had greater reductions in the mean change from baseline in CAT score compared to those with MITTs (treatment difference -1.5) in the INTREPID trial; however, the estimated MCID is two points for CAT scores.[118]

Rescue Medication and On-treatment Oxygen

In the Phase III trial, similar proportions of participants using single-inhaler FF/UMEC/VI used short-acting beta-agonists (SABA) for exacerbations during the treatment period compared to those using multi-inhaler FF/VI plus UMEC (5% vs 4%). More than double the patients in the single-inhaler FF/UMEC/VI group used oxygen for an exacerbation compared to the multi-inhaler FF/VI plus UMEC group (1.9% vs 0.7%).[52] The Phase IV trials reported that around 3% of single-inhaler FF/UMEC/VI group participants used SABA for exacerbation, compared to 1% of multi-inhaler BUD/FOR plus TIO participants. Four patients (<1%) receiving single-inhaler FF/UMEC/VI used oxygen compared to none in those with multi-inhaler BUD/FOR plus TIO in these trials.[54] See Supplement Table D3.6.

Clinical Benefits from Observational Studies

Adherence

Beeh et al. 2024 measured adherence using the test of adherence to inhalers (TAI) questionnaire (score 10 to 50, higher reflecting better adherence) in patients initiating therapy with single-inhaler FF/UMEC/VI.[57] There were statistically significant improvements in mean TAI scores of about 2 points among participants starting (i.e., escalating or switching to) single-inhaler FF/UMEC/VI triple therapy from prior dual therapies or multiple-inhaler triple therapies. See Supplement Table D3.9.

Persistence

In the Japanese observational study, persistence was primarily measured as the time between treatment initiation and discontinuation (i.e., a gap of ≥14 days).[63] The median time on treatment was statistically significantly higher in the single-inhaler FF/UMEC/VI group compared to the MITTs (2 vs. 1 month; HR 0.62; 95% CI 0.58, 0.66, p<0.001). Single-inhaler FF/UMEC/VI demonstrated a consistent advantage over both MITTs and single-inhaler BUD/FOR/GLY in additional sensitivity analyses using gaps of ≥30, ≥45, and ≥60 days for treatment non-persistence. A recent claims-based study conducted in the US also found that patients receiving single-inhaler FF/UMEC/VI had a longer median persistence duration than those in the single-inhaler BUD/FOR/GLY group (4 vs. 3 months).[59] See Supplement Tables D3.9-D3.10.

Moderate to Severe Exacerbation

Feldman et al. 2024 compared two single inhalers (once-daily FF/UMEC/VI vs. twice-daily BUD/FOR/GLY) in a parallel-group, new-user, propensity score-matched, cohort study design using a large, US-based claims database.[24] The incidence rate ratio for moderate to severe COPD exacerbations was 8% (RR 0.92, 95% CI 0.88, 0.96) lower among participants initiating FF/UMEC/VI compared to those initiating BUD/FOR/GLY. When stratified by severity of exacerbations, the rate ratio was only 7% (incident RR 0.93; 95% CI 0.89, 0.98) lower for moderate COPD exacerbations but 21% (incident RR 0.79; 95% CI 0.69, 0.92) lower for severe COPD exacerbations. Another claims-

based US study focusing on these two SITTs across different healthcare payer populations with COPD (i.e., Medicare fee-for-service (FFS), Medicare Advantage, Medicaid, and commercial insurance) reported similar results for moderate to severe exacerbations.[58] The rate ratio for moderate to severe COPD exacerbations was 12% (RR 0.88, 95% CI 0.85, 0.92) lower among Medicare FFS participants receiving FF/UMEC/VI compared to those in the BUD/FOR/GLY group. However, in the stratified analyses, the rate ratio remained statistically significant for moderate exacerbations (RR 0.86, 95% CI 0.83, 0.90) but not for severe exacerbations. Mannino et al 2024 also found similar results for moderate to severe exacerbations among COPD patients with Medicare Advantage, Medicaid, and commercial insurance.[58] See Supplement Table D3.7.

Hanania et al 2023 compared exacerbations between 12-month pre-index and 12-month post-index periods, with an index being the date when single-inhaler FF/UMEC/VI was initiated following MITT.[64] The proportion of patients with ≥1 moderate exacerbation dropped significantly from 54% to 48% (p <0.001), but not the proportion of patients with ≥1 severe exacerbation (23% vs 22%; p=0.33). Similar results were observed in a pre-post, observational study conducted in England.[65] Patients with COPD were switched to FF/UMEC/VI following MITT (N=2,533) and a statistically significantly smaller proportion of patients experienced ≥1 moderate to severe exacerbations compared to baseline (i.e., defined as 12 months prior to index) at both six and 12-month post-switch follow-up (29% vs 36%; p <0.0001 and 45% vs. 51%; p <0.001, respectively). However, when stratified, the proportions of patients with ≥1 severe exacerbation were no longer different between pre- and post-switch (21% vs 21%; p=0.96) at the 12-month follow-up.[65] See Supplement Table D3.6-D3.7.

COPD-Related Healthcare Resource Utilization (HCRU)

Only two out of seven observational studies reported COPD-related HCRU outcomes including hospital stays, emergency room visits, outpatient visits, office visits, ambulatory visits, and pharmacy use. Hanania et al 2023 compared MITT with subsequent initiation of single-inhaler FF/UMEC/VI at 12 months and found no statistically significant differences in the mean number of emergency room visits (0.4 vs 0.3) and inpatient hospital stays (2.6 vs 3 days).[64] While Bogart et al 2024 suggested similar findings for emergency room visits, the study reported statistically significantly longer inpatient days for patients receiving MITTs compared to those with single-inhaler FF/UMEC/VI (20 vs 17 days; p=0.02).[60] Rothnie et al 2024 presented variable results related to inpatient stays as rates were reduced at 6 months after switching to single-inhaler FF/UMEC/VI (RR 0.80; 95% CI 0.71, 0.90) but increased 12 months post-switch (RR 1.14; 95% CI 1.01, 1.27).[65] See Supplement Table D3.8.

Additional Harms

NMA Results

Here, we present our NMA findings related to discontinuations due to adverse events. Results suggest no statistically significant differences in discontinuations due to adverse events between single-inhaler FF/UMEC/VI and any of the included triple therapy combinations in patients with at least moderate COPD. See Supplement Table D2.5 below.

Table D2.5. NMA Results: Discontinuations Due to Adverse Events for Triple Therapy for COPD

FF/UMEC/VI									
1.96 (0.53, 7.49)	**BDP/FOR/ GLY**								
1.16 (0.34, 3.39)	0.59 (0.09, 3.16)	**BUD/FOR/ GLY**							
1.65 (0.57, 5.44)	0.85 (0.15, 5.05)	1.43 (0.32, 8.23)	**FF/VI + UMEC HD**						
1.52 (0.69, 3.5)	0.78 (0.17, 3.7)	1.32 (0.35, 5.92)	0.92 (0.31, 2.55)	**FF/VI + UMEC LD**					
2.29 (0.57, 9.85)	1.17 (0.46, 3.16)	2 (0.35, 13.56)	1.4 (0.22, 8.37)	1.51 (0.3, 7.81)	**BDP/FOR + TIO**				
0.92 (0.37, 2.19)	0.47 (0.13, 1.62)	0.8 (0.2, 3.49)	0.56 (0.12, 2.19)	0.61 (0.18, 1.93)	0.4 (0.09, 1.5)	**BUD/FOR + TIO**			
1.36 (0.32, 5.81)	0.7 (0.25, 1.9)	1.18 (0.2, 7.98)	0.82 (0.13, 5)	0.89 (0.17, 4.66)	0.59 (0.16, 2.02)	1.47 (0.37, 6.12)	**FP/SAL HD + TIO***		
0.96 (0.2, 4.68)	0.49 (0.12, 1.99)	0.84 (0.13, 6.32)	0.58 (0.08, 3.94)	0.63 (0.11, 3.7)	0.42 (0.1, 1.82)	1.04 (0.24, 4.97)	0.7 (0.16, 3.28)	**FP/SAL LD +TIO**	
1.65 (0.28, 9.81)	0.85 (0.19, 3.6)	1.43 (0.18, 12.59)	1 (0.12, 8.06)	1.09 (0.15, 7.52)	0.72 (0.14, 3.6)	1.79 (0.32, 10.4)	1.21 (0.43, 3.48)	1.72 (0.27, 10.3)	**FP/SAL + GLY**

Each box represents the estimated relative risk and 95% credible interval. The shaded column represents the comparisons for Trelegy Ellipta versus other triple therapies: all credible intervals include 1.0 indicating no statistically significant differences. Individual trial data can be found in Supplement Table D3.18.
BDP: beclomethasone dipropionate, BUD: budesonide, FF: fluticasone furoate, FOR: formoterol fumarate, FP: fluticasone propionate, GLY: glycopyrronium, HD: high dose, LD: low dose, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Harms from Trials

Frequent Adverse Events

The most frequent adverse events for patients receiving triple therapies were infections, cardiovascular events, and headaches. The incidence of these adverse events was similar across all triple therapy combinations.[52,54]

Mortality

Four deaths were reported during the treatment period in each arm for the Phase III trial, but none were determined to be related to the study treatment.[52] Only one death, also unrelated to study treatment, was reported in the two Phase IV trials and the patient was receiving multi-inhaler BUD/FOR plus TIO.[54]

Cardiovascular Outcomes & Urinary Tract Infections

The proportions of patients with COPD experiencing cardiovascular events were largely similar between single inhalers and multi-inhalers in Phase III and two replicated Phase IV trials of Trelegy Ellipta. Less than one percent of the patients with COPD experienced urinary tract infections during the treatment period in all arms and trials.[52,54] See Supplement Table D3.11.

Harms from Observational Studies

Additional observational data on long-term harms came from the single-arm study.[57] Around 5% of the study participants experienced a serious adverse event during the 12-month follow-up period after initiation of single-inhaler FF/UMEC/VI. Six patients died in this study and all of them were due to an adverse event. After initiating single-inhaler FF/UMEC/VI, only five patients (0.6%) had pneumonia. Of note, more than half of the study participants discontinued the treatment due to an adverse event. Bogart et al 2024 only reported data on discontinuations due to adverse events with 12 months of follow-up and it was higher in the MITTs compared to single-inhaler FF/UMEC/VI (82% vs 66%).[60] See Supplement Table D3.12.

D2.2 Breo Ellipta

Additional Evidence Base

Clinical Trials

In the main section, we described the inclusion criteria for the three Phase III trials comparing FF/VI with FP/SAL. Key exclusion criteria were a current diagnosis of asthma or experiencing a COPD exacerbation during the run-in period. The primary endpoint was change from baseline trough in 0-24 hour weighted mean FEV_1. COPD exacerbations were recorded as part of the safety assessments.[68]

A total of 1,858 patients were randomized to FF/VI (N=931) or FP/SAL (N=927) across three Phase III trials and had a mean treatment compliance of over 97% in all treatment arms. In the pooled data, the mean age was 61 years old, with a mean post-bronchodilator FEV_1 of 48%, and more than half of the included patients were current smokers.[68]

The trial comparing FF/VI 100/25 mcg with FP/SAL 500/50 mcg had similar inclusion and exclusion criteria.[72] An additional criterion was that participants had to be hospitalized or treated with corticosteroids or antibiotics for a COPD exacerbation in the last three years. The mean age of 528 participants was 63 years old, with a mean post-bronchodilator FEV_1 of 43%. The enrolled participants were mostly males (80%), Whites (79%), and current smokers (42%).[72] Additional details about design and baseline characteristics are available in Tables D2.6-D2.7 and Supplement Tables D3.13-D3.14.

Table. D2.6. Overview of Key Studies

Trial	Design and Treatments	N	Included Population	Key Outcomes and Timepoint
Clinical Trials				
Dransfield et al 2014[68] **NCT01323621** **NCT01323634** **NCT01706328**	Phase III, randomized, double-blind trial FF/VI 100/25 mcg vs FP/SAL 250/50 mcg	1,858	• ≥40 years of age and diagnosed with COPD • ≥ 10-pack-year smoking history • Post bronchodilator FEV_1/FVC ≤ 0.70 • No asthma diagnosis • No COPD exacerbation or UTI during run-in period	Change from baseline in trough FEV_1 at week 12
Agustí et al 2014[72] **NCT01342913**	Phase III, randomized, double-blind trial FF/VI 100/25 mcg vs FP/SAL 550/50 mcg	528	• ≥40 years of age and diagnosed with COPD • ≥ 10-pack-year smoking history • Post bronchodilator FEV_1/FVC ≤ 0.70 • Hospitalized or treated with corticosteroids or antibiotics for a COPD exacerbation in the last three years • No asthma diagnosis • No COPD exacerbation or UTI during run-in period	Change from baseline in trough FEV_1 at week 12
Observational Study				
Stanford et al 2019[74]	Retrospective cohort study FF/VI 100/25 mcg vs BUD/FOR 160/4.5 mcg	9,026	• ≥40 years of age with ≥1 COPD diagnosis code • Pharmacy claim for FF/VI or BUD/F • 12 months of continuous enrollment prior to index date, and 3 to 12 months of continuous enrollment following index date • No use of ICS/LABA during baseline	COPD-related health costs, adherence, and exacerbations

BUD: budesonide, COPD: chronic obstructive pulmonary disease, FEV_1: forced expiratory volume in one second, FF: fluticasone furoate, FOR: formoterol fumarate, FP: fluticasone propionate, FVC: forced vital capacity, ICS: inhaled corticosteroids, LABA: long-acting beta-agonist, mcg: microgram, N: total number, SAL: salmeterol, SD: standard deviation, UMEC: umeclidinium, UTI: urinary tract infection, VI: vilanterol, vs: versus

Table. D2.7. Key Baseline Characteristics of Breo Ellipta Studies

		Clinical Trials				Observational Study	
		Dransfield et al 2014*[68]		Agustí et al 2014[72]		Stanford et al 2019[74]	
Treatment Arm		FF/VI 100/25	FP/SAL 250/50	FF/VI 100/25	FP/SAL 500/50	FF/VI 100/25	BUD/FOR 160/4.5
N		931	927	266	262	4513	4513
Age	Mean (SD)	61 (9)	61 (9)	63 (8)	63 (9)	69	69
Sex, n (%)	Female	285 (31)	297 (32)	54 (20)	41 (16)	2413 (53)	2415 (54)
Race, n (%)	White	899 (97)	898 (97)	218 (82)	208 (79)	NR	
	Black	31 (3)	27 (3)	0	1 (<1)		
	Hispanic	9 (1)	5 (<1)	0	2 (<1)		
Smoking Status, n (%)	Current	496 (53)	522 (56)	97 (37)	125 (47)	NR	
Mean Post-Bronchodilator FEV_1, %		48 (12)	48 (12)	43 (12)	43 (12)	NR	
Current Asthma		0	0	NR	NR	1297 (29)	1298 (29)
Treatment History, n (%)	ICS	3 (<1)	2 (<1)	1 (<1)	1 (<1)	456 (10)	452 (10)
	LAMA	0	0	0	0	1367 (30)	1374 (30)
	LABA	2 (<1)	3 (<1)	1 (<1)	0	156 (3)	150 (3)
	LAMA/LABA	0	0	0	0	70 (2)	66 (1)

*Manuscript published by Dransfield et al. 2014 reported on three clinical trials (NCT01323621, NCT01323634, and NCT01342913) with the same trial design and thus reported pooled baseline characteristics.

BUD: budesonide, FEV_1: forced expiratory volume in one second, FF: fluticasone furoate, FOR: formoterol fumarate, FP: fluticasone propionate, ICS: inhaled corticosteroids, LABA: long-acting beta-agonist, LAMA: long-acting muscarinic antagonist, n: number, N: total number, NR: not reported, SAL: salmeterol, SD: standard deviation, UMEC: umeclidinium, VI: vilanterol

Additional Clinical Benefits

Clinical Benefits from Trials

Lung Function Outcomes

Lung function (i.e., 24-hour FEV_1 assessment) was the key primary endpoint in all four clinical trials of Breo Ellipta. Dransfield et al 2014 reported pooled analysis data from three replicated trials and showed a statistically significant improvement from baseline in 0-24 hour weighted mean FEV1 in the FF/VI 100/25 mcg group compared to FP/SAL 250/50 mcg group (treatment difference of 41 mL; 95% CI 17, 65; p <0.001) after 12 weeks of follow-up.[68] However, results were not statistically significant in two out of three trials, as such the pooled improvement was determined not to be clinically relevant. Agusti et al 2014 also found no statistically significant difference between FF/VI 100/25 mcg group and FP/SAL 500/50 mcg group in this primary endpoint.[72] See Supplement Table D3.15.

Rescue Medication and Oxygen Use

In the three trials that measured the use of rescue medications per 24 hours (NCT01323634, NCT01323621, and NCT01342913) there were no statistically significant differences between FF/VI and FP/SAL groups.[68,72] Pooled data from Dransfield et al. showed a similar proportion of FF/VI and FP/SAL group participants used oxygen during treatment (2.4% vs 1.4%).[68] See Supplement Table D3.15.

Clinical Benefits from Observational Study

Adherence

Stanford et al. 2019 reported a statistically significantly higher proportion of FF/VI participants achieved PDC ≥0.5 compared to the BUD/FOR group (43% vs 34%, p<0.001).[74] See Supplement Table D3.16.

Summary

Table 2.8. Evidence Ratings for Trelegy Ellipta and Breo Ellipta compared with Generic Alternatives

Treatment	Comparator	Evidence Rating
Patients with COPD requiring Triple Therapy		
Trelegy Ellipta	Budesonide/Formoterol Fumarate with Tiotropium	C+
Trelegy Ellipta	Fluticasone Propionate/Salmeterol Xinafoate with Tiotropium	C+
Trelegy Ellipta	Fluticasone Furoate/Vilanterol Trifenatate with Tiotropium	C+
Patients with COPD requiring Dual Therapy		
Breo Ellipta	Budesonide/Formoterol Fumarate	C+
Breo Ellipta	Fluticasone Propionate/Salmeterol	C+

D3. Evidence Tables

Table D3.1. Study Design – Trelegy Ellipta

Trial (Author, Year)	Study Design & Interventions	Included Population	Key Outcomes
Randomized Controlled Trials			
Bremner et al. 2018[52] **NCT02729051**	Study Design: Phase III, double-blind, parallel group, multicenter, non-inferiority, randomized 24-week trial Location: International Interventions: 1) FF/UMEC/VI (QD) 2) FF/VI + UMEC (QD)	Inclusions: - ≥40 years of age - COPD diagnosis - Current/former smokers with a ≥ 10-pack-year smoking history - COPD Assessment Test (CAT) score ≥ 10 - Post-albuterol/salbutamol FEV_1/FVC ratio < 0.70 - Post-bronchodilator FEV_1 < 50% of predicted and ≥1 moderate/ severe exacerbation in the previous 12 months, OR post-bronchodilator FEV_1 ≥ 50% to < 80% of predicted and ≥2 moderate exacerbations or ≥1 severe exacerbation requiring hospitalization in the previous 12 months Exclusions: - Current diagnosis of asthma - Other clinically significant respiratory disorders - Patients with a high risk for pneumonia included at the discretion of the investigator	- Change from baseline in trough FEV_1 - Change from baseline in SGRQ score - SGRQ responders - Change from baseline in TDI focal score - TDI responders - Time to first moderate/ severe exacerbations Timepoint: 24 weeks
Ferguson et al. 2020[54] **NCT03478683& NCT03478696**	Study Design: 2 Phase IV, 12-week, randomized, double-blind, triple-dummy, parallel-group, multicenter, non-inferiority replicate trials Location: United States, Europe Interventions: 1) FF/UMEC/VI (QD) 2) BUD/FOR (BD) + TIO (QD)	Inclusions: - ≥40 years of age - An established clinical history of COPD (defined by the American Thoracic Society/European Respiratory Society) - Current or former smokers with a history of ≥ 10 pack-years - Receiving daily maintenance therapy for ≥ 3 months - COPD Assessment Test (CAT) score ≥ 10. - Postbronchodilator FEV_1 of < 50% predicted (or < 80% predicted and ≥2 moderate exacerbations or 1 severe exacerbation in the prior 12 months) - Post-bronchodilator FEV_1/FVC ratio < 0.70 Exclusions: - Current diagnosis of asthma - Other clinically significant respiratory disorders - Pneumonia and/or a moderate to severe COPD exacerbation that had not resolved ≥14 days prior to screening and ≥ 30 days following the last dose of	- Change from baseline in FEV_1 - Change from baseline in SGRQ scores - SGRQ responders - Change from baseline in CAT scores - CAT responders Timepoint: 12 weeks

Trial (Author, Year)	Study Design & Interventions	Included Population	Key Outcomes
		oral/systemic corticosteroid (if applicable) - Respiratory tract infection that had not resolved ≥ 7 days prior to screening	
Observational Studies			
Young et al. 2024	Study Design: Retrospective weighted cohort study using IQVIA PharMetrics Plus Database Location: United States Interventions: 1) FF/UMEC/VI 2) BUD/GLY/FOR	Inclusions: - ≥40 years of age at index - ≥1 pharmacy claim for FF/UMEC/VI or BUD/GLY/FOR on or after October 1, 2020 (the first claim defined the index date and the study cohort [FF/UMEC/VI cohort versus BUD/GLY/FOR cohort]) - ≥12 months of continuous enrollment pre-index (baseline period) - ≥6 months of continuous enrollment post-index (follow-up period) - ≥2 medical claims with a diagnosis code of COPD Exclusions: - Patients were excluded if they had ≥ 1 pharmacy claim for FF/UMEC/VI or BUD/GLY/FOR during the baseline period or ≥ 1 medical claim with a diagnosis code of asthma during the baseline period or on the index date - ≥1 medical claim with a diagnosis code of cystic fibrosis, lung cancer, interstitial lung disease, or alpha-1 antitrypsin deficiency during baseline or on the index date	- Treatment adherence (proportion of days covered) - PDC ≥0.8 - PDC ≥0.5 - Persistence (time to discontinuation of therapy) - Median time to triple therapy discontinuation
Mannino et al. 2024	Study Design: Retrospective weighted cohort study using Komodo Research Data of Medicare FFS patients Location: United States Interventions: 1) FF/UMEC/VI 2) BUD/GLY/FOR	Inclusions: - Age 40 or older - ≥12 months of continuous Medicare FFS clinical activity pre-index (baseline) - ≥2 medical claims on separate dates with a diagnosis of COPD in any position during baseline or on the index date - Continuous clinical activity, defined as consecutive quarters with ≥ 1 medical and pharmacy Medicare FFS claims, used as a proxy for continuous insurance coverage since the latter is not available for Medicare FFS patients in KRD open-sourced data Exclusions: - ≥1 pharmacy claim for a SITT any time before the index date - ≥1 diagnosis of asthma, cystic fibrosis, lung cancer, interstitial lung disease, or alpha-1 antitrypsin in any position during the baseline period	- Annualized rate of moderate to severe exacerbations (12 months) - Risk of exacerbations (12 months) - Risk of all-cause mortality (12 months)
Feldman et al. 2024[24]	Study Design: New user cohort study using administrative health claims data from	Inclusions: - ≥40 years of age - Diagnosis of COPD: 3 outpatient claims or 1 in patient claim in prior 3 years of active COPD	- First moderate or severe COPD exacerbations

Trial (Author, Year)	Study Design & Interventions	Included Population	Key Outcomes
	Optum's Clinformatics Data Mart Location: United States Interventions: 1) FF/UMEC/VI 2) BUD/GLY/FOR	- ≥365 days of continuous enrollment in the dataset before cohort entry - Patients with COPD who also had prior asthma diagnoses were included Exclusions: - Received either BUD/GLY/FOR, FF/UMEC/VI, or an ICS/LAMA/LABA combination via separate inhalers during the 365 days before cohort entry. - Patients receiving both BUD/GLY/FOR, FF/UMEC/VI, or triple therapy plus another maintenance inhaler on the cohort entry date.	- First admission to hospital with pneumonia Timepoint: 12 months
Mannino et al. 2022[49]	Study Design: Retrospective weighted cohort study using IQVIA PharMetrics Plus claims database Location: United States Interventions: 1) FF/UMEC/VI 2) MITT	Inclusions: - ≥40 years of age - ≥12 months of continuous health insurance coverage prior to the index date and at least 6 months of coverage following the index date - ≥2 diagnoses of COPD in an outpatient setting, or ≥1 diagnosis of COPD in a hospitalization or emergency department (ED) setting - ≥1 dispensing of single-inhaler FF/UMEC/VI (100/62.5/25 mcg) or, if none, ≥1 overlapping day of supply with all three components of triple therapy Exclusions: - Patients were excluded if they used MITT during the baseline period	- Adherence (proportion of days covered) - Persistence (non-persistence identified as >30-day gap between fills) Timepoint: 12 months
Hanania et al. 2023[64]	Study Design: Retrospective database analysis using the Optum Research Database (ORD) Location: United States Interventions: 1) FF/UMEC/VI following MITT - 12 months pre-index (prescribed multiple inhalers) - 12 months post-index (prescribed Trelegy)	Inclusions: - ≥40 years of age as of the year of the index date - ≥2 medical claims with a diagnosis code for COPD in any position on separate dates of service during the study period - Pharmacy claim for FF/UMEC/VI during the patient identification period - ≥30 consecutive days of MITT during the 12 months prior to the index date - Continuous enrollment with medical and pharmacy coverage for 12 months prior to and including the index date (baseline period), and 12 months following the index date (follow-up period). Exclusions: - Medical claim with a diagnosis code for asthma, cystic fibrosis, or lung cancer during the study period - Pharmacy claim for FF/UMEC/VI during the baseline period - Had unknown or missing patient demographics	- Proportion of patients with ≥1 moderate to severe COPD exacerbation - COPD exacerbation-related costs - All-cause and COPD-related HCRU - All-cause and COPD-related costs Timepoint: 12 months

Trial (Author, Year)	Study Design & Interventions	Included Population	Key Outcomes
Bogart et al. 2024[60]	Study Design: Retrospective study of administrative claims data from Optum Research Database (ORD) Location: United States Interventions: 1) FF/UMEC/VI 2) MITT	Inclusions: - ≥40 years of age at index - ≥2 claims with a diagnosis code for COPD in any position on separate dates of service during the study period, AND - Pharmacy claim for triple therapy during the patient identification period Exclusions: - Overlapping supply with an inhaled corticosteroid (ICS), long-acting beta-agonist (LABA), and long-acting muscarinic antagonist (LAMA) (ie MITT) during the baseline period, excluding the index date - Medical claim with a diagnosis code for cystic fibrosis, lung cancer, or alpha-1 antitrypsin deficiency during the study period - Pharmacy claims for both MITT and FF/UMEC/VI on the index date - Unknown age, sex, geographic region, or insurance type.	- COPD exacerbation rates (any, severe, moderate) - Medication adherence (proportion of days covered) - all-cause and COPD-related HCRU Timepoint: 12 months
Rothnie et al. 2024[65]	Study Design: Retrospective cohort pre-post study using linked primary care electronic health record and secondary care administrative datasets Location: England Interventions: 1) MITT (12 months pre-index) 2) FF/UMEC/VI following MITT (6 months post-index)	Inclusions: - ≥35 years of age - ≥1 diagnosis code for COPD in the primary care setting - ≥1 observable prescription of single-inhaler FF/UMEC/VI following MITT that did not include FF-, UMEC- or VI-containing products - Current or former smoker prior to the index date - Record linked to HES and continuous registration with a GP for ≥12 months prior to the index date and ≥6 months after the index date. - Receiving MITT immediately prior to index: concomitantly received prescriptions for two or three different inhalers that form a triple therapy overlapping in days of supply of all three triple-therapy components of ≥1 day. - Patients switching from MITT to FF/UMEC/VI were included in the analysis with an intention-to-treat approach, regardless of any deviations from their MITT or FF/UMEC/VI therapy Exclusions: - ≥1 diagnosis code for any medical condition incompatible with a COPD diagnosis (conditions related to lung or bronchial developmental anomalies, degenerative processes, pulmonary resection or other significant respiratory disorders that can interfere with clinical COPD diagnosis) - Exposure to single-inhaler FF/UMEC/VI or beclomethasone	- Events and episodes of COPD exacerbation - Rate of moderate to severe COPD exacerbations - All-cause and COPD-related primary care (GP) consultations, hospital admissions, and A&E visits - All and COPD-related direct healthcare costs Timepoint: 12 months

Trial (Author, Year)	Study Design & Interventions	Included Population	Key Outcomes
		dipropionate/formoterol fumarate/glycopyrronium bromide in the 12 months prior to index date.	
Halpin et al. 2022[61]	Study Design: Retrospective cohort study of primary care data from the Clinical Practice Research Datalink (CPRD) Aurum and linked secondary care data from the Hospital Episode Statistics (HES) Admitted Patient Care database Location: England Interventions: 1) MITT 2) SITT 3) FF/UMEC/VI 4) BDP/GLY/FOR	**Inclusions**: - Age 35 or older - ≥1 diagnosis of COPD - FEV_1/forced vital capacity <0.7 at any time in their patient history either prior to or on the index date; patient records linked to HES - Continuous registration with a general practitioner for ≥1 year prior to and ≥6 months following the index date. **Exclusions**: - Patients with at least one diagnosis of any medical condition related to lung or bronchial developmental anomalies, degenerative processes (cystic fibrosis, pulmonary fibrosis), pulmonary resection or other significant respiratory disorders (other than COPD) which may have made ascertainment of a COPD diagnosis using electronic medical record data difficult or substantially change the natural history of the disease were excluded. **Patients with record of concomitant asthma were not excluded from the study population to reflect actual treatment/management of COPD in clinical practice.	- Adherence (proportion of days covered) - Persistence (measured with a gap of >30 days between the end of a prescription and the following refill) Timepoint: 12 months
Beeh et al. 2024[57] **DRKS00031897**	Study Design: Single-country, multicenter, open-label, non-interventional study Location: Germany Treatment Arm: 1) FF/UMEC/VI	Inclusions: - ≥18 years of age - Moderate to severe COPD (FEV_1 ≥30% - <80%) - Decision for the therapy with once-daily SITT (FF/UMEC/VI) was made in accordance with the current registration and independently from the participation in the study - ≥1 COPD exacerbation in the last 12 months prior to starting once-daily SITT - CAT ≥10 prior to starting treatment with once-daily SITT - Patients treated with once-daily SITT for the first time; this includes patients already on once-daily SITT for a maximum of 4 weeks prior to enrolment into the study, and whose COPD medication was not changed during this period Exclusions: - Patients hospitalized due to COPD exacerbation within the last 4 weeks prior to enrolment	- Change from baseline in CAT score Timepoint: 12 months

Trial (Author, Year)	Study Design & Interventions	Included Population	Key Outcomes
		- Any contraindication as per summary of product characteristics of once-daily SITT	
Vogelmeier et al. 2024[62]	Study Design: Retrospective cohort study using the Wissenschaftliches Institut für Gesundheitsökonomie und Gesundheitssystemforschung (WIG2) benchmark database Location: Germany Interventions: 1) MITT 2) SITT 3) FF/UMEC/VI 4) BDP/GLY/FOR	Inclusions: - ≥35 years of age at index - Confirmed COPD diagnosis (≥1 inpatient or ≥2 outpatient) at any time during the patient's medical history - Subsequent prescription for triple therapy (MITT or SITT) during the inclusion period were eligible to be included in the study (≥30 days' overlap in the treatment supply of all three MITT agents) - Continuously insured for a minimum of 1 year prior to index and have no record of prior prescriptions for triple therapy. Exclusions: - ≥1 diagnostic code for any medical condition interfering with clinical COPD diagnosis or substantially change the natural history of the disease (i.e., conditions related to lung or bronchial developmental anomalies, degenerative processes, pulmonary resection, or other significant respiratory disorders other than COPD).	- Adherence (proportion of days covered) - Persistence (time until treatment discontinuation) Timepoint: 12 months
Jokšaitė et al. 2024[63]	Study Design: Retrospective weighted cohort study using Medical Data Vison Co., Ltd database Location: Japan Interventions: 1) MITT 2) SITT 3) FF/UMEC/VI 4) BUD/GLY/FOR	Inclusions: - Age ≥40 years - ≥1 prescription of triple therapy within the indexing period - ≥1 inpatient diagnosis and/or ≥2 outpatient diagnoses of COPD - ≥1 diagnosis or medical claim record in the 12 months prior to index - ≥1 diagnosis or medical claim record in the 13–18 months prior to index - ≥6 months of data availability following but not including the index calendar month up to the earlier of the last/most recent diagnosis or medical claim record or the end of the study period - ≥1 pharmacy claim observable of FF/UMEC/VI within the indexing period - ≥1 overlapping days' supply with all three triple therapy components within the indexing period Exclusions: - ≥1 diagnostic code (ICD-10) of any medical conditions incompatible with a COPD diagnosis including conditions related to lung or bronchial developmental	- Adherence (proportion of days covered) - Persistence (time to discontinuation of therapy) Timepoint: 12 months

Trial (Author, Year)	Study Design & Interventions	Included Population	Key Outcomes
		anomalies, degenerative processes (cystic fibrosis, pulmonary fibrosis), pulmonary resection or other significant respiratory disorders (other than COPD) - ≥1 pharmacy claim for triple therapy within the 12 months prior to index	

BD: twice daily, BDP: beclomethasone dipropionate, BUD: budesonide, CAT: COPD Assessment Test, COPD: chronic obstructive pulmonary disease, FEV_1: forced expiratory volume in one second, FF: fluticasone furoate, FOR: formoterol, FVC: forced vital capacity, GLY: glycopyrronium, HCRU: health care resource utilization, ICS: inhaled corticosteroid, LABA: long-acting beta agonist, LAMA: long-acting muscarinic antagonist, MITT: multiple inhaler triple therapy, QD: once daily, SGRQ: St. George's Respiratory Questionnaire, SITT: single inhaler triple therapy, TIO: tiotropium, UK: United Kingdom, UMEC: umeclidinium, VI: vilanterol

Table D3.2. Baseline Characteristics – Randomized Trials of Trelegy Ellipta

Trial		Bremner 2018[52]		Ferguson 2020 Study 207608[122]		Ferguson 2020 Study 207609[122]	
Arm		FF/UMEC/VI 100/62.5/25 mcg	FF/VI + UMEC 100/25 + 62.5 mcg	FF/UMEC/VI 100/62.5/25 mcg	BUD/FOR + TIO 400/12 + 18 mcg	FF/UMEC/VI 100/62.5/25 mcg	BUD/FOR + TIO 400/12 + 18 mcg
N		527	528	363	365	366	366
Age	Mean (SD)	66.7 (8.5)	65.9 (8.8)	65.4 (7.9)	64.9 (8.1)	65.5 (8.2)	65.1 (6.4)
	65+	321 (60.9)	312 (59.2)	203 (55.9)	195 (53.4)	199 (54.4)	189 (51.6)
Sex	Male	391 (74)	394 (75)	NR	NR	NR	NR
	Female	136 (26)	134 (25)	180 (50)	164 (45)	180 (49)	179 (49)
Race/Ethnicity	White	417 (79)	420 (80)	327 (90)	330 (90)	319 (87)	338 (92)
	Black/African American	0	0	34 (9)	33 (9)	43 (12)	23 (6)
	Asian	72 (14)	68 (13)	1 (<1)	1 (<1)	3 (<1)	5 (1)
	American Indian/ Alaska Native	18 (3.4)	14 (2.7)	NR	NR	NR	NR
	Hispanic	71 (13)	77 (15)	39 (11)	46 (13)	50 (14)	58 (16)
Smoking Status	Current Smoker	209 (40)	192 (36)	186 (51)	168 (46)	170 (46)	190 (52)
	Former Smoker	318 (60)	336 (64)	177 (49)	197 (54)	196 (54)	176 (48)
Moderate/Severe Exacerbations in Prior 12 months	0	NR	NR	173 (48)	168 (46)	166 (45)	168 (46)
	1	236 (45)	227 (43)	60 (17)	69 (19)	69 (19)	75 (20)
	≥2	291 (55)	301 (57)	130 (36)	128 (35)	131 (36)	123 (34)
Post-BDR FEV_1 % predicted	Mean (SD)	44.5 (14.5)	45.5 (14.1)	42.5 (11.9)	42.3 (12.3)	41.4 (12.5)	42.8 (13.0)
CAT Score	Mean (SD)	19.6 (5.8)	20.1 (6.1)	21.6 (6.5)	22.0 (6.6)	22.2 (6.3)	22.3 (6.4)
GOLD Stage	1	0	1 (<1)	0	0	0	0
	2	174 (34)	189 (37)	76 (21)	82 (23)	71 (20)	84 (23)
	3	251 (49)	253 (49)	236 (65)	226 (62)	219 (60)	221 (60)
	4	90 (17)	69 (13)	51 (14)	56 (15)	72 (20)	61 (17)
Comorbidities	N with >1	NR	NR	299 (82)	296 (81)	304 (83)	308 (84)
	Asthma	0	0	0	0	0	0
Treatment History	ICS	NR	NR	3 (<1)	5 (1)	7 (2)	1 (<1)
	LABA	8 (2)	7 (1)	18 (5)	22 (6)	NR	NR
	LAMA	32 (6)	35 (7)	23 (6)	30 (8)	26 (7)	31 (8)
	ICS/LABA	144 (27)	137 (26)	121 (33)	137 (38)	123 (34)	115 (31)

Trial		Bremner 2018[52]		Ferguson 2020 Study 207608[122]		Ferguson 2020 Study 207609[122]	
Arm		FF/UMEC/VI 100/62.5/25 mcg	FF/VI + UMEC 100/25 + 62.5 mcg	FF/UMEC/VI 100/62.5/25 mcg	BUD/FOR + TIO 400/12 + 18 mcg	FF/UMEC/VI 100/62.5/25 mcg	BUD/FOR + TIO 400/12 + 18 mcg
N		527	528	363	365	366	366
	ICS/LAMA	7 (1)	9 (2)	NR	NR	NR	NR
	LAMA/ LABA	62 (12)	76 (14)	55 (15)	42 (12)	59 (16)	67 (18)
	ICS/LAMA/LABA	198 (38)	193 (37)	113 (31)	96 (26)	118 (32)	116 (32)

Units are n (%) unless otherwise stated.

BDR: bronchodilator, BUD: budesonide, CAT: COPD Assessment Test, FEV_1: forced expiratory volume in one second, FF: fluticasone furoate, FOR: formoterol, GOLD: Global Initiative for Chronic Obstructive Lung Disease, ICS: inhaled corticosteroid, LABA: long-acting beta agonist, LAMA: long-acting muscarinic antagonist, mcg: micrograms, N: total number, n: number, NR: not reported, SD: standard deviation, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table D3.3. Baseline Characteristics – Observational Studies of Trelegy Ellipta vs. Single Inhaler Triple Therapy

Trial		Mannino 2024[58]		Young 2024[59]		Feldman 2024[24]		Beeh 2024[57]
Location		United States		United States		United States		Germany
Arm		FF/UMEC/VI	BUD/GLY/FOR	FF/UMEC/VI	BUD/GLY/FOR	FF/UMEC/VI	BUD/GLY/FOR	FF/UMEC/VI *
N		32,312	12,230	8,912	2,685	20388	20388	906
Age	Mean (SD)	73.8 (8.6)	73.8 (8.4)	64.6 (9.1)	64.0 (8.8)	70.8 (9.0)	70.8 (8.9)	66.6 (9.8)
	65+	27,803 (86.0)	10,530 (86.1)	3,426 (38.4)	961 (35.8)	NR	NR	NR
Sex	Male	14,931 (46.2)	5,651 (46.2)	4,322 (48.5)	1,298 (48.3)	9,034 (44.3)	9,070 (44.5)	504 (55.6)
	Female	17,379 (53.8)	6,578 (53.8)	4,590 (51.5)	1,387 (51.7)	11,354 (55.7)	11,318 (55.5)	402 (44.4)
Race/Ethnicity	White	27,776 (86.0)	10,513 (86.0)	NR	NR	14,862 (72.9)	14,878 (73.0)	NR
	Black/AA	2,169 (6.7)	758 (6.2)	NR	NR	2,621 (12.9)	2,586 (12.7)	NR
	Asian	NR	NR	NR	NR	257 (1.3)	271 (1.3)	NR
	Hispanic	NR	NR	NR	NR	1,290 (6.3)	1,300 (6.4)	NR
	Unknown	527 (1.6)	186 (1.5)	NR	NR	NR	NR	NR
Smoker Status	Current	NR	NR	NR	NR	NR	NR	358 (39.6)
	Former	NR	NR	NR	NR	NR	NR	440 (48.6)
Insurance Type	Medicare	NR	NR	3,567 (40.0)	968 (36.1)	NR	NR	N/A
	Commercial	NR	NR	5,332 (59.8)	1,717 (63.9)	NR	NR	N/A
Mod/Severe Exacerbations in the prior 12 months	Moderate, mean (SD)	0.77 (1.21)	0.77 (1.19)	NR	NR	0.71 (1.15)	0.72 (1.15)	0.8 (0.8)
	Severe, mean (SD)	0.10 (0.38)	0.10 (0.38)	NR	NR	0.06 (0.28)	0.06 (0.28)	0.1 (0.4)
	N (%) with >1	15,640 (48.4)	5,889 (48.2)	1,785 (20.0)	582 (21.7)	NR	NR	906 (100)
Comorbidities	Asthma	NR	NR	NR	NR	NR	NR	87 (12.9)
Treatment History	ICS	2,387 (7.4)	904 (7.4)	541 (6.1)	163 (6.1)	1,321 (6.5)	1,300 (6.4)	NR
	LABA	390 (1.2)	174 (1.4)	62 (0.7)	28 (1.0)	176 (0.9)	169 (0.8)	NR
	LAMA	6,640 (20.6)	2,513 (20.6)	1,528 (17.1)	463 (17.2)	2,441 (12.0)	2,452 (12.0)	NR
	ICS/LABA	12,696 (39.3)	4,805 (39.3)	3,503 (39.3)	1,081 (40.3)	7,534 (37.0)	7,647 (37.5)	130 (14.3)
	LAMA/ LABA	5,497 (17.0)	2,081 (17.0)	1,780 (20.0)	536 (20.0)	2,978 (14.6)	2,965 (14.5)	449 (49.6)
	ICS/LAMA/LABA	5,001 (15.5)	1,893 (15.5)	NR	NR	NR	NR	207 (22.8)

Units are n (%) unless otherwise stated.

CAT: COPD Assessment Test, FF: fluticasone furoate, ICS: inhaled corticosteroid, LABA: long-acting beta agonist, LAMA: long-acting muscarinic antagonist, N: total number, mcg: micrograms, MITT: multiple inhaler triple therapy, n: number, NR: not reported, SD: standard deviation, UMEC: umeclidinium, VI: vilanterol

Table D3.4. Baseline Characteristics – Observational Studies of Trelegy Ellipta vs. Multiple Inhaler Triple Therapy (1/2)

Trial		Mannino 2022[49]		Bogart 2024[60]		Hanania 2023[64]	Rothnie 2024[65]
Location		United States		United States		United States	England
Arm		FF/UMEC/VI	MITT	FF/UMEC/VI	MITT	MITT*	MITT*
N		2782	7160	4659	9845	912	2533
Age	Mean (SD)	60.6 (7.8)	60.4 (7.8)	71.8 (8.7)	71.7 (8.8)	71.2 (8.1)	71.1 (9.9)
	65+	NR	NR	3780 (81)	7949 (81)	719 (79)	NR
Sex	Male	1266 (45.5)	3430 (47.9)	1955 (42)	4133 (42)	445 (48.8)	1320 (52.1)
	Female	1516 (54.5)	3730 (52.1)	2704 (58)	5712 (58)	467 (51.2)	1213 (47.9)
Race/Ethnicity	White	NR	NR	2864 (61.5)	6078 (61.7)	NR	NR
	Black/AA	NR	NR	734 (15.8)	1557 (15.8)	NR	NR
	Asian	NR	NR	54 (1.2)	109 (1.1)	NR	NR
	Hispanic	NR	NR	314 (6.8)	647 (6.6)	NR	NR
	Unknown	NR	NR	131 (15.9)	295 (15.6)	NR	NR
Insurance Type	Medicare	NR	NR	4659 (100)	9845 (100)	803 (88.1)	NR
	Commercial	NR	NR	0	0	109 (12.0)	NR
Smoking status	Current Smoker	NR	NR	NR	NR	NR	1104 (43.6)
	Former smoker	NR	NR	NR	NR	NR	1429 (56.4)
Exacerbations in prior year, mean (SD)	Moderate	1.1 (1.4)	1.1 (1.4)	0.88 (1.21)	0.83 (1.20)	1.1 (1.4)	NR
	Severe	0.28 (0.60)	0.27 (0.59)	0.34 (0.71)	0.35 (0.70)	0.3 (0.6)	NR
Mod/Severe Exacerbations in Prior year	0	NR	NR	NR	NR	NR	1273 (50.3)
	1	NR	NR	NR	NR	NR	677 (26.7)
	≥1	NR	NR	NR	NR	NR	1260 (49.7)
	2	NR	NR	NR	NR	NR	325 (12.8)
	≥3	NR	NR	NR	NR	NR	258 (10.2)
Post-BDR FEV1, % predicted	Mean (SD)	NR	NR	NR	NR	NR	55.4 (19.8)
CAT Score	Mean (SD)	NR	NR	NR	NR	36.2 (10.1)	NR
Comorbidities	N with >1	NR	NR	NR	NR	NR	2202 (86.9)
	Current asthma diagnosis	830 (29.8)	2233 (31.2)	NR	NR	NR	758 (29.9)
Treatment History	ICS	415 (14.9)	818 (11.4)	357 (7.7)	701 (7.1)	121 (13.3)	NR (1.7)
	LABA	32 (1.2)	110 (1.5)	48 (1)	108 (1.1)	13 (1.4)	*NR (0.8)*

Trial		Mannino 2022[49]		Bogart 2024[60]		Hanania 2023[64]	Rothnie 2024[65]
Location		United States		United States		United States	England
Arm		FF/UMEC/VI	MITT	FF/UMEC/VI	MITT	MITT*	MITT*
N		2782	7160	4659	9845	912	2533
	LAMA	835 (30.0)	1976 (27.6)	996 (21.4)	2164 (22)	810 (88.8)	2424 (95.7)
	ICS/LABA	1377 (49.5)	3769 (52.6)	2087 (44.8)	4353 (44.2)	827 (90.7)	2472 (97.6)
	LAMA/ LABA	433 (15.6)	1015 (14.2)	579 (12.4)	1219 (12.4)	174 (19.1)	*NR (10.9)*
	ICS/LAMA/LABA	NR	NR	NR	NR	NR	*NR (10.9)*

*Baseline characteristics of patients on MITT prior to initiation with FF/UMEC/VI

Units are n (%) unless otherwise stated. Italicized data have been digitized from figures, interpret with caution.

CAT: COPD Assessment Test, FF: fluticasone furoate, ICS: inhaled corticosteroid, LABA: long-acting beta agonist, LAMA: long-acting muscarinic antagonist, N: total number, mcg: micrograms, MITT: multiple inhaler triple therapy, n: number, NR: not reported, SD: standard deviation, UMEC: umeclidinium, VI: vilanterol

Table D3.5. Baseline Characteristics – Observational Studies of Trelegy Ellipta vs. Multiple Inhaler Triple Therapy (2/2)

Trial		Halpin 2022[61]		Vogelmeier 2024[62]		Jokšaitė et al. 2024[63]		
Location		England		Germany		Japan		
Arm		FF/UMEC/VI	MITT	FF/UMEC/VI	MITT	FF/UMEC/VI	BUD/GLY/FOR	MITT
N		1319	4092	675	4079	2,397	565	2,575
Age	Mean (SD)	69.9	68.5	66 (10.9)	66 (11.8)	74.2 (9.2)	74.5 (9.7)	71.8 (11.6)
	65+	NR	NR	NR	NR	NR	NR	NR
Sex	Male	57.2	54.2	409 (60.6)	2,248 (55.1)	1,895 (79.1)	411 (72.7)	1,710 (66.4)
	Female	42.8	45.8	266 (39.4)	1,831 (44.9)	499 (20.8)	154 (27.3)	851 (33.0)
Smoker status	Current	49.5	50.5	314 (46.5)	1,750 (42.9)	NR	NR	NR
	Former	48.8	46.4	NR	NR	1,185 (49.4)	251 (44.4)	1,142 (44.3)
Mod/Severe Exacerbations in Prior 12 months	Moderate, mean (SD)	0.59	0.48	NR	NR	NR	NR	NR
	Severe, mean (SD)	0.17	0.15	NR	NR	NR	NR	NR
	N (%) with >1	NR	NR	NR	NR	NR	NR	NR
Post-BDR FEV_1, % predicted	Mean (SD)	58.5	59.3	NR	NR	NR	NR	NR
Comorbidities	Asthma	378 (28.7)	1473 (36)	87 (12.9)	967 (23.7)	1,678 (70.0)	390 (69.0)	2,312 (89.8)
Treatment History	ICS	NR	NR	NR	NR	59 (2.5)	24 (4.2)	134 (5.2)
	LABA	NR	NR	NR	NR	39 (1.6)	13 (2.3)	21 (0.8)
	LAMA	NR	NR	NR	NR	180 (7.5)	37 (6.5)	436 (16.9)
	ICS/LABA	NR	NR	NR	NR	555 (23.2)	128 (22.7)	947 (36.8)
	LAMA/LABA	NR	NR	NR	NR	664 (27.7)	151 (26.7)	369 (14.3)
	ICS/LAMA/LABA	NR	NR	NR	NR	NR	NR	NR

Units are n (%) unless otherwise stated. Italicized data have been digitized from figures, interpret with caution.

BDR: bronchodilator, BUD: budesonide, CAT: COPD Assessment Test, FEV_1: forced expiratory volume in one second, FF: fluticasone furoate, FOR: formoterol, ICS: inhaled corticosteroid, LABA: long-acting beta agonist, LAMA: long-acting muscarinic antagonist, N: total number, mcg: micrograms, MITT: multiple inhaler triple therapy, n: number, NR: not reported, SD: standard deviation, UMEC: umeclidinium, VI: vilanterol

Table D3.6. Efficacy Outcomes - Randomized Trials of Trelegy Ellipta

Trial		Bremner 2018[52]		Ferguson 2020 Study 207608[122]		Ferguson 2020 Study 207609[122]	
Arm		FF/UMEC/VI 100/62.5/25 mcg	FF/VI + UMEC 100/25 + 62.5 mcg	FF/UMEC/VI 100/62.5/25 mcg	BUD/FOR + TIO 400/12 + 18 mcg	FF/UMEC/VI 100/62.5/25 mcg	BUD/FOR + TIO 400/12 + 18 mcg
Timepoint		24 weeks		12 weeks		12 weeks	
N		527	528	363	365	366	366
Moderate to Severe Exacerbations							
N evaluated		527	528	363	365	366	366
N with >1 Exacerbation, n (%)		129 (24)	142 (27)	33 (9)	35 (10)	47 (13)	42 (11)
Exacerbation Rate, mean		0.697	0.8449	0.4567	0.503	0.619	0.58
Rate Ratio; p-value		0.82*	reference	0.91*	reference	1.07*	reference
Moderate Exacerbations							
N evaluated		527	528	363	365	366	366
N with >1 Exacerbation, n (%)		111 (21)	118 (22)	19 (5)	33 (9)	40 (11)	37 (10)
Exacerbation Rate, mean		0.5858	0.6913	0.240	0.4665	0.510	0.5078
Rate Ratio; p-value		0.85*	reference	0.52*	reference	1.00*	reference
Severe Exacerbations							
N evaluated		527	528	363	365	366	366
N with >1 Exacerbation, n (%)		22 (4)	31 (6)	15 (4)	3 (0.8)	8 (2)	6 (2)
Exacerbation Rate, mean		0.1112	0.1536	0.2164	0.0368	0.1092	0.0725
Rate Ratio; p-value		0.72*	reference	5.88*	reference	1.51*	reference
Transitional Dyspnea Index (TDI) Focal Score							
Mean Score	N evaluated	482	481	NR	NR	NR	NR
	LS Mean (95%CI)	2.0 (1.8, 2.3)	1.9 (1.6, 2.1)	NR	NR	NR	NR
	Mean difference (95%CI); p-value	0.1 (-0.2, 0.5)	reference	NR	NR	NR	NR
Responders	N evaluated	482	481	NR	NR	NR	NR
	n (%)	268 (56)	271 (56)	NR	NR	NR	NR
	Odds Ratio (95%CI); p-value	0.95 (0.72, 1.25)	reference	NR	NR	NR	NR
St. George's Respiratory Questionnaire (SGRQ) Total Score							
Mean Score	N evaluated	489	483	344	342	343	342
	LS Mean (95%CI)	NR	NR	48.8 (47.8, 49.8)	48.7 (47.7, 49.7)	51.8 (50.7, 52.8)	51.7 (50.7, 52.8)

Trial		Bremner 2018[52]		Ferguson 2020 Study 207608[122]		Ferguson 2020 Study 207609[122]	
Arm		FF/UMEC/VI 100/62.5/25 mcg	FF/VI + UMEC 100/25 + 62.5 mcg	FF/UMEC/VI 100/62.5/25 mcg	BUD/FOR + TIO 400/12 + 18 mcg	FF/UMEC/VI 100/62.5/25 mcg	BUD/FOR + TIO 400/12 + 18 mcg
Timepoint		24 weeks		12 weeks		12 weeks	
N		527	528	363	365	366	366
	LS Mean CFB (95%CI)	-5.8 (-7.0, -4.7)	-4.9 (-6.1, -3.8)	-1.2 (-2.2, -0.2)	- 1.3 (- 2.3, -0.3)	-1.5 (- 2.6, -0.4)	-1.5 (- 2.6, - 0.4)
	Mean difference (95%CI); p-value	-0.9 (-2.5, 0.7)	reference	0.1 (-1.3, 1.5); p=0.926	reference	0.0 (-1.5 ,1.6); p=0.609	reference
Responders	N evaluated	489	483	345	343	343	344
	n (%)	243 (50)	247 (51)	117 (34)	117 (34)	124 (36)	119 (35)
	Odds Ratio (95%CI); p-value	0.92 (0.71, 1.20)	reference	1.01 (0.74, 1.40); p=0.928	reference	1.09 (0.79, 1.50); p=0.609	reference
COPD Assessment Test (CAT) Score							
Score	N evaluated	NR	NR	348	344	344	347
	LS Mean (95%CI)	NR	NR	19.8 (19.3, 20.3)	20.4 (19.8, 20.9)	21.1 (20.6, 21.6)	21.2 (20.7, 21.7)
	LS Mean CFB (95%CI)	NR	NR	-0.8 (-1.4, -0.3)	-0.2 (-0.8, 0.3)	- 0.2 (- 0.7, 0.3)	-0.1 (- 0.6, 0.4)
	Mean difference (95%CI); p-value	NR	NR	-0.6 (-1.4, 0.2); p=0.141	reference	-0.1 (-0.8, 0.6); p=0.746	reference
Responders	N evaluated	NR	NR	349	344	344	348
	n (%)	NR	NR	137 (39)	130 (38)	126 (37)	126 (36)
	Odds Ratio (95%CI); p-value	NR	NR	1.07 (0.78 1.47); p=0.655	reference	1.02 (0.74, 1.40); p=0.895	reference
Forced Expiratory Volume in 1 Second (FEV_1) – 0-24h FEV_1 (mL)							
Mean 0-24h FEV_1 (mL) Change from Baseline	N evaluated	NR	NR	358	362	354	357
	LS Mean (95%CI)	NR	NR	1210 (1191, 1230)	1195 (1175, 1215)	1185 (1163, 1206)	1174 (1153, 1195)
	LS Mean (95%CI)	NR	NR	45 (26, 65)	30 (10, 50)	39 (18, 61)	29 (7, 50)
	Mean difference (95%CI)	NR	NR	15 (-13, 43)	reference	11 (-20, 41)	reference
Concomitant Treatment for an Exacerbation							
SABA	n (%)	25 (5)	21 (4)	10 (3)	4 (1)	12 (3)	4 (1)
SAMA	n (%)	19 (4)	15 (3)	11 (3)	4 (1)	8 (2)	3 (<1)
Oxygen	n (%)	10 (2)	4 (<1)	2 (<1)	0	2 (<1)	0
Treatment Compliance							
Overall compliance, mean (SD)		98.8 (4.6)	98.3 (4.8)	98.2 (10.9)	96.6 (7.0)	98.2 (25.1)	96.9 (7.9)

*ICER calculated from raw data

95%CI: 95 percent confidence interval , BUD: budesonide, CAT: COPD Assessment Test, FEV_1: forced expiratory volume in one second, FF: fluticasone furoate, FOR: formoterol, LS: least squares, mcg: micrograms, n: number, N: total number, NR: not reported, SABA: short-acting beta-2 agonist, SAMA: short-acting anticholinergic, SD: standard deviation, SGRQ: St. George's Respiratory Questionnaire, TDI: Transitional Dyspnea Index, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table D3.7. Efficacy Outcomes – Observational Studies of Trelegy Ellipta vs. Single Inhaler Triple Therapy

Trial		Mannino 2024[58]		Feldman 2024[24]		Beeh 2024[57]	
Location		United States		United States		Germany	
Arm		FF/UMEC/VI	BUD/GLY/FOR	FF/UMEC/VI	BUD/GLY/FOR	FF/UMEC/VI	
Timepoint		12 Months		12 Months		Baseline*	12 Months
N		32,312	12,230	20,388	20,388	906	906
Moderate to Severe Exacerbations	n evaluated	NR	NR	NR	NR	NR	NR
	Rate	0.80	0.91	0.4828	5.357	NR	NR
	Rate Ratio (95%CI); p-value	0.88 (0.85, 0.92); p<0.001		1.09 (1.04, 1.14)*		NR	NR
Moderate Exacerbations	n evaluated	NR	NR	NR	NR	NR	NR
	Rate	0.67	0.78	0.4511	4.896	0.8	0.2
	Rate Ratio (95%CI); p-value	0.86 (0.83, 0.90); p<0.001		1.07 (1.02, 1.13)*		NR	NR
Severe exacerbations	n evaluated	NR	NR	NR	NR	906	906
	Rate	0.13	0.13	0.0419	0.544	0.1	0
	Rate Ratio (95%CI); p-value	0.99 (0.92, 1.07); p=0.822		1.29 (1.12, 1.48)*		NR	NR
Risk of all-cause mortality	Risk (%)	5.6	6.4	NR	NR	NR	NR
	Hazard Ratio (95%CI); p-value	0.89 (0.80, 0.98); p=0.020		NR	NR	NR	NR

* Baseline values are of patients on once-daily single triple therapy (SITT) prior to initiation with FF/UMEC/VI

† Hazard ratio (95%CI)

95%CI: 95 percent confidence interval, BUD: budesonide, FF: fluticasone furoate, FOR: formoterol, GLY: glycopyrronium, n: number, N: total number, NR: not reported, SD: standard deviation, UMEC: umeclidinium, VI: vilanterol

Table D3.8. Efficacy Outcomes – Observational Studies of Trelegy Ellipta vs. Multiple Inhaler Triple Therapy

Trial		Bogart 2024[60]				Hanania 2023[64]		Rothnie 2024[65]	
Arm		FF/UMEC/VI	MITT	FF/UMEC/VI	MITT	FF/UMEC/VI		MITT	FF/UMEC/VI
Timepoint		Baseline		12 months		Baseline	12 months	12 months pre-switch	12 months post-switch
N		4659	9845	4659	9845	912	912	1603	1603
COPD Exacerbations									
Moderate-Severe Exacerbations	n evaluated	NR	NR	NR	NR	912	912	1603	1603
	N (%) with >1 exacerbation	NR	NR	NR	NR	569 (62.4)	514 (56.4)	NR (50.7)	NR (45.0)
	% difference; p-value	NR	NR	NR	NR	NR; p=0.001		NR; p=0.0003	
	Mean exacerbations (SD)	NR	NR	NR	NR	1.4 (1.6)	1.2 (1.5)	NR	NR
	% difference; p-value	NR	NR	NR	NR	-14.3; p=0.001		NR	NR
Moderate Exacerbations	n evaluated	4659	9845	4659	9845	912	912	1603	1603
	N (%) with >1 exacerbation	2284 (49.0)	4676 (47.5)	1962 (42.1)	4060 (41.2)	496 (54.4)	436 (47.8)	NR (39.1)	NR (31.8)
	% difference; p-value	3.07%*; p=0.119		NR; p=0.367		NR; p<0.001		NR; p<0.0001	
	Mean exacerbations (SD)	NR	NR	NR	NR	1.1 (1.4)	0.9 (1.3)	NR	NR
	% difference; p-value	NR	NR	NR	NR	-18.2; p<0.001		NR	NR
	Exacerbation rate	0.88 (1.2)	0.83 (1.2)	0.75 (1.2)	0.71 (1.1)	NR	NR	NR	NR
	Rate ratio; p-value	3.77%*; p=0.062		NR; p=0.093		NR	NR	NR	NR
Severe Exacerbations	n evaluated	4659	9845	4659	9845	912	912	1603	1603
	N (%) with >1 exacerbation	1169 (25.1)	2521 (25.6)	840 (18.0)	2002 (20.3)	209 (22.9)	202 (22.2)	NR (21.3)	NR (21.1)
	% difference; p-value	−1.17%*; p=0.573		NR; p=0.005		NR; p=0.331		NR; p=0.9601	
	Mean exacerbations (SD)	NR	NR	NR	NR	0.3 (0.6)	0.3 (0.6)	NR	NR
	% difference; p-value	NR	NR	NR	NR	no diff; p=0.415		NR	NR
	Exacerbation rate	0.34 (0.7)	0.35 (0.7)	0.26 (0.7)	0.29 (0.7)	NR	NR	NR	NR
	Rate ratio; p-value	−0.61%*; p=0.786		NR; p=0.014		NR	NR	NR	NR
COPD-Related Health Care Resource Utilization (HCRU)									
Ambulatory visit	Utilization, n (%)	3694 (79.3)	7715 (78.4)	3669 (78.8)	7674 (78.0)	827 (90.7)	781 (85.6)	NR	NR
	% difference; p-value	2.25%**; p=0.276		NR; p=0.327		p<0.001		NR	NR
	Count, mean (SD)	4.53 (8.4)	4.19 (7.7)	5.04 (9.5)	5.38 (10.5)	6.1 (8.9)	6.6 (13.6)	NR	NR
	% difference; p-value	4.28%**; p=0.043		NR; p=0.098		p=0.860		NR	NR

Trial		Bogart 2024[60]				Hanania 2023[64]		Rothnie 2024[65]	
Arm		FF/UMEC/VI	MITT	FF/UMEC/VI	MITT	FF/UMEC/VI		MITT	FF/UMEC/VI
Timepoint		Baseline		12 months		Baseline	12 months	12 months pre-switch	12 months post-switch
N		4659	9845	4659	9845	912	912	1603	1603
Office visit	Utilization, n (%)	3260 (70.0)	6799 (69.1)	3245 (69.7)	6679 (67.8)	776 (85.1)	729 (79.9)	NR	NR
	% difference; p-value	2.00%**; p=0.333		NR; p=0.053		NR	p<0.001	NR	NR
	Count, mean (SD)	2.37 (3.2)	2.16 (2.7)	2.25 (3.0)	2.21 (3.2)	3.1 (2.8)	2.7 (2.7)	NR	NR
	% difference; p-value	7.11%*; p<0.001		NR; p=0.576		p<0.001		NR	NR
Outpatient visits	Utilization, n (%)	1685 (36.2)	3522 (35.8)	1750 (37.6)	3812 (38.7)	382 (41.9)	371 (40.7)	NR	NR
	% difference; p-value	0.82%*; p=0.679		NR; p=0.232		p=0.267		NR	NR
	Count, mean (SD)	2.17 (7.5)	2.03 (6.8)	2.80 (8.7)	3.17 (9.6)	3.0 (8.1)	3.9 (13.0)	NR	NR
	% difference; p-value	1.89%*; p=0.377		NR; p=0.045		p=0.979		NR	NR
Emergency Room visits	Utilization, n (%)	1136 (24.4)	2447 (24.9)	915 (19.7)	2000 (20.3)	182 (20.0)	159 (17.4)	NR	NR
	% difference; p-value	−1.09%*; p=0.592		NR; p=0.410		p=0.059		NR	NR
	Count, mean (SD)	0.51 (1.4)	0.52 (1.5)	0.43 (1.3)	0.45 (1.5)	0.4 (1.1)	0.3 (1.1)	NR	NR
	% difference; p-value	−0.75%*; p= 0.711		NR; p=0.467		p=0.186		NR	NR
Inpatient stay	Utilization, n (%)	950 (20.4)	2082 (21.2)	750 (16.1)	1744 (17.7)	187 (20.5)	178 (19.5)	NR	NR
	% difference; p-value	−1.87%*; p=0.3		NR; p=0.037		p=0.279		NR	NR
	Count, mean (SD)	0.29 (0.8)	0.29 (0.7)	0.24 (0.7)	0.27 (0.8)	0.3 (0.7)	0.3 (0.7)	NR	NR
	% difference; p-value	−0.82%*; p=0.703		NR; p=0.009		p=0.358		NR	NR
	Mean days (SD)	2.84 (10.5)	3.58 (14.6)	17.30 (22.7)	20.10 (25.9)	2.6 (10.1)	3.0 (10.2)	NR	NR
	% difference; p-value	−5.81%*; p=0.003		NR; p=0.016		p=0.785		NR	NR
Pharmacy use	Utilization, n (%)	4440 (95.3)	9380 (95.3)	4659 (100.0)	9845 (100.0)	912 (100.0)	904 (99.1)	NR	NR
	% difference; p-value	0.13%*; p=0.938		NA		p=NR		NR	NR
	Count, mean (SD)	9.56 (8.3)	9.58 (8.6)	11.88 (8.8)	16.02 (10.7)	23.0 (11.8)	17.8 (11.5)	NR	NR
	% difference; p-value	−0.26%*; 0.897		NR; p<0.001		p<0.001		NR	NR
Primary Care Consultations	RR (95%CI); p-value	NR	NR	NR	NR	NR	NR	0.73 (0.71, 0.76); p<0.0001	
Inpatient Stay	RR (95%CI); p-value	NR	NR	NR	NR	NR	NR	1.14 (1.01, 1.27); p=0.0338	
A&E Attendances	RR (95%CI); p-value	NR	NR	NR	NR	NR	NR	0.95 (0.83, 1.10); p=0.5195	

*Value represents robust standardized difference
Italicized data are digitized, interpret with caution
95%CI: 95 percent confidence interval, COPD: chronic obstructive pulmonary disease, diff: difference, FF: fluticasone furoate, HCRU: health care resource utilization, mcg: micrograms, MITT: multiple inhaler triple therapy, N/A: not applicable, n: number, N: total number, NR: not reported, p: p-value, SD: standard deviation, UMEC: umeclidinium, VI: vilanterol

Table D3.9. Adherence – Observational Studies of Trelegy Ellipta versus Single and/or Multiple Inhaler Triple Therapy (1/2)

Trial	Mannino 2022[49]		Bogart 2024[60]		Young et al 2024[59]		Beeh 2024[57]	
Arm	**FF/UMEC/VI**	**MITT**	**FF/UMEC/VI**	**MITT**	**FF/UMEC/VI**	**BUD/GLY/FOR**	**FF/UMEC/VI**	
Timepoint	**12 months**		**12 months**		**12 months**		**Baseline**	**12 months**
N	1337	3442	4659	9845	5,367	1,268	**906**	**906**
Mean PDC (SD)	0.60 (0.34)	0.40 (0.32)	0.51 (0.3)	0.37 (0.3)	0.57	0.5	NR	NR
PDC ≥8, n (%)	577 (43.2)	598 (17.4)	1211 (26.0)	1287 (13.1)	1884 (35.1)	314 (24.8)	NR	NR
TAI "Good" Adherence, n (%)	NR	NR	NR	NR	NR	NR	NR (*62.4*)	NR (77.1); p<0.0001
Proportion (%) of persistent patients	35.7	13.9	NR	NR	NR (31.0)*	NR (23.6)*	NR	NR
Median Persistence duration, months†	NR	NR	NR	NR	4.3	3	NR	NR

Italicized data are digitized, interpret with caution
* Kaplan Meier estimates
† 30-day permissible gap
FF: fluticasone furoate, mcg: micrograms, MITT: multiple inhaler triple therapy, n: number, N: total number, NR: not reported, PDC: proportion of days covered, SD: standard deviation, TAI: Test of Adherence to Inhalers, UMEC: umeclidinium, VI: vilanterol

Table D3.10. Adherence – Observational Studies of Trelegy Ellipta versus Single and/or Multiple Inhaler Triple Therapy (2/2)

Trial	Timepoint (months)	Vogelmeier 2024[62]		Halpin 2022[61]		Jokšaitė et al. 2024[63]		
Arm		FF/UMEC/VI	MITT	FF/UMEC/VI	MITT	FF/UMEC/VI	MITT	BUD/GLY/FOR
N		675	4079	622	3169	1,401	1,909	1328
Mean PDC (SD)	12	54.3 (11.2)	35.5 (6.7)	0.61	0.39	0.435	0.311	NR
	18	50.6 (11.5)	31.5 (6.7)	0.58	0.36	0.395	0.279	NR
PDC ≥8, n (%)	12	54.7	29.9	33.6	14.9	92 (6.6)	73 (3.8)	NR
	18	51.0	26.8	28.1	12.1	57 (4.1)	18 (1.4)	NR
Proportion (%) of persistent patients	12	23	4.4	2.3	14.4	NR	NR	NR
	18	38.1	16.5	36.3	10.7	NR	NR	NR
Median Persistence duration, months†	18	NR	NR	NR	NR	2.23	1.51	1.41

*Data is digitized, interpret with caution

†30-day permissible gap

FF: fluticasone furoate, mcg: micrograms, MITT: multiple inhaler triple therapy, n: number, N: total number, NR: not reported, p: p-value, PDC: proportion of days covered, SD: standard deviation, UMEC: umeclidinium, VI: vilanterol

Table D3.11. Safety Outcomes - Randomized Trials of Trelegy Ellipta

Trial		Bremner 2018[52]		Ferguson 2020 Study 207608[122]		Ferguson 2020 Study 207609[122]	
Arm		FF/UMEC/VI 100/62.5/25 mcg	FF/VI + UMEC 100/25 + 62.5 mcg	FF/UMEC/VI 100/62.5/25 mcg	BUD/FOR + TIO 400/12 + 18 mcg	FF/UMEC/VI 100/62.5/25 mcg	BUD/FOR + TIO 400/12 + 18 mcg
Timepoint		24 weeks		12 weeks		12 weeks	
N		527	528	363	365	366	366
Adverse events (AEs)	Any	255 (48)	253 (48)	131 (36)	121 (33)	92 (25)	109 (30)
	Serious	52 (10)	57 (11)	25 (7)	14 (4)	12 (3)	17 (5)
Treatment Discontinuations	Any	30 (6)	32 (6)	16 (4)	22 (6)	18 (5)	14 (4)
	due to AEs	20 (4)	11 (2)	8 (2)	8 (2)	2 (<1)	6 (2)
Mortality	Any	4 (<1)	4 (<1)	0	0	0	1 (<1)
	due to AEs	4 (<1)	4 (<1)	0	0	0	1 (<1)
Pneumonia	Any	14 (3)	21 (4)	5 (1)	6 (2)	2 (< 1)	3 (< 1)
Cardiovascular events	Any	30 (6)	28 (5)	10 (3)	8 (2)	11 (3)	8 (2)
Urinary Tract Risks	Urinary Tract Infection	5 (<1)	4 (<1)	2 (<1)	1 (<1)	3 (<1)	2 (<1)
	Urinary retention	0	0	NR	NR	NR	NR

Data are presented as n (%)

AEs: adverse events, BUD: budesonide, FF: fluticasone furoate, FOR: formoterol, mcg: micrograms, N: total number, n: number, NR: not reported, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table D3.12. Safety Outcomes – Observational Studies of Trelegy Ellipta versus Single and/or Multiple Inhaler Triple Therapy

Trial		Bogart 2024[60]		Beeh 2024[57]	Feldman 2024[24]	
Arm		FF/UMEC/VI	MITT	FF/UMEC/VI	FF/UMEC/VI	BUD/GLY/FOR
Timepoint		12 months		12 months	12 months	
N		4659	9845	906	20388	20388
Adverse Events (AEs)	Any	NR	NR	148 (16.3)	NR	NR
	Serious	NR	NR	42 (4.6)	NR	NR
Treatment Discontinuations	Any	3074 (66.0)	8089 (82.2)	461 (50.9)	NR	NR
	Due to adverse events	NR	NR	29 (3.2)	NR	NR
Mortality	Any	NR	NR	6 (0.6)	0.0686*	0.0712*
	Due to adverse events	NR	NR	6 (0.6)	NR	NR
Pneumonia	Any	NR	NR	5 (0.6)	NR	NR
Hospitalization with Pneumonia	Any	NR	NR	NR	1.039*	1.060*
Cardiovascular Events	Any	NR	NR	NR	NR	NR

Data are presented as n (%) unless otherwise specified

*Data represent events per one person year

AEs: adverse events, FF: fluticasone furoate, mcg: micrograms, MITT: multiple inhaler triple therapy, N: total number, n: number, NR: not reported, UMEC: umeclidinium, VI: vilanterol

Table D3.13. Study Design – Breo Ellipta

Trial (Author, Year)	Study Design & Interventions	Included Population	Key Outcomes
Randomized Controlled Trials			
Dransfield 2014[68] **NCT01323621, NCT01323634, NCT01706328**	Study Design: Three Phase 3, multicenter, double-blind, double-dummy, parallel-group, 12-week randomized trials Location: Czech Republic, Germany, Italy, Poland, Romania, Russia, South Africa, Spain, Ukraine, United States Interventions: 1) FF/VI 100/25 mcg QD 2) FP/SAL 250/50 mcg BD	Inclusions: - ≥40 years of age - Clinical history of COPD as defined by ATS/ERS criteria - Post-albuterol FEV_1/forced vital capacity (FVC) ratio of ≤0.70 and FEV_1 ≤70% of that predicted using NHANES III equations - ≥10 pack-year history of cigarette smoking. - Exacerbation frequency was not a study entry criterion. Exclusions: - Current diagnosis of asthma - Respiratory disorders including active tuberculosis, α1-antitrypsin deficiency, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases - Poorly controlled COPD 6 weeks prior to screening or hospitalization for poorly controlled COPD within 12 weeks of screening	- Change from Baseline Trough in 24-hour Weighted-mean FEV_1 - Time to onset of action (increase in FEV_1 of 100mL from baseline 4h post-dose) - Change from baseline in FVC - Rescue medication (albuterol) use Timepoint: 12 weeks
Agustí 2014[72] **NCT01342913**	Study Design: Phase 3, double-blind, double-dummy, multicenter, parallel group 12-week randomized trial Location: Belgium, France, Germany, Italy, Philippines, Poland, Russia, Spain, Ukraine Interventions: 1) FF/VI 100/25 mcg QD 2) FP/SAL 250/50 mcg BD	Inclusions: - ≥ 40 years of age - Established clinical history of COPD by ATS/ERS definition - Former or current smoker > 10 pack years - Post-albuterol spirometry criteria: FEV_1/FVC ratio ≤ 0.70 and FEV_1 ≤ 70% of predicted normal (NHANES III) - Hospitalized or treated with oral corticosteroids or antibiotics for their COPD within the last 3 years prior to screening Exclusions: - Current diagnosis of asthma - Respiratory disorders including active tuberculosis, α1-antitrypsin deficiency, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases - Poorly controlled COPD 6 weeks prior to screening or hospitalization for poorly controlled COPD within 12 weeks of screening	- Change from Baseline Trough in 24-hour Weighted-mean FEV_1 - Time to Onset - Change From Baseline in Trough FEV_1 Timepoint: 12 weeks

Observational Study			
Study (Author, Year)	**Study Design & Interventions**	**Included Population**	**Key Outcomes**
Stanford 2019[74]	Study Design: Retrospective database analysis using the Optum Research Database (ORD) Location: United States Interventions: 1) FF/VI 100/25 mcg QD 2) BUD/FOR 160/4.5 mcg	Inclusions: - ≥ 40 years of age - ≥ 1 COPD diagnosis code prior to or at index - Pharmacy claim for FF/VI (100/25) or BUD/FOR (160/4.5) - 12 months of continuous enrollment in health plan prior to index date (baseline period), and between 3 and 12 months of continuous enrollment following index date (follow-up) Exclusions: - Use of any ICS/LABA including FF/VI or BUD/FOR during the baseline period - Claims for both FF/VI and BUD/FOR on the index date	- COPD-related healthcare costs - Incidence/time to first mod/severe COPD-related exacerbations - Proportion of days covered (PDC) Timepoint: 12 months

ATS: American Thoracic Society, BD: twice daily, BUD/FOR: budesonide/formoterol, COPD: chronic obstructive pulmonary disorder, ERS: European Respiratory Society, FEV_1: forced expiratory volume in one second, FF/VI : fluticasone furoate/vilanterol, FVC: forced viral capacity, h: hour, ICS/LABA: inhaled corticosteroids/long-acting beta-agonists, mcg: micrograms, NHANES: The National Health and Nutrition Examination Survey, PDC: proportion of days covered, QD: once daily

Table D3.14. Baseline Characteristics – Breo Ellipta

Trial		**Dransfield 2014[68]**		**Agusti 2014[72]**		**Stanford 2019[74]**	
Arm		**FF/VI 100/25 mcg**	**FP/SAL 250/50 mcg**	**FF/VI 100/25 mcg**	**FP/SAL 500/50 mcg**	**FF/VI 100/25 mcg**	**BUD/FOR 160/4.5 mcg**
N		**931**	**927**	**266**	**262**	**4513**	**4513**
Age	**Mean (SD)**	61 (9)	61 (9)	63.0 (8.1)	62.9 (9.1)	69.2 (NR)	69.1 (NR)
	65+	NR	NR	NR	NR	NR	NR
Sex	**Male**	646 (69)	630 (68)	212 (80)	221 (84)	2100 (46.53)	2098 (46.49)
	Female	285 (31)	297 (32)	54 (20)	41 (16)	2413 (53.47)	2415 (53.51)
Race/Ethnicity	**White**	899 (97)	898 (97)	218 (82)	208 (79)	NR	NR
	Black/African American	31 (3.3)	27 (2.9)	0	1 (<1)	NR	NR
	Asian	NR	NR	48 (18)	53 (20)	NR	NR
	American Indian and Alaska native	1 (0.1)	1 (0.1)	NR	NR	NR	NR

Trial		Dransfield 2014[68]		Agusti 2014[72]		Stanford 2019[74]	
Arm		FF/VI 100/25 mcg	FP/SAL 250/50 mcg	FF/VI 100/25 mcg	FP/SAL 500/50 mcg	FF/VI 100/25 mcg	BUD/FOR 160/4.5 mcg
N		931	927	266	262	4513	4513
	Native Hawaiian and other pacific islander	NR	NR	NR	NR	NR	NR
	Hispanic	9 (1)	5 (0.5)	0	2 (<1)	NR	NR
Insurance Type	Medicare	NR	NR	NR	NR	3239 (71.77)	3239 (71.77)
	Commercial	NR	NR	NR	NR	NR	NR
Smoking status	Current Smoker	496 (53)	522 (56)	97 (37)	125 (47)	NR	NR
	Former smoker	NR	NR	165 (63)	141 (53)	NR	NR
Treatment History	ICS	NR	NR	NR	NR	456 (10.1)	452 (10.02)
	LABA	NR	NR	NR	NR	156 (3.46)	150 (3.32)
	LAMA	NR	NR	NR	NR	1367 (30.29)	1374 (30.45)
	OCS	NR	NR	NR	NR	2857 (63.31)	2841 (62.95)
	ICS/LABA	NR	NR	NR	NR	NR	NR
	LAMA/ LABA	NR	NR	NR	NR	70 (1.55)	66 (1.46)
Moderate Exacerbations in prior year, mean (SD)		NR	NR	NR	NR	NR	NR
Severe Exacerbations in prior year, mean (SD)		NR	NR	NR	NR	0.34 (NR)	0.34 (NR)
Post-BDR FEV_1, mean % (SD)		48 (12)	48 (12)	47.9 (11.5)	47.6 (11.9)	NR	NR
Current Asthma Diagnosis		0	0	0	0	1297 (28.74)	1298 (28.74)

Data are presented as n (%) unless otherwise specified.

BDR: bronchodilator, BUD: budesonide, FEV_1: forced expiratory volume in one second, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, ICS: inhaled corticosteroids, LABA: long-acting beta-agonist, LAMA: long-acting muscarinic agonist, mcg: micrograms, N: total number, n: number, NR: not reported, OCS: oral corticosteroid, SAL: salmeterol, SD: standard deviation, VI: vilanterol

Table D3.15. Efficacy Outcomes – Breo Ellipta

Trial		Dransfield 2014[68]		Agusti 2014[72]		Stanford 2019[74]	
Timepoint		12 weeks		12 weeks		12 months	
Arm		FF/VI 100/25 mcg	FP/SAL 250/50 mcg	FF/VI 100/25 mcg	FP/SAL 500/50 mcg	FF/VI 100/25 mcg	BUD/FOR 160/4.5 mcg
N		931	927	266	262	4513	4513
Moderate-Severe Exacerbations	N evaluated	931	927	266	262	NR	NR
	>1 exacerbation, n (%)	34 (4)	27 (3)	6 (2)	7 (3)	NR	NR
	Hazard Ratio (95%CI); p-value	NR	NR	NR	NR	reference	0.91 (0.85, 0.96); p<0.001
	Rate (SD)	NR	NR	NR	NR	0.26*	0.29*
	Rate Ratio (95%CI); p-value	NR	NR	NR	NR	IRR: 0.91; p=0.041	reference
SGRQ-C Total Score	N evaluated	NR	NR	266	262	NR	NR
	LS Mean CFB (SD)	NR	NR	-4.3 (11.8)	-3.0 (11.8)	NR	NR
	LSM difference (95%CI)	NR	NR	-1.3 (-3.5–0.8)	reference	NR	NR
EQ-5D VAS Score	N evaluated	NR	NR	243	246	NR	NR
	Mean (SD)	NR	NR	67.3 (15.9)	67.4 (16.9)	NR	NR
	Mean difference (SD)	NR	NR	4.2 (13.2)	2.8 (14.0)	NR	NR
Weighted mean (0-24 h) FEV_1, mL	N evaluated	931	927	266	262	NR	NR
	LS Mean CFB (95%CI)	162 (SE: 9)	122 (SE: 9)	130 (SD: 222)	108 (DS: 221)	NR	NR
	Mean difference (95%CI)	41 (17, 65); p<0.001	reference	22 (NR); p=0.282	reference	NR	NR
Rescue use, occasions over 24 h	N evaluated	500†	494†	254	256	NR	NR
	LS Mean CFB (SE)	-0.58 (0.06)	-0.52 (0.06)	-0.64 (0.08)	-0.58 (0.08)	NR	NR
	LS Mean difference (95%CI)	-0.06 (-0.19, 0.07); p=0.352	reference	-0.064 (-0.24, 0.11); p=0.478	reference	NR	NR
Oxygen used during treatment	N evaluated	931	927	NR	NR	NR	NR
	n (%)	22 (2.4)	13 (1.4)	NR	NR	NR	NR

*Mean incident (of any) exacerbations per 100-person days

†Data available for 2/3 studies

95%CI: 95 percent confidence interval, BUD: budesonide, CFB: change from baseline, FEV_1: forced expiratory volume in one second, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, IRR: incidence rate ratio, LS: least squares, mcg: micrograms, n: number, N: total number, NR: not reported, SAL: salmeterol, SD: standard deviation, SE: standard error, SGRQ-C: St. George's Respiratory Questionnaire for COPD, UMEC: umeclidinium, VI: vilanterol

Table D3.16. Safety Outcomes & Adherence – Breo Ellipta

Trial		**Dransfield 2014[68]**		**Agusti 2014[72]**		**Stanford 2019[74]**	
Arm		**FF/VI 100/25 mcg**	**FP/SAL 250/50 mcg BD**	**FF/VI 100/25 mcg**	**FP/SAL 500/50 mcg BD**	**FF/VI 100/25 mcg**	**BUD/FOR 160/4.5 mcg**
Timepoint		**12 weeks**		**12 weeks**		**12 months**	
N		**931**	**927**	**266**	**262**	**4513**	**4513**
Adverse Events	Any	250 (27)	261 (28)	73 (27)	68 (26)	NR	NR
	Serious	21 (2)	31 (3)	6 (2)	3 (1)	NR	NR
Treatment Discontinuations	Any	87 (9.3)	84 (9.1)	23 (9)	16 (6)	NR	NR
	Due to adverse events	23 (2.5)	24 (2.6)	6 (2)	3 (1)	NR	NR
Mortality	Any	NR	NR	0	0	NR	NR
	Due to adverse events	2 (<1)	4 (<1)	0	0	NR	NR
Pneumonia	Any	8 (<1)	4 (<1)	1 (<1)	2 (<1)	NR	NR
Cardiovascular events	Any	22 (2)	21 (2)	9 (3)	1 (<1)	NR	NR
Adherence	Proportion of days covered (PDC), mean (SD)	NR	NR	NR	NR	0.46 (0.31)	0.41 (0.29)
	PDC ≥ 0.8	NR	NR	NR	NR	1128 (25)	812 (18)

BD: twice daily, BUD: budesonide, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, mcg: micrograms, n: number, N: total number, NR: not reported, PDC: proportion of days covered, SAL: salmeterol, SD: standard deviation, VI: vilanterol

Table D3.17. Network Meta Analysis Inputs (Moderate to Severe Exacerbations)

Trial (Author, Year)	Treatment Arm (Dose)	Timepoint (Weeks)	N	Rate Ratio	Standard Error
Aaron 2017	FP/SAL + TIO (500/50 + 18 mcg)	52	145	0.85	0.14
	SAL + TIO (50 + 18 mcg)	52	148	1.09	0.13
	TIO (18 mcg)	52	156	NA	NA
Bansal 2021	FF/UMEC/VI (100/62.5/25 mcg)	12	400	0.59	0.23
	TIO (18 mcg)	12	400	NA	NA
Bremner 2018	FF/UMEC/VI (100/62.5/25 mcg)	24	527	0.83	0.11
	FF/VI + UMEC (100/25 + 62.5 mcg)	24	528	NA	NA
Chapman 2018	FP/SAL + TIO (500/50 + 18 mcg)	26	526	NA	NA
	GLY/IND (50/100 mcg)	26	527	1.08	0.13
Ferguson 2018	BUD/GLY/FOR (320/18/9.6 mcg)	24	639	NA	NA
	BUD/FOR (320/9.6 mcg)	24	314	1.22	0.18
	GLY/FOR (18/9.6 mcg)	24	625	2.08	0.14
Ferguson 2020 Study 207608	BUD/FOR + TIO (320/9 + 18 mcg)	12	363	NA	NA
	FF/UMEC/VI (100/62.5/25 mcg)	12	365	0.91	0.23
Ferguson 2020 Study 207609	BUD/FOR + TIO (320/9 + 18 mcg)	12	366	NA	NA
	FF/UMEC/VI (100/62.5/25 mcg)	12	366	1.07	0.20
Hanania 2012	FP/SAL + TIO (250/50 + 18 mcg)	24	173	0.86	0.33
	TIO (18 mcg)	24	169	NA	NA
Lipson 2017	BUD/FOR (320/9.6 mcg)	52	899	NA	NA
	FF/UMEC/VI (100/62.5/25 mcg)	52	911	0.65	0.14
Lipson 2018	FF/UMEC/VI (100/62.5/25 mcg)	52	4151	NA	NA
	FF/VI (100/25 mcg)	52	4134	1.18	0.03
	UMEC/VI (62.5/25 mcg)	52	2070	1.33	0.04
Papi 2018	BDP/FOR/GLY (100/6/10 mcg)	52	764	0.85	0.08
	GLY/IND (50/100 mcg)	52	768	NA	NA
Rabe 2020	BUD/FOR (320/9.6 mcg)	52	2131	1.15	0.05
	BUD/GLY/FOR (320/18/9.6 mcg)	52	2137	NA	NA
	GLY/FOR (18/9.6 mcg)	52	2120	1.32	0.05
Singh 2016	BDP/FOR (100/6 mcg)	52	680	NA	NA
	BDP/FOR/GLY (100/6/10 mcg)	52	687	0.77	0.09
Siler 2016 Study 116135*	FP/SAL + UMEC (250/50 + 125 mcg)	12	205	0.53	0.47
	FP/SAL + UMEC (250/50 + 62.5 mcg)	12	204	0.67	0.43

Trial (Author, Year)	Treatment Arm (Dose)	Timepoint (Weeks)	N	Rate Ratio	Standard Error
	FP/SAL (250/50 mcg)	12	205	NA	NA
Siler 2016 Study 116136*	FP/SAL + UMEC (250/50 + 125 mcg)	12	202	0.38	0.42
	FP/SAL + UMEC (250/50 + 62.5 mcg)	12	203	0.48	0.39
	FP/SAL (250/50 mcg)	12	201	NA	NA
Siler 2015 Study 200109	FF/VI + UMEC (100/25 + 125 mcg)	12	207	1.99	0.46
	FF/VI + UMEC (100/25 + 62.5 mcg)	12	206	0.86	0.56
	FF/VI (100/25 mcg)	12	206	NA	NA
Siler 2015 Study 200110	FF/VI + UMEC (100/25 + 125 mcg)	12	207	0.22	0.56
	FF/VI + UMEC (100/25 + 62.5 mcg)	12	206	0.34	0.47
	FF/VI (100/25 mcg)	12	206	NA	NA
Vestbo 2017	BDP/FOR + TIO (100/6 + 18 mcg)	52	537	0.79	*0.09*
	BDP/FOR/GLY (100/6/10 mcg)	52	1077	0.80	*0.07*
	TIO (18 mcg)	52	1076	NA	NA
Welte 2009	BUD/FOR + TIO (320/9 + 18 mcg)	12	329	0.38	*0.21*
	TIO (18 mcg)	12	331	NA	NA
Zheng 2021	BDP/FOR/GLY (100/6/10 mcg)	24	353	0.57	*0.15*
	BUD/FOR (160/4.5 mcg)	24	355	NA	NA

Italicized values are ICER calculated from raw data.

"/" denotes medication are taken together in a single inhaler, "+" denotes medication delivered from a separate inhaler.

*Not included in the NMA due to lack of connection to the network

95%CI: 95 percent confidence interval, BDP: beclomethasone dipropionate, BUD: budesonide, FF: fluticasone furoate, FP: fluticasone propionate, FOR: formoterol, GLY: glycopyrronium, IND: indacaterol, mcg: microgram, N: total number, NA: not applicable, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table D3.18. Network Meta Analysis Inputs (Discontinuation due to Adverse Events)

Trial (Author, Year)	Treatment Arm (Dose)	Timepoint (Weeks)	N	Responders, n (%)
Aaron 2017	FP/SAL + TIO (500/50 + 18 mcg)	52	145	8 (6)
	SAL + TIO (50 + 18 mcg)	52	148	6 (4)
	TIO (18 mcg)	52	156	8 (5)
Bansal 2021	FF/UMEC/VI (100/62.5/25 mcg)	12	400	7 (2)
	TIO (18 mcg)	12	400	3 (1)
Bremner 2018	FF/UMEC/VI (100/62.5/25 mcg)	24	527	21 (4)
	FF/VI + UMEC (100/25 + 62.5 mcg)	24	528	11 (2)
Chapman 2018	FP/SAL + TIO (500/50 + 18 mcg)	26	526	15 (3)
	GLY/IND (50/100 mcg)	26	527	17 (3)
Ferguson 2018	BUD/GLY/FOR (320/18/9.6 mcg)	24	639	30 (5)
	BUD/FOR (320/9.6 mcg)	24	314	11 (4)
	GLY/FOR (18/9.6 mcg)	24	625	30 (5)
Ferguson 2020 Study 207608	BUD/FOR + TIO (320/9 + 18 mcg)	12	363	8 (2)
	FF/UMEC/VI (100/62.5/25 mcg)	12	365	8 (2)
Ferguson 2020 Study 207609	BUD/FOR + TIO (320/9 + 18 mcg)	12	366	6 (2)
	FF/UMEC/VI (100/62.5/25 mcg)	12	366	2 (1)
Frith 2015	FP/SAL + GLY (500/50 + 50 mcg)	12	257	14 (5)
	FP/SAL + TIO (500/50 + 18 mcg)	12	258	17 (7)
	FP/SAL (500/50 mcg)	12	257	17 (7)
Hanania 2012	FP/SAL + TIO (250/50 + 18 mcg)	24	173	12 (7)
	TIO (18 mcg)	24	169	10 (6)
Lipson 2017	FF/UMEC/VI (100/62.5/25 mcg)	24	911	28 (3)
	BUD/FOR (320/9.6 mcg)	24	899	25 (3)
Lipson 2018	FF/UMEC/VI (100/62.5/25 mcg)	52	4151	252 (6)
	FF/VI (100/25 mcg)	52	4134	327 (8)
	UMEC/VI (62.5/25 mcg)	52	2070	187 (9)
Papi 2018	BDP/FOR/GLY (100/6/10 mcg)	52	764	37 (5)
	GLY/IND (50/100 mcg)	52	768	47 (6)
Rabe 2020	BUD/GLY/FOR (320/18/9.6 mcg)	52	2144	119 (6)
	GLY/FOR (18/9.6 mcg)	52	2125	146 (7)
	BUD/FOR (320/9.6 mcg)	52	2136	140 (7)
Singh 2016	BDP/FOR/GLY (100/6/10 mcg)	52	687	35 (5)

Trial (Author, Year)	Treatment Arm (Dose)	Timepoint (Weeks)	N	Responders, n (%)
	BDP/FOR (100/6 mcg)	52	680	33 (5)
Siler 2016 Study 116135*	FP/SAL + UMEC (250/50 + 125 mcg)	12	205	10 (5)
	FP/SAL + UMEC (250/50 + 62.5 mcg)	12	204	4 (2)
	FP/SAL (250/50 mcg)	12	205	6 (3)
Siler 2016 Study 116136*	FP/SAL + UMEC (250/50 + 125 mcg)	12	202	6 (3)
	FP/SAL + UMEC (250/50 + 62.5 mcg)	12	203	9 (4)
	FP/SAL (250/50 mcg)	12	201	12 (6)
Siler 2015 Study 200109	FF/VI + UMEC (100/25 + 125 mcg)	12	207	6 (3)
	FF/VI + UMEC (100/25 + 62.5 mcg)	12	206	3 (1)
	FF/VI (100/25 mcg)	12	207	5 (2)
Siler 2015 Study 200110	FF/VI + UMEC (100/25 + 125 mcg)	12	206	2 (1)
	FF/VI + UMEC (100/25 + 62.5 mcg)	12	207	7 (3)
	FF/VI (100/25 mcg)	12	206	9 (4)
Vestbo 2017	BDP/FOR + TIO (100/6 + 18 mcg)	52	537	15 (3)
	BDP/FOR/GLY (100/6/10 mcg)	52	1077	33 (3)
	TIO (18 mcg)	52	1076	62 (6)
Welte 2009	BUD/FOR + TIO (320/9 + 18 mcg)	12	329	8 (2)
	TIO (18 mcg)	12	331	10 (3)
Zheng 2021	BDP/FOR/GLY (100/6/10 mcg)	24	353	7 (2)
	BUD/FOR (160/4.5 mcg)	24	355	4 (1)

"/" denotes medication are taken together in a single inhaler, "+" denotes medication from a separate inhaler.

*Not included in the NMA due to lack of connection to the network

BDP: beclomethasone dipropionate, BUD: budesonide, FF: fluticasone furoate, FP: fluticasone propionate, FOR: formoterol, GLY: glycopyrronium, IND: indacaterol, mcg: microgram, n: number, N: total number, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table D3.19. Network Meta Analysis Inputs (SGRQ Total Score)

Study (Author, Year)	Treatment	Timepoint (Weeks)	N	Mean Total Score	Standard Error
Aaron 2017	FP/SAL + TIO (500/50 + 18 mcg)	52	145	-8.6	NA[†]
	SAL + TIO (50 + 18 mcg)	52	148	-6.3	NA[†]
	TIO (18 mcg)	52	154	-4.5	NA[†]
Bansal 2021	FF/UMEC/VI (100/62.5/25 mcg)	12	380	-5.8	0.65
	TIO (18 mcg)	12	386	-2.6	0.64
Bremner 2018	FF/UMEC/VI (100/62.5/25 mcg)	24	489	-5.84	0.59
	FF/VI + UMEC (100/25 + 62.5 mcg)	24	483	-4.94	0.59
Chapman 2018	FP/SAL + TIO (500/50 + 18 mcg)	26	526	-2.5	0.52
	GLY/IND (50/100 mcg)	26	527	-1	0.54
Ferguson 2018	BUD/GLY/FOR (320/18/9.6 mcg)	24	621	-7.5	0.47
	BUD/FOR (320/9.6 mcg)	24	298	-7.1	0.61
	GLY/FOR (18/9.6 mcg)	24	595	-6.3	0.47
Ferguson 2020 Study 207608	BUD/FOR + TIO (320/9.6 + 18 mcg)	12	344	-1.2	0.51
	FF/UMEC/VI (100/62.5/25 mcg)	12	342	-1.3	0.51
Ferguson 2020 Study 207609	BUD/FOR + TIO (320/9.6 + 18 mcg)	12	343	-1.5	0.55
	FF/UMEC/VI (100/62.5/25 mcg)	12	342	-1.5	0.55
Frith 2015	FP/SAL + GLY (500/50 + 50 mcg)	12	257	-2.81	0.67
	FP/SAL + TIO (500/50 + 18 mcg)	12	258	-3.90	0.68
	FP/SAL (500/50 mcg)	12	257	-0.65	0.69
Hanania 2012	FP/SAL + TIO (250/50 + 18 mcg)	24	173	NA	NA
	TIO (18 mcg)	24	169	NA	NA
Lipson 2017	FF/UMEC/VI (100/62.5/25 mcg)	52	846	-6.6	0.45
	BUD/FOR (320/9.6 mcg)	52	791	-4.3	0.46
Lipson 2018	FF/UMEC/VI (100/62.5/25 mcg)	52	3318	-5.5	0.23
	FF/VI (100/25 mcg)	52	3026	-3.7	0.24
	UMEC/VI (62.5/25 mcg)	52	1470	-3.7	0.35
Papi 2018	BDP/FOR/GLY (100/6/10 mcg)	52	760	-3.49	0.44
	GLY/IND (50/100 mcg)	52	763	-1.85	0.44
Rabe 2020	BUD/GLY/FOR (320/18/9.6 mcg)	52	1681	-6.4	0.35
	GLY/FOR (18/9.6 mcg)	52	1562	-4.5	0.36
	BUD/FOR (320/9.6 mcg)	52	1631	-4.9	0.36
Singh 2016	BDP/FOR/GLY (100/6/10 mcg)	12	559	-5.12	0.54

Study (Author, Year)	Treatment	Timepoint (Weeks)	N	Mean Total Score	Standard Error
	BDP/FOR (100/6 mcg)	12	532	-3.43	0.55
Siler 2016 Study 116135*	FP/SAL + UMEC (250/50 + 125 mcg)	12	205	-2.77	0.70
	FP/SAL + UMEC (250/50 + 62.5 mcg)	12	204	-3.57	0.70
	FP/SAL (250/50 mcg)	12	205	-2.26	0.70
Siler 2016 Study 116136*	FP/SAL + UMEC (250/50 + 125 mcg)	12	202	-4.54	0.70
	FP/SAL + UMEC (250/50 + 62.5 mcg)	12	203	-3.5	0.71
	FP/SAL (250/50 mcg)	12	201	-1.5	0.77
Siler 2015 Study 200109	FF/VI + UMEC (100/25 + 125 mcg)	12	194	-3.05	0.77
	FF/VI + UMEC (100/25 + 62.5 mcg)	12	186	-1.77	0.78
	FF/VI (100/25 mcg)	12	190	-2.23	0.69
Siler 2015 Study 200110	FF/VI + UMEC (100/25 + 125 mcg)	12	195	-1.56	0.70
	FF/VI + UMEC (100/25 + 62.5 mcg)	52	203	-1.04	0.70
	FF/VI (100/25 mcg)	52	192	0.59	0.59
Vestbo 2017	BDP/FOR/GLY (100/6/10 mcg)	52	899	-5.74	0.58
	BDP/FOR + TIO (100/6 + 18 mcg)	52	463	-7.32	0.61
	TIO (18 mcg)	52	860	-4.14	0.44
Zheng 2021	BDP/FOR/GLY (100/6/10 mcg)	12	351	*-3.4*	0.77
	BUD/FOR (160/4.5 mcg)	12	355	*-0.3*	0.77
Welte 2009	BUD/FOR + TIO (320/9.6 + 18 mcg)	24	329	-2.3	0.03
	TIO (18 mcg)	24	331	REF	REF

Italicized values are ICER calculated from raw data.

"/" denotes medication are taken together in a single inhaler, "+" denotes medication from a separate inhaler.

*Not included in the NMA due to lack of connection to the network

†For missing standard error data, we assumed the value based upon the largest standard error value from the trials of the same type of therapy (e.g., triple, dual, single) as the most conservative estimate of standard error.

BDP: beclomethasone dipropionate, BUD: budesonide, FF: fluticasone furoate, FP: fluticasone propionate, FOR: formoterol, GLY: glycopyrronium, IND: indacaterol, mcg: microgram, N: total number, NA: not applicable, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

D4. Ongoing Studies

We searched ClinicalTrials.gov for ongoing studies of Trelegy Ellipta and Breo Ellipta to identify evidence that would not be published during the timeline of our assessment but would be relevant to a future update. We did not identify any such trials of Trelegy Ellipta or Breo Ellipta whose study design would meet our inclusion criteria.

D5. Previous Systematic Reviews

We identified five network meta-analyses (NMAs) evaluating the efficacy of triple therapies including Trelegy Ellipta for the treatment of COPD. Their results are described below with an emphasis on two NMAs: Lee et al whose methodology we deemed to be strongest, and Ismaila et al whose results differed from the rest.[22,23] Table D5.1 compares the statistical significance of the estimates between Ismaila et al, Lee et al, and our NMA for rate of moderate to severe exacerbations. See the footnotes for frequently used abbreviations of triple therapy combinations used below. We also describe results from an additional meta-analysis on the association between adherence and exacerbations.[123]

Lee et al. (2021). "Comparisons of Efficacy and Safety between Triple (Inhaled Corticosteroid/Long-Acting Muscarinic Antagonist/Long-Acting Beta-Agonist) Therapies in Chronic Obstructive Pulmonary Disease: Systematic Review and Bayesian Network Meta-Analysis"[23]

Lee et al. conducted a systematic literature review and NMA to compare efficacy and safety of different combinations of ICS/LAMA/LABA in patients with moderate to very severe COPD. A Bayesian NMA using a random-effects model with heterogenous variance structure was conducted and included 21 studies relating to nine different triple therapies across 29,892 patients. Results of the NMA found no significant differences in the key assessed outcomes of total exacerbations and all-cause mortality. There were no significant differences in moderate to severe exacerbations, COPD-related mortality, or risk of major cardiovascular adverse events, but there were less data on these three outcomes. The risk of pneumonia was significantly lower with FP/SAL + GLY compared only to FP/SAL + TIO and FP/SAL + UMEC.

The lack of statistically significant differences between triple therapies is consistent with the findings of the updated NMA we performed for this review. See Table D5.1. Limitations highlighted in the review included heterogeneity of patient characteristics, eligibility criteria, and disease severity, but they were not statistically significant. The lack of data on moderate to severe exacerbations for some trials limited the number of comparisons. Finally, the majority of trials had durations shorter than 52 weeks.

Ismaila et al. (2022). "Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) Triple Therapy Compared with Other Therapies for the Treatment of COPD: A Network Meta-Analysis"[22]

Ismaila et al. conducted a systematic literature review (N trials=31) and NMA (N trials=23) as of October 2020 to evaluate the comparative efficacy of FF/UMEC/VI (100/62.5/25 mcg) and other triple and dual therapies in adults with COPD. Trials were mostly double-blinded and enrolled a total of 10,367 patients with a mean age of 61-68 years and variable COPD severity, exacerbation history, and smoking history. Outcomes included the annualized rate of moderate to severe exacerbations, SGRQ score, TDI score, rescue medication use, and adverse events, including withdrawals and pneumonia. A frequentist NMA was conducted using both fixed-effects and random-effects models. When a fixed-effects model was used, the results found favorable efficacy with FF/UMEC/VI single inhaler triple therapy versus LAMA/LABA, ICS/LABA, multiple inhaler triple therapy, and other single inhaler triple therapies. A statistically significant improvement in the rate of moderate to severe exacerbations for FF/UMEC/VI was reported compared with only one of nine evaluated interventions (BUD/GLY/FOR) across 17 trials, but the measure of heterogeneity was high (I^2 = 87%) suggesting that a fixed effects model was inappropriate. Greater improvements with FF/UMEC/VI versus other triple therapies were also reported for SGRQ score, TDI, and rescue medication use, although this was only statistically significant for rescue medication use. Safety outcomes were similar across treatments.

The results of this NMA differed from all five other NMAs including the NMA performed for this review and the NMA described above (Lee et al. 2021). Comparing findings between the three NMAs for rates of moderate to severe exacerbations, both the ICER NMA and Lee et al found no significant difference between the triple therapies while Ismaila et al. noted a statistically significant difference between FF/UMEC/VI and both doses of BUD/FOR/GLY. See Table D5.1. for this comparison. Limitations highlighted in the NMA (Ismaila et al. 2022) included heterogeneity in study design and inclusion/exclusion criteria and incomplete reporting of outcomes of interest in several trials reducing possible comparisons. A critique of the NMA highlighted the limitation of reporting of fixed effects results of the NMA despite high heterogeneity.[124]

Table D5.1. Rates of Moderate to Severe Exacerbations: FF/UMEC/VI versus Triple Therapies

FF/UMEC/VI versus:	ICER NMA RR (95% CrI)	Lee et al. 2021 OR (95% CrI)	Ismaila et al. 2022 IR Ratio (95% CI)
FF/VI + UMEC	non-significant	non-significant	non-significant
BUD/GLY/FOR (320/18/9.6 mcg)	non-significant	non-significant*	$p = 0.0044$
BUD/GLY/FOR (160/18/9.6 mcg)	non-significant		$p = 0.0034$
BDP/FOR/GLY	non-significant	non-significant	non-significant
BDP/FOR + TIO	non-significant	non-significant	non-significant
FF/VI + TIO	non-significant	NA†	non-significant
BUD/FOR + TIO	non-significant	NA†	non-significant
FP/SAL (250/50) + TIO	non-significant	non-significant*	non-significant
FP/SAL (500/50) + TIO	non-significant		non-significant
FP/UMEC/SAL	NA	NA†	NA
FP/GLY/SAL	NA	NA†	NA

*Lee et al 2021 merged the two doses of BUD/GLY/FOR and FP/SAL + TIO

†Triple therapy included in assessment, no data available

BDP: beclomethasone dipropionate, BUD: budesonide, CI: confidence interval, CrI: credible interval, FF: fluticasone furoate, FOR: formoterol fumarate, FP: fluticasone propionate, GLY: glycopyrronium, IR: incidence rate, NA: not assessed, OR: odds ratio, RR: relative risk, SAL: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Bourdin et al. (2021). "Efficacy and Safety of Budesonide/Glycopyrronium/Formoterol Fumarate versus Other Triple Combinations in COPD: A Systematic Literature Review and Network Meta-analysis"[20]

Bourdin et al. conducted a systematic literature review and NMA to compare BUD/GLY/FOR (320/18/9.6 mcg) with other triple therapies in patients with moderate to severe COPD. A three-level hierarchical Bayesian NMA prioritizing random-effects model was conducted. The NMA included 19 studies, 15 of which were double-blind RCTs, of 37,741 total patients assessing outcomes such as rate of moderate to severe exacerbations, change in SGRQ total score and proportion of responders, adverse events, and withdrawals over 24 and 52 weeks. The triple therapy BUD/GLY/FOR showed comparable reduction of moderate to severe exacerbations to FF/UMEC/VI and BDP/GLY/FOR fixed-dose combinations, and six additional open triple combinations. BUD/GLY/FOR was comparable in improvement in SGRQ total score and responders with five and three other evaluable triple combinations, respectively, up to 52 weeks. Overall withdrawals and those due to adverse events were also comparable between BUD/GLY/FOR and five evaluable triple therapies. Limitations of the NMA included consolidation of LAMA/LABA combinations into a single node to resolve disconnection in the network reducing intra-class difference, although literature suggests these combinations should not be different. Included studies also differed in study design and patient characteristics; meta-regression and sensitivity analyses were conducted to explore heterogeneity in study design (double-blind vs. open-label trials), baseline exacerbation history, and trial duration. Sensitivity analysis findings were broadly in line with the base-case results.

Ferguson et al. (2020). "Efficacy of Budesonide/Glycopyrronium/Formoterol Fumarate Metered Dose Inhaler (BGF MDI) Versus Other Inhaled Corticosteroid/Long-Acting Muscarinic Antagonist/ Long-Acting b2-Agonist (ICS/LAMA/LABA) Triple Combinations in COPD: A Systematic Literature Review and Network Meta-analysis"[37]

Ferguson et al is a prior iteration of Bourdin et al. not including the ETHOS trial of BUD/GLY/FOR. The findings of Bourdin et al. are consistent with Ferguson et al. showing all fixed-dose and open combinations are to be comparable in reducing exacerbation rates and lung function over 24 weeks.

Rogliani et al. (2022). "Comparing the Efficacy and Safety Profile of Triple Fixed-Dose Combinations in COPD: A Meta-Analysis and IBiS Score"[51]

Rogliani et al conducted a Bayesian NMA of four trials of four fixed-dose triple therapies (FF/UMEC/VI, BUD/GLY/FOR 320/18/9.6 mcg, BUD/GLY/FOR 160/18/9.6 mcg, BDP/FOR/GLY) in 21,809 patients with COPD assessing comparability in the risk of moderate to severe exacerbations, change from baseline in SGRQ, transition dyspnea index, trough FEV_1, and safety. Results of the NMA indicated no significant differences ($p>0.05$) among the triple therapies for any assessed efficacy or safety outcome.

Vauterin et al. (2024). "Medication adherence to inhalation therapy and the risk of COPD exacerbations: a systematic review with meta-analysis"[123]

Vauterin et al. conducted a systematic literature and meta-analysis to investigate the association between adherence and exacerbations in patients with COPD. Five observational studies of adult patients with COPD treated with single, dual, or triple therapy and reporting on adherence and exacerbations were included. Results show that approximately 30% of patients with COPD had good adherence. Poor adherence was found to be significantly associated with higher risk of COPD exacerbation (odds ratio: 1.40; 95% CI: 1.21, 1.62; I^2 = 85%). Limitations included lack of analyses conducted by class of medication and the inclusion of a small number of studies including only one study on triple therapy.

D6. Heterogeneity and Subgroups

We sought data from randomized controlled trials and observational studies for the following subgroups of interest: individuals with disabilities, those with end-stage renal disease (ESRD), those with terminal illness, or Medicare-aged population (≥65 years). No data were reported on individuals with disabilities, those with end-stage renal disease (ESRD), and those with terminal illness subgroups for Trelegy Ellipta or Breo Ellipta.

Medicare-Aged Population (≥65 years)

While no data were available for the subgroup of individuals 65 years of age or older in the clinical trials, four observational studies comparing Trelegy Ellipta with any SITT or MITTs reported data on this subgroup. An observational study (Bogart et al 2024)[60] assessed the efficacy of initiating Trelegy Ellipta or multiple inhaler triple therapy (MITT) in a population of adults 40 years of age or above enrolled in Medicare Advantage with Part D. Mannino et al 2024[58] assessed the efficacy of initiating Trelegy Ellipta or budesonide/glycopyrronium/ formoterol (BUD/GLY/FOR) in patients 40 years of age or above enrolled in the Medicare Fee-For-Service (FFS) program. More than a quarter of the Trelegy Ellipta and BUD/GLY/FOR cohort populations had Medicare Advantage insurance in another claims-based study.[59] An observational study of Trelegy Ellipta initiators (Hanania et al 2023)[64] included patients enrolled in either Medicare Advantage with Part D or commercial insurance, with the former making up 88% of included patients. These studies are described in the main report, Section 3.2 and in the supplement, Section D2.1.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	X	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[125]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Therefore, the evLY complies with the law as described in the Inflation Reduction Act, as described in our public comment letter to CMS regarding its initial program guidance.[126] Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[127]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Detailed Methods Overview

We developed a decision analytic model leveraging ICER's assessment of ensifentrine in COPD and informed by key clinical trials and prior relevant economic models.[1] Costs and outcomes were discounted at 3% per year.

The model focused on an intention-to-treat analysis, with a hypothetical cohort of patients entering the model with at least moderate COPD being treated with triple therapy or dual therapy. Model cycle length was monthly, in line with clinical and adherence data, and a lifetime time horizon was used.

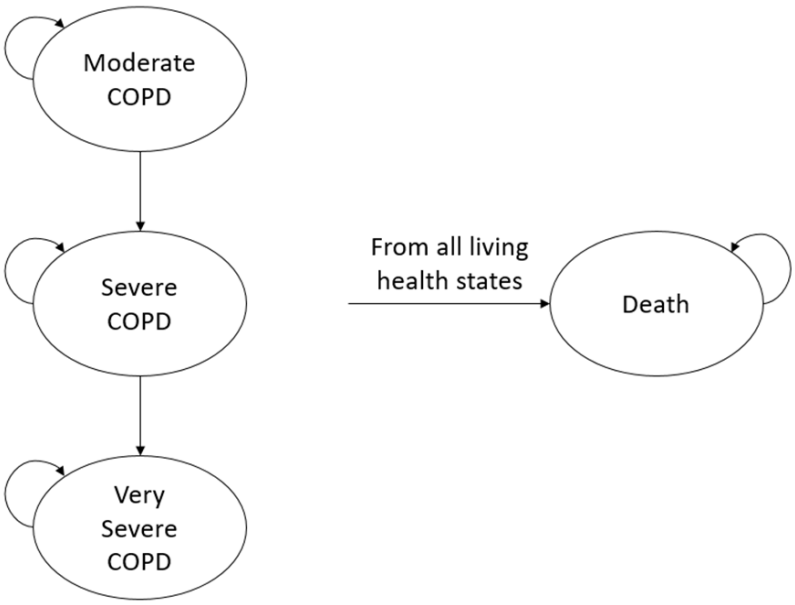
The model had four primary health states (Figure E1.1.), including three health states defined by COPD severity based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification and a fourth health state defined by death.[2,3] Members of the modeled cohort only transitioned to more severe health states, and within each severity stage, exacerbations were tracked as events. Exacerbations were defined based on the health care utilization required.[4] A moderate exacerbation was defined as an exacerbation that led to a prescription of a corticosteroid and/or an antibiotic but did not result in a hospitalization, and a severe exacerbation was defined as

an exacerbation that led to a hospitalization for COPD. Exacerbations impacted mortality, quality of life, and costs.[4]

Patients stayed on their treatment based on monthly persistence rates from identified literature.[5-7]

Patients remained in the model until they died. All patients transitioned to death from all cause or COPD-specific mortality from any of the alive health states.

Figure E1.1. Model Schematic



Each living health state included a potential for an exacerbation event, with different probabilities of exacerbation by COPD severity and treatment.

E2 Key Model Choices and Assumptions

Our model included several assumptions stated in Table E2.1.

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Table E2.1. Key Model Assumptions

Assumption	Rationale
Members of the modeled cohort only transitioned to more severe health states.	COPD is a progressive disease with irreversible effects on lung function.
The COPD medications included in the model did not affect health state transition probabilities between the COPD severity health states.	None of the COPD medications were expected to be disease-modifying, thus they were not modeled to impact disease progression.
Transition probabilities between COPD severity states did not differ by age, but they depended on smoking status.	In past economic models that incorporated age and smoking status into disease progression estimations, age had not been significant, but smoking cessation was.[4,8]
The same AE rates were used among all triple therapies and among all LABA/ICS dual therapies.	Prior clinical trials and systematic reviews have shown adverse events were similar among triple therapies and among dual therapies.[9,10]
Among triple therapy users, those who discontinue due to an AE switched to a LAMA/LABA.	The GOLD guidelines cite studies that showed ICS use had excess AE risk and among dual therapies, the guidelines recommend a LAMA/LABA combination. [2,11]
Among dual therapy users, those who discontinue due to an AE switched to tiotropium	Tiotropium may be more convenient than some LABAs with its once daily dosing and in a meta-analysis, LAMA showed better efficacy than LABA for moderate to severe exacerbations.[9]
Patients who discontinued for any reason other than an AE switched to no treatment	Patients who cannot persist with the convenience of a single inhaler therapy are likely to find other single or multi-inhaler regimens equally or more challenging, thus avoiding treatment altogether.

Breo Ellipta

Table E2.2. Key Model Assumptions

Assumption	Rationale
Members of the modeled cohort only transitioned to more severe health states.	COPD is a progressive disease with irreversible effects on lung function.
The COPD medications included in the model did not affect health state transition probabilities between the COPD severity health states.	None of the COPD medications were expected to be disease-modifying, thus they were not modeled to impact disease progression.
Transition probabilities between COPD severity states did not differ by age, but they depended on smoking status.	In past economic models that incorporated age and smoking status into disease progression estimations, age had not been significant, but smoking cessation was.[4,8]
Among triple therapy users, those who discontinue due to an AE switched to a LAMA/LABA.	The GOLD guidelines cite studies that showed ICS use had excess AE risk and among dual therapies, the guidelines recommend a LAMA/LABA combination. [2,11]
Among dual therapy users, those who discontinue due to an AE switched to tiotropium	Tiotropium may be more convenient than some LABAs with its once daily dosing and in a meta-analysis, LAMA showed better efficacy than LABA for moderate to severe exacerbations.[9]
Patients who discontinued for any reason other than an AE switched to no treatment	Patients who cannot persist with the convenience of a single inhaler therapy are likely to find other single or multi-inhaler regimens equally or more challenging, thus avoiding treatment altogether.

Target Population

The population of focus for the economic evaluation included adult patients who reflected the Medicare population with at least moderate COPD at baseline. Table E2.2. reports the baseline population characteristics that defined the cohort at the start of the model.

Table E2.3. Baseline Population Characteristics

	Value	Source
Mean Age, Years	67	Pace et al., 2022[12]
Female, %	56.4%	Pace et al., 2022[12]
Moderate COPD* at Baseline, %	78.1%	Mannino et al., 2022[13]
Severe COPD† at Baseline, %	21.9%	Mannino et al., 2022[13]
Current Smokers, %	41.2%	Pace et al., 2022[12]

COPD: chronic obstructive pulmonary disease

*Defined as an FEV_1 of 50%-79%, GOLD 2

†Defined as an FEV_1 of 30% to 49%, GOLD 3

Treatment Strategies

Trelegy Ellipta

The list of interventions was developed based on the expectation of inclusion and with input from patient organizations, clinicians, manufacturers, and payers and includes[14]:

Triple therapy

- FF/UMEC/VI (Trelegy Ellipta®)

Breo Ellipta

The list of interventions was developed based on the expectation of inclusion and with input from patient organizations, clinicians, manufacturers, and payers and includes[14]:

Dual therapy

- FF/VI (Breo Ellipta®)

Comparators

Trelegy Ellipta

The comparator(s) for these interventions were:
Triple therapy

- Budesonide/formoterol fumarate (BUD/FOR) (Symbicort®) in combination with tiotropium (TIO) (Spiriva®)
- Fluticasone propionate/salmeterol xinafoate (FP/SALM) (Advair Diskus®) in combination with TIO (Spiriva®)
- Fluticasone furoate/vilaneterol (Breo Ellipta®) in combination with TIO (Spiriva®)

Breo Ellipta

The comparator(s) for these interventions were:
Dual therapy

- BUD/FOR (Symbicort®)
- FP/SALM (Advair Diskus®)

E3. Model Inputs and Assumptions

Model Inputs

Clinical Inputs

The clinical inputs for this model included inputs specific to COPD disease progression, exacerbations, mortality, discontinuation, adverse events, and smoking cessation.

Table E3.1. Monthly Transition Probabilities

Smoking Status	Moderate COPD* to Severe COPD†	Severe COPD† to Very Severe COPD‡	Source	Notes
Non Smoker / Past Smoker	0.60%	0.52%	Atsou et al., 2011 [15]	Average of the transition probabilities between age 67 and 100 to align with the ages of the modeled population
Current Smoker	0.99%	0.82%		

*Defined as an FEV_1 of 50%-79%, GOLD 2
†Defined as an FEV1 of 30% to 49%, GOLD 3
‡Defined as an FEV_1 of less than 30%, GOLD 4

Clinical Probabilities/Response to Treatment

COPD disease progression was modeled by way of transitioning to more severe health states in the economic model. Table E3.1. reports the transition probabilities between each of the alive health states. These transition probabilities were conditioned on a member of the modeled cohort not dying within the cycle. Transition probabilities were not age-adjusted but were dependent on smoking status and disease severity.

Exacerbations

Within each of the alive health states, the frequency and severity of exacerbations were tracked as events. Exacerbations were defined using an event-based definition based on the health care utilization required.[4] A moderate exacerbation was defined as an exacerbation that led to a prescription of a corticosteroid +/- an antibiotic but did not result in a hospitalization, and a severe exacerbation was defined as an exacerbation that led to a hospitalization for COPD.[4] Subsequent sections of this model analysis plan describe how exacerbations impacted mortality, quality of life, and costs.

Table E3.2. reports the exacerbation parameters that were used in the economic model for single therapy alone, including the total number of exacerbations per model cycle and the severity distribution of the exacerbations, stratified by health state. These estimates were derived from a systematic literature review that included randomized controlled trials and cohort studies that assessed a basket of interventions including self-management, single, and dual therapies.[16] Since most of the interventions in the studies involved single therapies, including tiotropium, we assumed that the monthly exacerbation rates in Table E3.2 reflected those for patients on tiotropium.

Table E3.2. Exacerbation Parameters, Single Therapy Alone

Health State	Exacerbations[§] per Month[4,16]	Severe Exacerbations per Month[#]	Moderate Exacerbations per Month[¤]	Notes
Moderate COPD[*]	0.10 (0.09, 0.11)	0.01	0.09	The proportion of total exacerbations that were severe were assumed to be 7%, 18%, and 33% in GOLD Stage 2, 3, and 4, respectively.[17]
Severe COPD[†]	0.13 (0.12, 0.15)	0.02	0.11	
Very Severe COPD[‡]	0.18 (0.16, 0.19)	0.06	0.12	

*Defined as an FEV_1 of 50%-79%, GOLD 2

†Defined as an FEV1 of 30% to 49%, GOLD 3

‡Defined as an FEV1 of less than 30%, GOLD 4

[§]Either a moderate to severe exacerbation.

[#]A severe exacerbation is defined as an exacerbation leading to a hospitalization for COPD.

[¤]A moderate exacerbation is defined as an exacerbation leading to a prescription of systemic corticosteroids +/- antibiotics.

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Table E3.3. reports the exacerbation rate ratios for triple therapy, dual therapy, and no treatment compared to single therapy. ICER conducted a network meta-analysis (NMA) focused on the efficacy of triple therapy in double-blinded clinical trials that explicitly did not capture differences in outcomes due to improved adherence with single inhaler therapy versus multiple inhaler therapy. Additionally, ICER highlighted a Cochrane NMA focused on efficacy outcomes for dual therapies that found no differences between combination ICS/LABA inhalers.[4] Based on ICER's analyses, we assumed that there were no differences in efficacy among the triple therapies and among the dual therapies (ICS/LABA) under consideration in this review when used as prescribed, with variations in outcomes likely due to other factors such as adherence/discontinuation rather than the therapies themselves.[9] As a result, a single treatment effect on total exacerbations was applied to the triple and dual therapies as shown in Table E3.3. The percentages of total exacerbations that were severe versus moderate were the same for all interventions.

Table E3.3. Interventions and Comparators Treatment Effect Against Single Therapy

Treatment	Exacerbation Rate Ratio	Source / Notes
Triple Therapy	0.70 (95% CrI: 0.56, 0.85)	From ICER's NMA of trial data
Dual Therapy (ICS/LABA)	0.95 (95% CrI: 0.75, 1.18)	From ICER's NMA of trial data
Dual Therapy (LAMA/LABA)	0.99 (95% CI: 0.76, 1.25)*	Cochrane Review network meta-analysis[9]
No Treatment	1.14 (95% CI: 1.08, 1.20)*	Cochrane Review meta-analysis[18]

CI: confidence interval; CrI: credible interval; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist

*Odds ratio converted to relative risk assuming baseline exacerbation risk of 45%[19]

Breo Ellipta

Table E3.4. reports the exacerbation rate ratios for dual therapy and no treatment compared to single therapy. ICER conducted a network meta-analysis (NMA) focused on the efficacy of dual therapy, specifically ICS/LABA, in double-blinded clinical trials and did not explicitly capture differences in outcomes due to improved adherence with single inhaler therapy versus multiple inhaler therapy. Based on ICER's NMA, we assumed that there were no differences in efficacy among the dual therapies (ICS/LABA) under consideration in this review, with most variations in outcomes likely due to other factors such as discontinuation rather than the therapies themselves.[9] As a result, a single treatment effect on total exacerbations was applied to the dual therapies as shown in Table E3.4. The percentages of total exacerbations that were severe versus moderate were the same for all interventions.

Table E3.4. Interventions and Comparators Treatment Effect Against Single Therapy

Treatment	Exacerbation Rate Ratio	Source / Notes
Dual Therapy (ICS/LABA)	0.96 (95% CrI: 0.76, 1.18)	From ICER's NMA of trial data
Dual Therapy (LAMA/LABA)	0.98 (95% CI: 0.85, 1.11)*	Cochrane Review network meta-analysis[9]
No Treatment	1.14 (95% CI: 1.08, 1.20)*	Cochrane Review meta-analysis[18]

CI: confidence interval; CrI: credible interval; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist

*Odds ratio converted to relative risk assuming baseline exacerbation risk of 45%[19]

Discontinuation

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We assumed treatment discontinuation rates due to AE were the same across all triple therapies and all dual therapies,[9,10] and these rates were informed from the clinical trials of FF/UMEC/VI and FF/VI (Table E3.5.). For triple therapies, the discontinuation rates due to AE for FF/UMEC/VI were aggregated across six Phase 3-4 trials and adjusted for varying trial duration. These were then

transformed to a monthly probability to fit the model cycle with the calculated monthly treatment discontinuation probability due to AE resulting in 0.411%. A similar process was done for dual therapies across seven trials with the resultant monthly treatment discontinuation probability due to AE being 0.751%.

Table E3.5. Discontinuation Due to Adverse Event

Intervention	Trial	Trial Duration	Sample Size	Number (%) discontinued	Phase
FF/UMEC/VI	IMPACT (NCT02164513)	52 weeks	4151	249 (6.00%)	3
FF/UMEC/VI	FULFIL (NCT02345161)	52 weeks	911	34 (3.73%)	3
FF/UMEC/VI	NCT01957163	12 weeks	206	2 (0.97%)	3
FF/UMEC/VI	NCT02119286	12 weeks	206	7 (3.40%)	3
FF/UMEC/VI	NCT03478683	12 weeks	363	8 (2.20%)	4
FF/UMEC/VI	NCT03478696	12 weeks	366	2 (0.55%)	4

FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol

All-cause discontinuation rates were derived from Kaplan-Meier (KM) persistence curves from claims-based real-world studies, which defined discontinuation as a gap in prescription drug claims lasting ≥30 days for triple and dual therapies and ≥60 days for single therapies.[5-7] The KM persistence curves were digitized and extrapolated based on the best fitting parametric curve (exponential, weibull, log logistic, or log normal). The log normal distributions were applied to estimate treatment discontinuation over the patient's lifetime.

To estimate discontinuation for reasons other than AEs, we subtracted the monthly rates of discontinuation due to AEs from the all-cause discontinuation rates.

In the study used for multi-inhaler triple therapies, discontinuation was defined as a lack of persistence with any component of the treatment regimen.[6] For all other single, dual, and triple therapies administered by a single inhaler, discontinuation was defined as a lack of persistence with the inhaler of interest. Subsequent treatment, if any, was based on the reason for discontinuation. Patients on triple therapy who discontinue due to AE were assumed to transition to treatment with a LAMA/LABA, while patients on dual therapy who discontinue due to AE were assumed to transition to tiotropium. When patients discontinue treatment for reasons other than AE, we assumed they no longer use any treatment.

Breo Ellipta

We assumed treatment discontinuation rates due to AE were the same across all dual therapies[9,10], and these rates were informed from the clinical trials of FF/VI (Table E3.6.). For dual therapies, the discontinuation rates due to AE for FF/VI were aggregated across seven Phase III trials and adjusted

for varying trial duration. These were then transformed to a monthly probability to fit the model cycle with the calculated monthly treatment discontinuation probability due to AE resulting in 0.751%.

Table E3.6. Discontinuation Due to Adverse Event

Intervention	Trial	Trial Duration	Sample Size	Number (%) Discontinued	Phase
FF/VI	IMPACT (NCT02164513)	52 weeks	4134	325 (7.86%)	3
FF/VI	NCT01957163	52 weeks	206	5 (2.43%)	3
FF/VI	NCT02119286	12 weeks	206	9 (4.37%)	3
FF/VI	NCT01009463	52 weeks	403	29 (7.20%)	3
FF/VI	NCT01017952	52 weeks	403	35 (8.68%)	3
FF/VI	NCT01053988	24 weeks	206	14 (6.80%)	3
FF/VI	NCT01054885	24 weeks	205	19 (9.27%)	3

FF: fluticasone furoate; VI: vilanterol

All-cause discontinuation rates were derived from Kaplan-Meier (KM) persistence curves from claims-based real-world studies, which defined discontinuation as a gap in prescription drug claims lasting ≥30 days for triple and dual therapies and ≥60 days for single therapies.[128,129] The KM persistence curves were digitized and extrapolated based on the best fitting parametric curve (exponential, weibull, log logistic, or log normal). The log normal distributions were applied to estimate treatment discontinuation over the patient's lifetime.

To estimate discontinuation for reasons other than AEs, we subtracted the monthly rates of discontinuation due to AEs from the all-cause discontinuation rates.

No literature specifically assessing persistence with FF/VI in COPD populations was identified. However, we found a study comparing FF/VI to BUD/FOR in asthma patients, which reported a HR for discontinuation.[130] Considering the differences in disease characteristics and how treatments are used between COPD and asthma, we determined that the KM curves from the asthma population were not suitable for direct use in our base-case analysis. Instead, we used the HR for discontinuation of FF/VI compared to BUD/FOR from the asthma study and applied it to the digitized dual-therapy persistence KM curve in COPD patients. This approach allowed us to approximate FF/VI discontinuation in a COPD population while maintaining the relative impact of once-daily (QD) versus twice-daily (BID) dosing observed in the asthma population.

For all other single and dual therapies administered by a single inhaler, discontinuation was defined as a lack of persistence with the inhaler of interest. Subsequent treatment, if any, was based on the reason for discontinuation. Patients on dual therapy who discontinue due to AE were assumed to transition to tiotropium. When patients discontinue treatment for reasons other than AE, we assumed they no longer use any treatment.

Adverse Events

Adverse events associated with each of the COPD treatment regimens only impacted discontinuation. No costs or consequences were assigned to any specific adverse event.

Mortality

All patients could have transitioned to the death health state due to all-cause mortality, COPD-attributable mortality not due to an exacerbation, and exacerbation-related mortality. All-cause mortality was sourced from age- and sex-adjusted actuarial life tables.[20]

Standardized mortality ratios for patients with COPD not due to exacerbations were applied to the all-cause mortality. Table E3.7. reports these standardized mortality ratios stratified by health state.

Table E3.7. COPD Standardized Mortality Ratios

Health State	Standardized Mortality Ratio	Source	Notes
Moderate COPD*	1.6	Atsou et al., 2011[15]	Applied to age- and sex-adjusted all-cause mortality
Severe COPD†	1.9		
Very Severe COPD‡	1.9		

*Defined as an FEV_1 of 50%-79%, GOLD 2
†Defined as an FEV1 of 30% to 49%, GOLD 3
‡Defined as an FEV_1 of less than 30%, GOLD 4

Severe exacerbations were associated with an additional risk of mortality. The case-fatality rate per severe exacerbation was modeled as 15.6% (10.2%-21.9%).[4]

Smoking Cessation

Because the transition probabilities for disease progression were dependent on smoking status, smoking status was tracked in the model. The percentage of the cohort that were current smokers at baseline is described in Table E3.1. During each model cycle, a current smoker had a 0.76% probability of smoking cessation.[21] Successful smoking cessation was defined as more than 6 months without smoking a cigarette. Literature suggests that 22% of individuals that had stopped smoking for 182 days will resume smoking.[22] Therefore, we modeled that 0.59% (0.76% * (100%-22%)) of the cohort would permanently stop smoking each model cycle.

Utilities

Health state utility estimates are reported in Table E3.8. These utility values were derived from a study of 1,235 patients with COPD from 13 countries that were enrolled in a clinical trial that assessed tiotropium. Patients completed the EQ-5D-3L at baseline and the US value set based on time-tradeoff was used. The UK value set of the utilities from this study were used in prior

economic models and in ICER's assessment of ensifentrine for COPD. [1,4,23] The UK value set was used as a scenario analysis.

Table E3.8. Health State Utility Values

Health State	Utility	Source/Notes	Notes
Moderate COPD*	0.832 (0.821, 0.843)	Rutten-van Mölken et al. 2006[23]	Elicited using the US value set for the EQ-5D-3L from patients with COPD
Severe COPD †	0.803 (0.790, 0.816)	-	-
Very Severe COPD‡	0.731 (0.699, 0.762)	-	-

COPD: chronic obstructive pulmonary disease

*Defined as an FEV_1 *of 50%-79%, GOLD 2*

†Defined as an FEV1 of 30% to 49%, GOLD 3

‡Defined as an FEV_1 of less than 30%, GOLD 4

Exacerbations resulted in a disutility for the duration of one model cycle. The disutility estimation followed a similar approach to prior studies but restricted the time period to calculate the disutility from the start of the exacerbation until return to baseline.[4,24,25] This resulted in a disutility of 0.008 for moderate exacerbations and 0.085 for severe exacerbations. Applying these disutilities resulted in health impact losses of -0.0015 and -0.034 for each moderate and severe exacerbation, respectively. The disutilities per exacerbation are presented in Table E3.9.

Table E3.9. Disutility Values

Event	Disutility	Source	Notes
Moderate Exacerbation*	-0.008	Hoogendoorn et al. 2011[4], Goossens et al. 2008[24], O'Reilly et al. 2007[25]	The disutility for a moderate exacerbation was derived based on a 42 day period by Goossens et al., while the disutility for a severe exacerbation was calculated using a 146 day period from O'Reilly et al. [24,25]
Severe Exacerbation†	-0.085	-	-

*A moderate exacerbation was defined as an exacerbation leading to a prescription of systemic corticosteroids +/- antibiotics.

†A severe exacerbation was defined as an exacerbation leading to a hospitalization for COPD.

Economic Inputs

All costs used in the model were updated to 2024 dollars.

Drug Acquisition Costs

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For branded COPD medication costs, we used net pricing estimates based on the median WAC from Red Book (across all applicable formulations) and the Medicare-specific rebate benchmark estimate reported by IPD Analytics Rebate Monitor.[131] For all generic COPD medication costs, we used the median WAC across all generic versions and no separate net price was calculated. Drug costs are presented in Table E3.10.

Table E3.10. Drug Cost Inputs

Drug	WAC per Dose	Discount from WAC* (if applicable)	Net Price per Dose	Net Price per Year (if applicable)
Tiotropium Bromide	$15.36 (18 mcg)	NA	$15.36	$5,607
BUD / FOR	$3.64 (160mcg/4.5 mcg)	NA	$3.64	$2,662
FP / SAL	$1.94 (250mcg/50mcg)	NA	$1.94	$1,417
FF / VI (Authorized Generic)	$8.32 (100mcg/25mcg)	NA	$8.32	$4,955
FF / VI (Breo Ellipta®)	$13.57 (100mcg/25mcg)	62.5%	$5.09	$1,858
FF / UMEC / VI	$21.92 (100mcg/62.5mcg/25mcg)	52.5%	$10.41	$3,800

BUD: budesonide; FF: fluticasone furoate; FOR: formoterol; FP: fluticasone propionate; mcg: microgram; SAL: salmterol; UMEC: umeclidinium; VI: vilanterol; WAC: wholesale acquisition cost
*Medicare-specific rebate benchmark estimate reported by IPD Analytics Rebate Monitor.[131]

Breo Ellipta

For branded COPD medication costs, we used net pricing estimates based on the median WAC from Red Book (across all applicable formulations) and the Medicare-specific rebate benchmark estimate reported by IPD Analytics Rebate Monitor.[131]. For all generic COPD medication costs, we used the median WAC across all generic versions and no separate net price was calculated. Drug costs are presented in Table E3.11.

Table E3.11. Drug Cost Inputs

Drug	WAC per Dose	Discount from WAC* (if applicable)	Net Price per Dose	Net Price per Year (if applicable)
Tiotropium Bromide	$15.36 (18 mcg)	NA	$15.36	$5,607
BUD / FOR	$3.64 (160mcg/4.5 mcg)	NA	$3.64	$2,662
FP / SAL	$1.94 (250mcg/50mcg)	NA	$1.94	$1,417
FF / VI (Authorized Generic)	$8.32 (100mcg/25mcg)	NA	$8.32	$4,955
FF / VI (Breo Ellipta®)	$13.57 (100mcg/25mcg)	62.5%	$5.09	$1,858

BUD: budesonide; FF: fluticasone furoate; FOR: formoterol; FP: fluticasone propionate; mcg: microgram; SAL: salmterol; UMEC: umeclidinium; VI: vilanterol; WAC: wholesale acquisition cost

*Medicare-specific rebate benchmark estimate reported by IPD Analytics Rebate Monitor.[131]

Administration and Monitoring Costs

Administration and monitoring costs were not included, as the treatments are self-administered in a home setting.

Health Care Utilization Costs

Table E3.12. reports the health state costs that were used in the economic model. These costs include COPD-related health care utilization costs excluding emergency department, inpatient, and pharmacy costs as those costs are included elsewhere in the model. The pharmacy costs are included in the drug costs detailed in the section above and the emergency department and inpatient costs are assumed to be included in the exacerbation-related costs detailed in the section below. The COPD-specific health state costs in Table 5.12 were added on to gender- and age-specific future unrelated health care costs were incorporated.[26]

Table E3.12. Health State Costs

Health State	Monthly Cost	Source	Notes
Moderate COPD*	$134	Wallace et al., 2019[27]	Inflated from 2015 US dollars to 2024 US dollars
Severe COPD†	$239		
Very Severe COPD‡	$306		
Future Unrelated Health Care Costs (background health care costs)	Varies by age and gender	Jiao et al. 2021[26]	-

*Defined as an FEV_1 of 50%-79%, GOLD 2

†Defined as an FEV1 of 30% to 49%, GOLD 3

‡Defined as an FEV_1 of less than 30%, GOLD 4

Exacerbation Costs

Table E3.13. reports the costs associated with a moderate and a severe exacerbation.

Table E3.13. Exacerbation Costs

Exacerbation Severity	Cost per Event	Source	Notes
Moderate Exacerbation*	$2,488	Bogart et al., 2020[28]	Inflated from 2017 US dollars to 2024 US dollars
Severe Exacerbation†	$26,844		

*A moderate exacerbation was defined as an exacerbation leading to a prescription of systemic corticosteroids +/- antibiotics.

†A severe exacerbation was defined as an exacerbation leading to a hospitalization for COPD.

Productivity Costs

We modeled a loss in productivity associated with each exacerbation. Each exacerbation was associated with 106 hours of lost productivity.[29] Lost productivity time was monetized using an average hourly wage of $35.36 as reported by the Bureau of Labor Statistics.[30]

Caregiver Costs

On average, caregivers of patients with COPD provide 20 hours of care per week.[31] This estimate was equally applied to all members of the modeled cohort residing in any of the alive health states. Evidence to suggest a differential in caregiver time based on exacerbation status was not identified; therefore, the same estimate was used across all health states. Caregiver time was monetized using an average hourly wage of $35.36 as reported by the Bureau of Labor Statistics.[30]

Model Outcomes

Model outcomes included total life years (LYs) gained, equal-value life years (evLYs) gained, exacerbations averted, and total costs for each intervention over a lifetime time horizon Importantly, evLYs are a measure of health that captures the impact of treatment on both length of life and quality of life while weighing the value of extended life of all individuals in exactly the same way. Costs, LYs, and evLYs gained were also reported by COPD severity to understand the contribution of different costs elements. Total costs, LYs, and evLYs gained were reported as discounted values, using a discount rate of 3% per annum. Undiscounted outcomes were reported in the scenario analysis section.

Model Analysis

Trelegy Ellipta

Cost-effectiveness was estimated using the incremental cost-effectiveness ratios, with incremental analyses comparing FF/UMEC/VI to the other multi-inhaler triple therapies (BUD/FOR + TIO, FP/SALM + TIO, FF/VI + TIO). The base case analysis took a health care system perspective (i.e., focus on direct medical care costs only). Patient and caregiver productivity impacts were considered in the modified societal perspective analysis. Additionally, we presented a cost per exacerbation avoided.

Breo Ellipta

Cost-effectiveness was estimated using the incremental cost-effectiveness ratios, with incremental analyses comparing FF/VI to BUD/FOR and FP/SALM. The base case analysis took a health care system perspective (i.e., focus on direct medical care costs only). Patient and caregiver productivity impacts were considered in the modified societal perspective analysis. Additionally, we presented a cost per exacerbation avoided.

E4. Results

Trelegy Ellipta

Table E4.1. Lifetime Health Outcomes by Triple Therapy Treatment Strategy

Treatment	Exacerbations (Undiscounted)	Life Years (Undiscounted)	evLYs (Undiscounted)
FF/UMEC/VI	14.17	10.35	8.33
BUD/FOR + TIO	14.53	10.27	8.26
FP/SALM + TIO	14.53	10.27	8.26
FF/VI + TIO	14.53	10.27	8.26

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, LY: Life year, SALM: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table E4.2. Lifetime Average Non-Intervention Health Care Sector Costs by Triple Therapy Treatment Strategy

Treatment	Subsequent COPD Drug Costs (Undiscounted)	Health State Costs (Undiscounted)	Exacerbation Costs (Undiscounted)	Future Unrelated Health State Costs (Undiscounted)	Total Non-Intervention Health Care Sector Costs (Undiscounted)
FF/UMEC/VI	14,200	24,900	80,100	200,000	319,000
BUD/FOR + TIO	12,000	24,600	82,100	198,000	317,000
FP/SALM + TIO	12,000	24,600	82,100	198,000	317,000
FF/VI + TIO	12,000	24,600	82,100	198,000	317,000

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, LY: Life year, SALM: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table E4.3. Incremental Lifetime Results for FF/UMEC/VI versus BUD/FOR + TIO and FP/SALM + TIO and FF/VI + TIO

Treatment	Exacerbations	Life Years (Undiscounted)	evLYs (Undiscounted)	Non-Intervention Health Care Sector Costs (Undiscounted)
FF/UMEC/VI vs. BUD/FOR + TIO	-0.36	0.08	0.07	1,900
FF/UMEC/VI vs. FP/SALM + TIO	-0.36	0.08	0.07	1,900
FF/UMEC/VI vs. FF/VI + TIO	-0.36	0.08	0.07	1,900

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, LY: Life year, SALM: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Breo Ellipta

Table E4.4. Lifetime Health Outcomes by Triple Therapy Treatment Strategy

Treatment	Exacerbations	Life Years (Undiscounted)	evLYs (Undiscounted)
FF/VI	15.64	10.03	8.07
BUD/FOR	15.74	10.01	8.05
FP/SALM	15.74	10.01	8.05

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propioinate, LY: Life year, SALM: salmeterol, VI: vilanterol

Table E4.5. Lifetime Average Non-Intervention Health Care Sector Costs by Dual Therapy Treatment Strategy

Treatment	Subsequent COPD drug costs (Undiscounted)	Health State Costs (Undiscounted)	Exacerbation Costs (Undiscounted)	Future Unrelated Health State Costs (Undiscounted)	Total Non-Intervention Health Care Sector Costs (Undiscounted)
FF/VI	11,200	24,000	88,400	194,000	317,000
BUD/FOR	10,000	23,900	88,900	193,000	316,000
FP/SALM	10,000	23,900	88,900	193,000	316,000

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propioinate, LY: Life year, SALM: salmeterol, VI: vilanterol

Table E4.6. Incremental Lifetime Results for FF/VI versus BUD/FOR and FP/SALM

Treatment	Exacerbations	Life Years (Undiscounted)	evLYs (Undiscounted)	Non-Intervention Health Care Sector Costs (Undiscounted)
FF/VI vs. BUD/FOR	-0.10	0.02	0.02	1,100
FF/VI vs. FP/SALM	-0.10	0.02	0.02	1,100

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propioinate, LY: Life year, SALM: salmeterol, VI: vilanterol

E5. Sensitivity Analyses

Trelegy Ellipta

We conducted one-way sensitivity analyses on incremental costs per evLY to identify the impact of parameter uncertainty and key drivers of model outcomes. Figures E5.1, E5.2, and E5.3 present the results from the one-way sensitivity analysis from the health care sector perspective for FF/UMEC/VI compared to the three comparators (BUD/FOR + TIO, FP/SALM + TIO, FF/VI + TIO). Tables E5.2, E5.3, and E5.4 present the lower and upper incremental cost-effectiveness ratios based on the lower and upper limit inputs for the model parameters. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. The results are shown in Table E5.5, E5.6, and E5.7.

Figure E5.1. Tornado Diagram for FF/UMEC/VI versus BUD/FOR + TIO

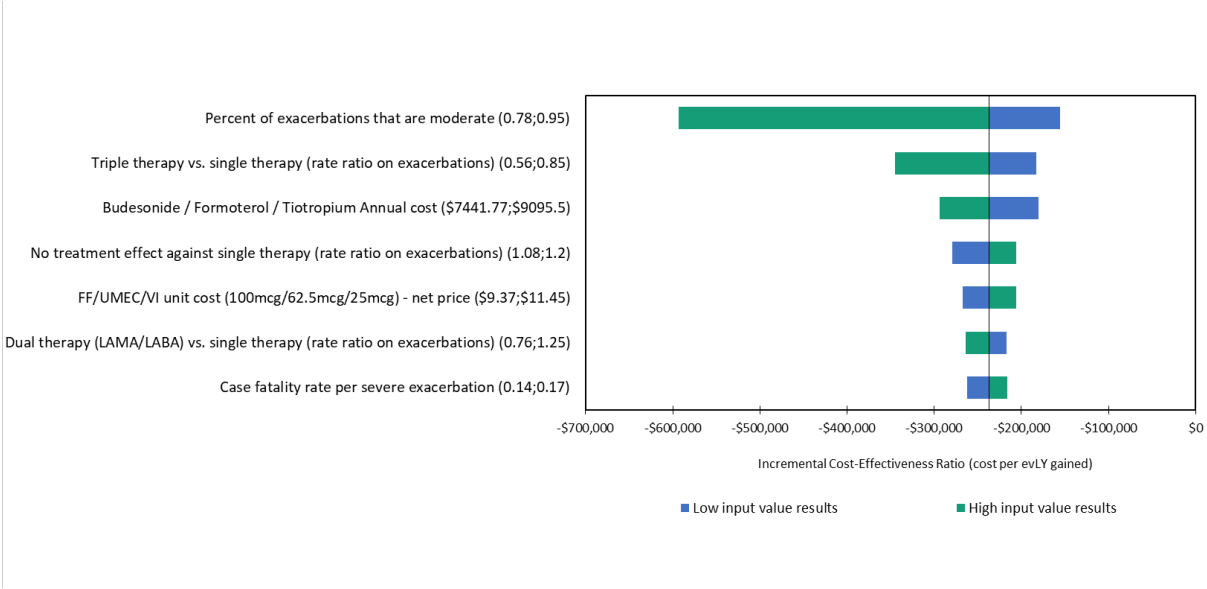

Figure E5.2. Tornado Diagram for FF/UMEC/VI versus FP/SALM + TIO

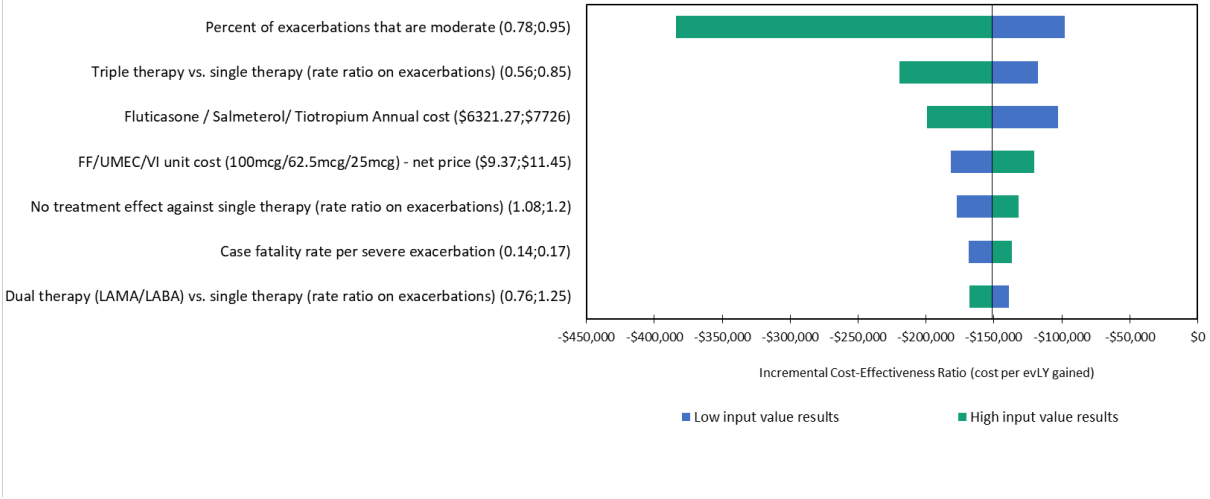

Figure E5.3. Tornado Diagram for FF/UMEC/VI versus FF/VI + TIO

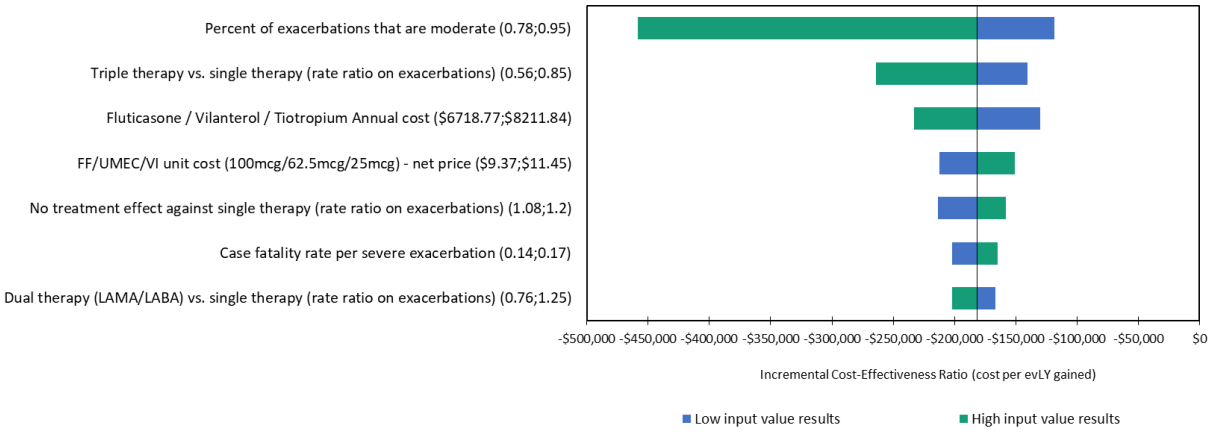

Table E5.1. Tornado Diagram Inputs and Results for FF/UMEC/VI versus BUD/FOR + TIO

Parameter	Lower Input*	Upper Input*	Lower incremental CE ratio	Upper Incremental CE Ratio
Percent of exacerbations that are moderate	0.78	0.95	-593,000	-155,000
Triple therapy vs. single therapy (rate ratio on exacerbations)	0.56	0.85	-345,000	-183,000
Budesonide / Formoterol / Tiotropium Annual cost	7,400	9,100	-294,000	-180,000
No treatment effect against single therapy (rate ratio on exacerbations)	1.08	1.2	-279,000	-206,000
FF/UMEC/VI Annual cost	9.37	11.45	-268,000	-206,000
Dual therapy (LAMA/LABA) vs. single therapy (rate ratio on exacerbations)	0.76	1.25	-264,000	-217,000
Case fatality rate per severe exacerbation	0.14	0.17	-262,000	-216,000

CE: cost-effectiveness, FF: fluticasone furoate, UMEC: umeclidinium, VI: vilanterol

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E5.2. Tornado Diagram Inputs and Results for FF/UMEC/VI versus FP/SALM + TIO

Parameter	Lower Input*	Upper Input*	Lower incremental CE ratio	Upper Incremental CE Ratio
Percent of exacerbations that are moderate	0.78	0.95	-384,000	-97,800
Triple therapy vs. single therapy (rate ratio on exacerbations)	0.56	0.85	-220,000	-117,000
Fluticasone / Salmeterol/ Tiotropium Annual cost	6,300	7,700	-199,000	-103,000
FF/UMEC/VI unit cost (100mcg/62.5mcg/25mcg) - net price	9.37	11.45	-182,000	-120,000
No treatment effect against single therapy (rate ratio on exacerbations)	1.08	1.20	-178,000	-132,000
Case fatality rate per severe exacerbation	0.14	0.17	-169,000	-137,000
Dual therapy (LAMA/LABA) vs. single therapy (rate ratio on exacerbations)	0.76	1.25	-168,000	-139,000

CE: cost-effectiveness, FF: fluticasone furoate, UMEC: umeclidinium, VI: vilanterol

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E5.3. Tornado Diagram Inputs and Results for FF/UMEC/VI versus FF/VI + TIO

Parameter	Lower Input*	Upper Input*	Lower incremental CE ratio	Upper Incremental CE Ratio
Percent of exacerbations that are moderate	0.78	0.95	-458,000	-118,000
Triple therapy vs. single therapy (rate ratio on exacerbations)	0.56	0.85	-264,000	-141,000
Fluticasone / Vilanterol / Tiotropium Annual cost	6,700	8,200	-233,000	-130,000
FF/UMEC/VI unit cost (100mcg/62.5mcg/25mcg) - net price	9.37	11.45	-212,000	-151,000
No treatment effect against single therapy (rate ratio on exacerbations)	1.08	1.20	-214,000	-158,000
Case fatality rate per severe exacerbation	0.14	0.17	-202,000	-165,000
Dual therapy (LAMA/LABA) vs. single therapy (rate ratio on exacerbations)	0.76	1.25	-202,000	-167,000

CE: cost-effectiveness, FF: fluticasone furoate, UMEC: umeclidinium, VI: vilanterol

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E5.4. Results of Probabilistic Sensitivity Analysis for FF/UMEC/VI versus BUD/FOR + TIO

	FF/UMEC/VI Mean	BUD/FOR + TIO Mean	Incremental
Costs	272,000	284,000	-11,700
evLYs	6.82 (95% CrI: 5.99, 7.54)	6.77 (95% CrI: 5.92, 7.51)	0.05 (95% CrI: 0.02, 0.08)
Incremental CE Ratio	FF/UMEC/VI was less costly and more effective compared to BUD/FOR + TIO		

BUD: budesonide, CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year, FF: fluticasone furoate, FOR: formoterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table E5.5. Results of Probabilistic Sensitivity Analysis for FF/UMEC/VI versus FP/SALM + TIO

	FF/UMEC/VI Mean	FP/SALM + TIO Mean	Incremental
Costs	272,000	280,000	-7,400
evLYs	6.82 (95% CrI: 5.99, 7.54)	6.77 (95% CrI: 5.92, 7.51)	0.05 (95% CrI: 0.02, 0.08)
Incremental CE Ratio	FF/UMEC/VI was less costly and more effective compared to FP/SALM + TIO		

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year, FF: fluticasone furoate, FP: fluticasone propionate, SALM: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table E5.6. Results of Probabilistic Sensitivity Analysis for FF/UMEC/VI versus FF/VI + TIO

	FF/UMEC/VI Mean	FF/VI + TIO Mean	Incremental
Costs	272,000	281,000	-8,900
evLYs	6.82 (95% CrI: 5.99, 7.54)	6.77 (95% CrI: 5.92, 7.51)	0.05 (95% CrI: 0.02, 0.08)
Incremental CE Ratio	FF/UMEC/VI was less costly and more effective compared to FF/VI + TIO		

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year, FF: fluticasone furoate, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table E5.7. Probabilistic Sensitivity Analysis Cost per evLY Gained Results

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
FF/UMEC/VI vs. BUD/FOR + TIO	100%	100%	100%	100%
FF/UMEC/VI vs. FP/SALM + TIO	100%	100%	100%	100%
FF/UMEC/VI vs. FF/VI + TIO	100%	100%	100%	100%

BUD: budesonide, evLYs: equal-value life year, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, SALM: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Breo Ellipta

We conducted one-way sensitivity analyses on incremental costs per evLY to identify the impact of parameter uncertainty and key drivers of model outcomes. Figures E5.1 and E5.2 present the results from the one-way sensitivity analysis from the health care sector perspective for FF/VI compared to the two comparators (BUD/FOR, FP/SALM). Tables E5.2 and E5.3 present the lower and upper incremental cost-effectiveness ratios based on the lower and upper limit inputs for the model parameters. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. The results are shown in Table E5.4 and E5.5.

Figure E5.4. Tornado Diagram for FF/VI versus BUD/FOR

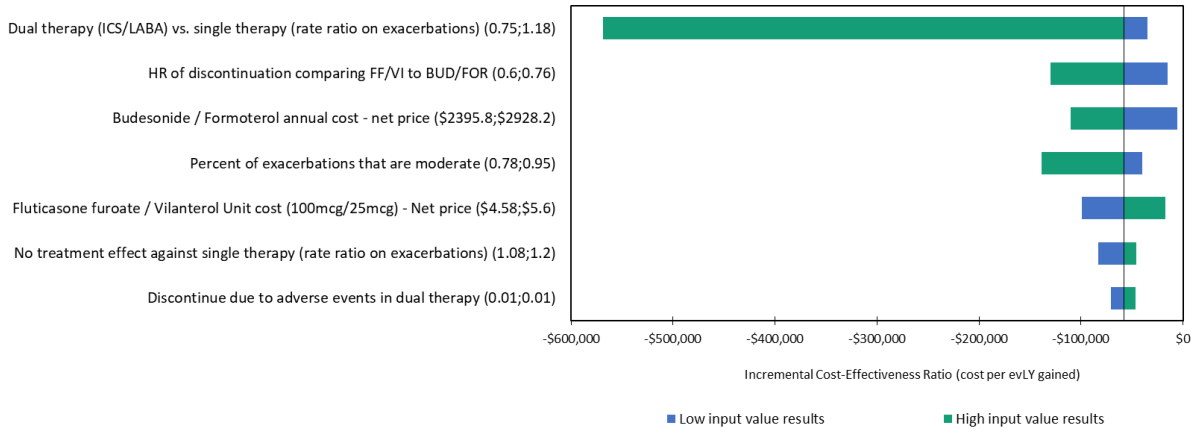

Figure E5.5. Tornado Diagram for FF/VI versus FP/SALM

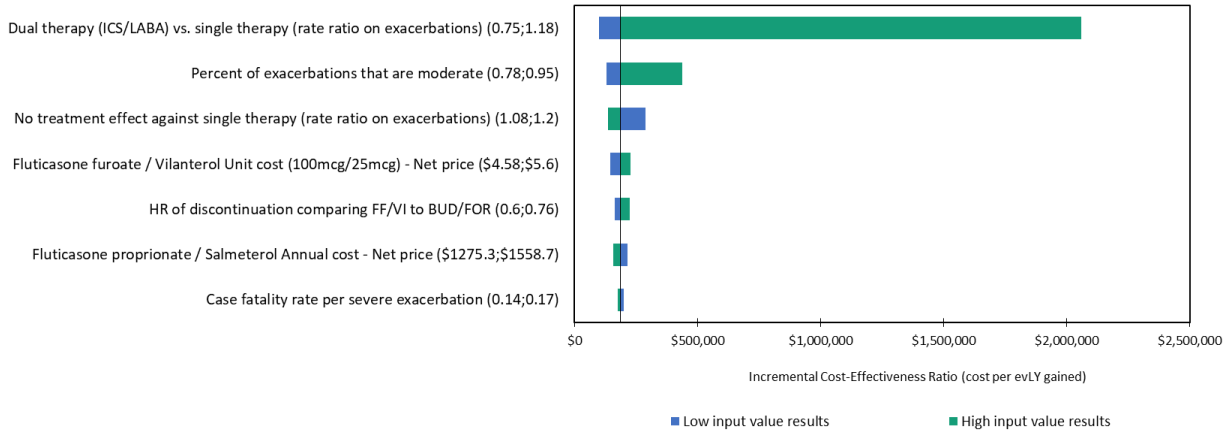

Table E5.7. Tornado Diagram Inputs and Results for FF/VI versus BUD/FOR

Parameter	Lower Input*	Upper Input*	Lower Incremental CE ratio	Upper Incremental CE Ratio
Dual therapy (ICS/LABA) vs. single therapy (rate ratio on exacerbations)	0.75	1.18	-569,000	-34,700
HR of discontinuation comparing FF/VI to BUD/FOR	0.60	0.76	-130,000	-14,800
Budesonide / Formoterol annual cost - net price	2,400	2,900	-111,000	-5,700
Percent of exacerbations that are moderate	0.78	0.95	-139,000	-39,700
Fluticasone furoate / Vilanterol Unit cost (100mcg/25mcg) - Net price	4.58	5.60	-99,000	-17,200
No treatment effect against single therapy (rate ratio on exacerbations)	1.08	1.20	-82,900	-46,000
Discontinuation due to adverse events in dual therapy	0.01	0.01	-70,500	-46,900

CE: cost-effectiveness, FF: fluticasone furoate, VI: vilanterol

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E5.8. Tornado Diagram Inputs and Results for FF/VI versus FP/SALM

Parameter	Lower Input*	Upper Input*	Lower Incremental CE ratio	Upper Incremental CE Ratio
Dual therapy (ICS/LABA) vs. single therapy (rate ratio on exacerbations)	0.75	1.18	101,000	2,058,000
Percent of exacerbations that are moderate	0.78	0.95	131,000	438,000
No treatment effect against single therapy (rate ratio on exacerbations)	1.08	1.20	138,000	289,000
Fluticasone furoate / Vilanterol Unit cost (100mcg/25mcg) - Net price	4.58	5.60	146,000	228,000
HR of discontinuation comparing FF/VI to BUD/FOR	0.60	0.76	163,000	227,000
Fluticasone proprionate / Salmeterol Annual cost - Net price	1,300	1,600	159,000	215,000
Case fatality rate per severe exacerbation	0.14	0.17	176,000	201,000

CE: cost-effectiveness, FF: fluticasone furoate, VI: vilanterol

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E5.9. Results of Probabilistic Sensitivity Analysis for FF/VI versus BUD/FOR

	FF/VI Mean	BUD/FOR Mean	Incremental
Costs	262,000	263,000	-760
evLYs	6.63 (95% CrI: 5.75, 7.42)	6.62 (95% CrI: 5.73, 7.41)	0.01 (95% CrI: 0.00, 0.03)
Incremental CE Ratio	FF/VI was less costly and more effective compared to BUD/FOR		

BUD: budesonide, CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year, FF: fluticasone furoate, FOR: formoterol, VI: vilanterol

Table E5.10. Results of Probabilistic Sensitivity Analysis for FF/VI versus FP/SALM

	FF/VI Mean	FP/SALM Mean	Incremental
Costs	262,000	260,000	2,500
evLYs	6.63 (95% CrI: 5.75, 7.42)	6.62 (95% CrI: 5.73, 7.41)	0.01 (95% CrI: 0.00, 0.03)
Incremental CE Ratio	$208,000/evLYG for FF/VI compared to FP/SALM		

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year, FF: fluticasone furoate, FP: fluticasone propionate, SALM: salmeterol, VI: vilanterol

E6. Scenario Analyses

Trelegy Ellipta

The following scenario analyses were conducted:

1. Modified societal perspective that includes patient and caregiver productivity impacts.

2. Alternative utility values based on the UK value set from the same study as the base case.

3. Using a fixed estimate of $24,105 for future unrelated health care costs, based on data from all Medicare patients but was not COPD-specific.

Table E6.1. Scenario Analysis Results for Total Health Outcomes

Intervention	Exacerbations	LYs	evLYs
Scenario 1: Modified Societal Perspective			
FF/UMEC/VI	11.29	8.45	6.82
BUD/FOR + TIO	11.61	8.39	6.77
FP/SALM + TIO	11.61	8.39	6.77
FF/VI + TIO	11.61	8.39	6.77
Scenario 2: Alternative Utility Values			
FF/UMEC/VI	11.29	8.45	6.82
BUD/FOR + TIO	11.61	8.39	6.77
FP/SALM + TIO	11.61	8.39	6.77
FF/VI + TIO	11.61	8.39	6.77
Scenario 3: Using a Fixed Estimate of $24,105 for Future Un-Related Health Care Costs			

FF/UMEC/VI	11.29	8.45	6.82
BUD/FOR + TIO	11.61	8.39	6.77
FP/SALM + TIO	11.61	8.39	6.77
FF/VI + TIO	11.61	8.39	6.77

BUD: budesonide, evLYs: equal-value life years, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, LY: Life year, SALM: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table E6.2. Scenario Analysis Results for Total Costs

Intervention	Intervention Costs	Subsequent COPD Drug Costs	Health State Costs	Exacerbation Costs	Future Unrelated Health State Costs	Total Costs
Scenario 1: Modified Societal Perspective						
FF/UMEC/VI	15,300	10,600	19,900	63,800	163,000	626,000
BUD/FOR + TIO	28,100	9,000	19,700	65,600	161,000	637,000
FP/SALM + TIO	23,900	9,000	19,700	65,600	161,000	633,000
FF/VI + TIO	25,400	9,000	19,700	65,600	161,000	634,000
Scenario 2: Alternative Utility Values						
FF/UMEC/VI	15,300	10,600	19,900	63,800	163,000	272,000
BUD/FOR + TIO	28,100	9,000	19,700	65,600	161,000	284,000
FP/SALM + TIO	23,900	9,000	19,700	65,600	161,000	280,000
FF/VI + TIO	25,400	9,000	19,700	65,600	161,000	281,000
Scenario 3: Using a Fixed Estimate of $24,105 for Future Un-Related Health Care Costs						
FF/UMEC/VI	15,300	10,600	19,900	63,800	204,000	313,000
BUD/FOR + TIO	28,100	9,000	19,700	65,600	202,000	325,000
FP/SALM + TIO	23,900	9,000	19,700	65,600	202,000	321,000
FF/VI + TIO	25,400	9,000	19,700	65,600	202,000	322,000

BUD: budesonide, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, SALM: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Table E6.3. Scenario Analysis Results (Incremental Cost-Effectiveness Ratios)

Intervention	Comparator	Incremental Cost-Effectiveness Ratios	
		Cost per LY gained	Cost per evLY gained
Scenario 1: Modified Societal Perspective			
FF/UMEC/VI	**BUD/FOR + TIO**	Less costly, more effective	Less costly, more effective
FF/UMEC/VI	**FP/SALM + TIO**	Less costly, more effective	Less costly, more effective
FF/UMEC/VI	**FF/VI + TIO**	Less costly, more effective	Less costly, more effective
Scenario 2: Alternative Utility Values			
FF/UMEC/VI	**BUD/FOR + TIO**	Less costly, more effective	Less costly, more effective
FF/UMEC/VI	**FP/SALM + TIO**	Less costly, more effective	Less costly, more effective
FF/UMEC/VI	**FF/VI + TIO**	Less costly, more effective	Less costly, more effective
Scenario 3: Using a Fixed Estimate of $24,105 for Future Un-Related Health Care Costs			

FF/UMEC/VI	**BUD/FOR + TIO**	Less costly, more effective	Less costly, more effective
FF/UMEC/VI	**FP/SALM + TIO**	Less costly, more effective	Less costly, more effective
FF/UMEC/VI	**FF/VI + TIO**	Less costly, more effective	Less costly, more effective

BUD: budesonide, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, SALM: salmeterol, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol

Breo Ellipta

The following scenario analyses were conducted:

1. Modified societal perspective that includes patient and caregiver productivity impacts.
2. Alternative utility values based on the UK value set from the same study as the base case.
3. Using a fixed estimate of $24,105 for future un-related health care costs, based on data from all Medicare patients but was not COPD-specific.

Table E6.4. Scenario Analysis Results for Total Health Outcomes

Intervention	Exacerbations	LYs	evLYs
Scenario 1: Modified Societal Perspective			
FF/VI	12.58	8.22	6.63
BUD/FOR	12.67	8.20	6.61
FP/SALM	12.67	8.20	6.61
Scenario 2: Alternative Utility Values			
FF/VI	12.58	8.22	6.63
BUD/FOR	12.67	8.20	6.61
FP/SALM	12.67	8.20	6.61
Scenario 3: Using a Fixed Estimate of $24,105 for Future Un-Related Health Care Costs			
FF/VI	12.58	8.22	6.63
BUD/FOR	12.67	8.20	6.61
FP/SALM	12.67	8.20	6.61

BUD: budesonide, evLYs: equal-value life year, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, LY: life year, SALM: salmeterol, VI: vilanterol

Table E6.5. Scenario Analysis Results for Total Costs

Intervention	Intervention Costs	Subsequent COPD Drug Costs	Health State Costs	Exacerbation Costs	Future Unrelated Health State Costs	Total Costs
Scenario 1: Modified Societal Perspective						
FF/VI	5,300	8,500	19,300	71,100	158,000	612,000
BUD/FOR	6,800	7,600	19,200	71,600	158,000	613,000
FP/SALM	3,600	7,600	19,200	71,600	158,000	610,000
Scenario 2: Alternative Utility Values						
FF/VI	5,300	8,500	19,300	71,100	158,000	262,000
BUD/FOR	6,800	7,600	19,200	71,600	158,000	263,000
FP/SALM	3,600	7,600	19,200	71,600	158,000	260,000
Scenario 3: Using a Fixed Estimate of $24,105 for Future Un-Related Health Care Costs						
FF/VI	5,300	8,500	19,300	71,100	198,000	302,000
BUD/FOR	6,800	7,600	19,200	71,600	198,000	303,000
FP/SALM	3,600	7,600	19,200	71,600	198,000	300,000

BUD: budesonide, evLYs: equal-value life year, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, LY: life year, SALM: salmeterol, VI: vilanterol

Table E6.6 Scenario Analysis Results (Incremental Cost-Effectiveness Ratios)

Intervention	Comparator	Incremental Cost-Effectiveness Ratios	
		Cost per LY gained	Cost per evLY gained
Scenario 1: Modified Societal Perspective			
FF/VI	**BUD/FOR**	Less costly, more effective	Less costly, more effective
FF/VI	**FP/SALM**	175,000	220,000
Scenario 2: Alternative Utility Values			
FF/VI	**BUD/FOR**	Less costly, more effective	Less costly, more effective
FF/VI	**FP/SALM**	159,000	216,000
Scenario 3: Using a Fixed Estimate of $24,105 for Future Un-Related Health Care Costs			
FF/VI	**BUD/FOR**	Less costly, more effective	Less costly, more effective
FF/VI	**FP/SALM**	164,000	206,000

BUD: budesonide, evLYs: equal-value life year, FF: fluticasone furoate, FOR: formoterol, FP: fluticasone propionate, LY: life year, SALM: salmeterol, VI: vilanterol

E7. Model Validation

We used several approaches to validate the model. First, we provided preliminary model structure, methods and assumptions to manufacturers and patient groups. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments. The outputs from the model were validated against the trial/study data of the interventions and any relevant observational datasets.

Prior Economic Models

Our current model builds upon the framework of a previously established ICER COPD model that assessed ensifentrine compared to maintenance therapy. We incorporated the same fundamental structure and methodological approach. Specifically, we followed the key assumptions outlined in the prior model, ensuring consistency in the disease progression framework and mortality assumptions. As in the previous model, transition probabilities were adapted based on COPD disease severity and smoking status, closely aligned with the methods described by Hansen et al.[132] Exacerbations were modeled as discrete events, consistent with the approach by Hoogendorn et al.[133] For mortality estimates, we similarly estimated all-cause mortality using life tables and adjusted by exacerbation-related and COPD-attributable morality by age and disease severity, in alignment with the methods detailed by Hoogendoorn et al.[133,134]

To validate our current model, we replicated the inputs and treatment assumptions used in the aforementioned ensifentrine ICER COPD model. Our model outcomes were similar to the results reported in the prior COPD model, particularly with incremental costs and health impacts, reflecting similar approaches to how we modeled disease progression, exacerbation, and mortality. Given this alignment, our findings are also consistent with the broader evidence base summarized in the prior COPD model, including studies by Hoogendorn et al and Rutten-van Molken et al.[133,135]