Ensifentrine for the Treatment of Chronic Obstructive Pulmonary Disease: Effectiveness and Value

Final Evidence Report

July 16, 2024

Prepared for

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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 this 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.

For a list of stakeholders from who we requested input from, or who have submitted public comments so far, please visit:
https://icer.org/wp-content/uploads/2024/05/COPD-Key-Stakeholder-List_053024.pdf

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List of Acronyms and Abbreviations Used in this Report

%	Percent
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
BID	Twice daily
CAT	COPD Assessment Test
CDR	Clinical trial Diversity Rating tool
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
EQ-5D-5L	EuroQol-5-Domain Questionnaire
E-RS	Evaluating-Respiratory Symptoms Tool
evLY	Equal Value of Life Year
evLYG	Equal Value of Life Years Gained
FDA	Food and Drug Administration
FEV	Forced expiratory volume
FVC	Forced vital capacity
GOLD	Global Initiative for Obstructive Lung Disease
HIDI	Health Improvement Distribution Index
HR	Hazard ratio
ICS	Inhaled corticosteroids
LABA	Long-acting β2 agonist
LAMA	Long-acting antimuscarinic antagonist
MCID	Minimal clinically important difference
MD	Mean difference
mg	Milligrams
ml	Milliliters
mMRC	modified Medical Research Council scale
N	Total number
NE	Not estimated
NR	Not reported
PDE	Phosphodiesterase
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SE	Standard error
SGRQ	St. George's Respiratory Questionnaire
TDI	Transition Dyspnea Index
TEAE	Treatment-emergent adverse event
US	United States
WAC	Wholesale acquisition cost

Executive Summary

Chronic obstructive pulmonary disease (COPD) is a group of lung diseases characterized by progressive and persistent airflow obstruction in the lungs. The most common forms of COPD are emphysema and chronic bronchitis; cigarette smoking, including secondhand smoke, is the leading cause of COPD in the United States (US).[1] COPD affects nearly 16 million people in the US, is the 6th leading cause of death,[2] results in more than one million emergency department visits and 500,000 hospitalizations, and results in costs of almost $50 billion per year.[3]

Symptoms of COPD include persistent shortness of breath, fatigue, wheezing, chest tightness, sputum production, and cough. Symptom burden is high, with more than 50% of people living with COPD experiencing daily symptoms,[4] particularly shortness of breath and fatigue, which can limit activities. In people with more severe disease, reliance on caregivers for many routine independent activities of daily living (e.g., dishwashing, laundry) is common. Although inhaled therapy can be effective, currently available medications do not necessarily address all COPD symptoms, and side effects can be burdensome for some. Oxygen therapy may be required for people with severe COPD and may limit mobility outside of the home due to the weight of the oxygen tanks or the limited battery life of a portable oxygen concentrator.

Treatment of COPD includes non-pharmacologic measures such as smoking cessation, vaccinations, and pulmonary rehabilitation, as well as pharmacologic therapy.[5] The goals of pharmacologic therapy are to improve symptoms and reduce exacerbations. The mainstay of therapy is inhaled bronchodilators, including long-acting beta-2-agonists (LABA) and antimuscarinics (LAMA) to relieve symptoms, improve lung function, and reduce exacerbations.[5] Combination therapy with LAMA + LABA therapy, when indicated, is more effective than monotherapy.[6] The addition of inhaled corticosteroids (ICS) can be considered for patients with frequent exacerbations and a blood eosinophil count of ≥300 cells/µl.[7] For patients with frequent exacerbations, additional treatment options such as roflumilast, azithromycin, or N-acetylcysteine may be added. For patients with severe or very severe disease, long-term, continuous supplemental oxygen may be needed; lung volume reduction surgery may be considered in certain cases.

Despite therapy, nearly two-thirds of patients report continuing to have symptoms of COPD.[8] Ensifentrine (Ohtuvayre; Verona Pharma) is a novel inhaled dual inhibitor of PDE3 and PDE4 enzymes that relaxes airway smooth muscle and decreases inflammation. It was approved by the US Food and Drug Administration (FDA) on June 26, 2024 as maintenance treatment of COPD in adult patients.[9] It is delivered twice daily via standard jet nebulizer. Ensifentrine was evaluated in two 24-week multicenter, randomized, placebo-controlled trials, (ENHANCE-1 and -2) with ENHANCE-1 including an additional 24-week safety extension.[10] Participants had moderate to severe COPD and were on stable background therapy, including no therapy or LAMA or LABA, with or without ICS. Patients on dual LAMA+LABA therapy or triple LAMA+LABA+ICS were excluded from

the trials. Participants in the trials had a mean age of around 65 years and were mainly white; 50-60% had moderate disease, 20-25% had an exacerbation within the last 15 months, and 30-45% were on no background therapy at baseline.

Treatment with ensifentrine met the primary endpoint of the trials of improving measures of lung function, including average FEV_1, at 12 weeks. It also decreased the annualized rate of moderate to severe exacerbations by 40%, with a pooled rate ratio of 0.60 (95% confidence interval [CI] 0.41, 0.79) at week 24. Time to first exacerbation was also delayed by 40% at week 24, a benefit that was maintained to week 48 in the safety extension of ENHANCE-1. Ensifentrine had mixed impact on quality of life measures with statistically significant improvements in some measures but not in others or in only one of the two trials. Ensifentrine was well-tolerated with similar rates of adverse events and discontinuation in the ensifentrine and placebo arms.

The trials were conducted during the COVID-19 pandemic, leading to multiple trial withdrawals either from COVID infection or, presumably, because of patient concerns about trial participation during the pandemic. These withdrawals increase uncertainty and could potentially bias results. The exclusion of patients on LAMA+LABA or triple inhaler therapy raises questions about the benefits of ensifentrine when added on to some of the most recommended regimens.

While the results of ENHANCE-1 and -2 are promising, there remains some uncertainty about the magnitude of overall benefit in patients receiving the most optimized modern inhaler therapies for COPD, although there was no effect modification by background therapy type in the trials. We do not have significant concerns about harms with ensifentrine. For these reasons, we have high certainty that ensifentrine added to maintenance therapy, compared with maintenance therapy alone, results in at least a small net health benefit, and may result in substantial net health benefit (**"B+"**). We have somewhat greater certainty in the benefits when ensifentrine is added to the regimens studied than to regimens that combine LABA and LAMA therapy.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with moderate to severe COPD		
Ensifentrine + Maintenance Therapy	Maintenance therapy alone	B+

COPD: Chronic obstructive pulmonary disease

In cost-effectiveness analyses, ensifentrine results in fewer exacerbations and in greater QALYs, evLYs, and life years. At a wholesale acquisition cost of $35,400 per year, the incremental cost-effectiveness ratios for ensifentrine are $492,000 per QALY gained and $426,000 per evLY gained. Ensifentrine would meet commonly used cost-effectiveness thresholds at an annual price between $7,500 and $12,700. If ensifentrine is shown to increase the day-to-day quality of life of patients living with COPD, beyond quality of life improvements associated with fewer exacerbations, the

cost-effectiveness would improve, but would continue to exceed commonly used cost-effectiveness thresholds at an annual price of $35,400.

Assuming ensifentrine's current wholesale acquisition cost, approximately 0.5% of the roughly 9.1 million US patients with moderate to severe COPD could be treated within five years without crossing the Institute for Clinical and Economic Review potential budget impact threshold of $735 million per year. Although the proportion of moderate to severe COPD patients who have suboptimal control of symptoms is not known, one clinical expert suggested that between 30-50% of patients may be candidates for treatment with ensifentrine. Even if the estimated potentially eligible patient population was reduced by 50%, the potential budget impact would remain substantial with less than 1% of the potentially eligible population treated without crossing the potential budget impact threshold. Additional efforts to achieve affordability and access must be considered, thus we are issuing an access and affordability alert for ensifentrine for the maintenance treatment of COPD.

Appraisal committee votes on questions of comparative effectiveness and value, along with policy recommendations regarding pricing, access, and future research are included in the Report. Several key themes are highlighted below:

- All stakeholders have an important role to play in ensuring that effective treatment options for COPD are implemented in a manner to reduce health inequities. For example, manufacturers should set up broad distribution networks, payers should cover all effective smoking cessation therapies, and all stakeholders should advocate for better access to all effective therapies for COPD, including drugs, supplemental oxygen, and pulmonary rehabilitation.

- By setting the price of ensifentrine far above commonly used cost-effectiveness thresholds, the manufacturer has missed an opportunity to provide broad access and increased uptake of the drug.

- The diagnosis of COPD is based on spirometry, which is currently underused. Thus, there is a role for all stakeholders to improve the infrastructure for diagnosis. This includes increasing access to spirometry (including new paradigms of care), ensuring adequate reimbursement for spirometry, and developing and implementing new biomarkers for the diagnosis of COPD.

- All stakeholders should endeavor to ensure that future research – whether clinical trials or observational cohorts – includes diverse populations reflective of the COPD population as a whole, including never smokers.

- Since clinical trials for new drugs do not often include head-to-head comparisons with current standard of care, researchers should conduct research that directly compares real-world treatment options and sequential treatment effectiveness to aid decision-making for clinicians and patients.

1. Background

Chronic obstructive pulmonary disease (COPD) is a group of lung diseases characterized by progressive and persistent airflow obstruction in the lungs. COPD affects approximately 15.7 million people in the United States (US), with higher rates among non-Hispanic White individuals, American Indian/Alaska Native individuals, women, and adults older than 65.[11] There is also significant geographic variation in rates of COPD in the US -- states in the midwestern and southern United States having the highest rates of disease, with up to 12% of the population affected in some states.[12] COPD is the 6th leading cause of death among Americans and is the cause of over 500,000 hospitalizations, one million emergency department visits per year, and 16.4 million lost working days per year. [2,3,13] The total economic burden of COPD is estimated to be almost $50 billion per year, with $29.5 billion attributable to direct medical costs; having COPD may also lead to lost time from work and premature retirement, costing persons with COPD more than $300,000 in estimated lifetime income.[3,14]

The two most common forms of COPD are chronic bronchitis and emphysema. Chronic bronchitis is characterized by airway inflammation that causes mucus production; the hallmark of emphysema is destruction of alveoli causing difficulty with oxygen exchange. Both forms of the disease cause persistent shortness of breath, fatigue, wheezing, chest tightness, sputum production, and cough, and they often coexist. 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.[4] In very severe COPD, patients may lose weight, have anorexia, or develop right-sided heart failure. Cigarette smoking, including secondhand smoke, is the leading cause of COPD in the US.[1] Workplace exposures such as dust, fumes, gases, chemicals are the most common causes of COPD among non-smokers.[15] Other causes include pre-existing lung injury (e.g., prematurity, prior infections) and alpha-1-antitrypsin deficiency.[1] 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.[16,17] Lower socioeconomic status has been linked with greater disease progression.[18] The presence of chronic bronchitis symptoms such as cough and phlegm has also been associated with worse quality of life, poorer lung function, and more frequent exacerbations.[19] Multimorbidity is often present in patients with COPD, with chronic diseases such as cardiovascular disease, osteoporosis, depression, anxiety, and lung cancer coexisting with COPD, and may also influence exacerbation risk and mortality independent of COPD.[5]

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.[5] Initial classification of COPD is based on airflow limitation measured by FEV_1 (Table 1.1). Additionally, exacerbations are an important marker of disease, as they are associated with substantial decrements in health, including association with an increased risk of cardiovascular events (particularly heart failure decompensation) in the peri-exacerbation period, predict a greater risk of

future severe exacerbations and death, and potentially accelerate disease progression.[21,22] Exacerbations also impact health-related quality of life and account for a large portion of COPD spending. [20,22] Symptoms and exacerbations may not necessarily correlate only with the degree of airflow obstruction. Thus, treatment of COPD is based on a combined assessment of the severity of airflow limitation, exacerbation history, and symptom status (Supplement Figure A1).

Table 1.1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) Classification of COPD

Classification of Airflow Limitation		
	COPD Classification	**Definition**
Mild	GOLD Stage 1	$FEV_1 \geq 80\%$ predicted
Moderate	GOLD Stage 2	$FEV_1 \geq 50\%$ predicted but < 80% predicted
Severe	GOLD Stage 3	$FEV_1 \geq 30\%$ predicted but < 50% predicted
Very Severe	GOLD Stage 4	$FEV_1 < 30\%$ predicted
Classification of Symptoms and Risk of Exacerbation		
GOLD Category A		mMRC 0-1 or CAT < 10 AND 0-1 moderate exacerbations per year
GOLD Category B		mMRC ≥ 2 or CAT ≥ 10 AND 0-1 moderate exacerbations per year
GOLD Category E		≥ 2 moderate exacerbations or ≥ 1 exacerbation leading to hospitalization per year

COPD: Chronic obstructive pulmonary disease, FEV_1: Forced expiratory volume in 1 second, GOLD: Global Initiative for Chronic Obstructive Lung Disease, mMRC: modified Medical Research Council questionnaire, CAT: COPD Assessment Test

Treatment of COPD includes both non-pharmacologist and pharmacologic approaches. In patients who currently smoke, smoking cessation is a key component of treatment. Other non-pharmacologic therapies such as pulmonary rehabilitation can also improve exercise capacity, symptoms and quality of life, and impact mortality.[23] Vaccinations against respiratory diseases such as influenza, pneumonia, pertussis, respiratory syncytial virus, and COVID can decrease the incidence of lower respiratory infections and are recommended for all COPD patients.

The goals of pharmacologic therapy in COPD are to improve symptoms and reduce exacerbations. The mainstays of pharmacologic therapy are inhaled bronchodilators, including long-acting beta-2-agonists (LABA) and antimuscarinic (LAMA) drugs, which improve airflow by relaxing airway smooth muscle tone.[5] These therapies are helpful for relieving symptoms, improving lung function, dyspnea, health status, and reducing exacerbations. Furthermore, dual therapy with LAMA and LABA (LAMA+LABA), when indicated, is more effective than monotherapy.[6]

Initial therapy choice is driven by symptoms and exacerbation risk. For patients with less severe symptoms and infrequent exacerbations, monotherapy with a long-acting bronchodilator monotherapy is recommended. For patients with more severe symptoms and more frequent exacerbations, dual therapy with LAMA+LABA is recommended. For certain patients with frequent exacerbations, particularly those with a blood eosinophil count ≥300 cells/µL, triple therapy with LAMA, LABA, and inhaled corticosteroids (LAMA+LABA+ICS) is recommended, as it is more effective

than bronchodilators alone in improving lung function and reducing exacerbations, and may reduce mortality.[7] However, long-term use of ICS may increase risk of pneumonia.[24] For patients who continue to have exacerbations and/or symptoms on maximal inhaled therapy, there may be a role for the oral phosphodiesterase-4 (PDE4) inhibitor roflumilast, azithromycin, or N-acetylcysteine. Dupilumab has also been shown to reduce exacerbations and is currently under FDA review for a label expansion for the treatment of COPD.[25] In patients with hypoxemia, long-term continuous oxygen therapy has been shown to decrease mortality.[26] Lung volume reduction surgery or endobronchial valve placement may be considered in selected patients with emphysema.[5] Despite therapy, nearly two-thirds of patients report continuing to have symptoms of COPD.[8]

Ensifentrine (Ohtuvayre; Verona Pharma) is a novel inhaled dual inhibitor of PDE3 and PDE4. Inhibition of PDE3 and PDE4 enzymes can relax airway smooth muscle, decrease inflammatory cells, improve ciliary function, and activate the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), which can reduce mucous viscosity and improve mucociliary clearance.[27] The drug is delivered twice-daily via nebulizer. Ensifentrine was approved by the US Food and Drug Administration (FDA) for maintenance treatment of COPD on June 26, 2024.[28]

Table 1.2. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Ensifentrine	PDE3/PDE4 inhibitor	Standard jet nebulizer	3 mg nebulized twice daily

PDE: Phosphodiesterase, mg: milligrams

2. Patient and Caregiver Perspectives

This report was developed with input from diverse stakeholders, including patients, clinicians, researchers, payers, and manufacturer of the agent of focus in this review. We interviewed six people living with COPD and talked with two patient advocacy groups. We also spoke with nine clinicians, all specialists in pulmonary medicine, and two payers, as well the manufacturer of ensifentrine. Additional details about the interviews can be found in the Supplement.

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.

Treatment for COPD can be complex. Inhaled medications are a mainstay of therapy; however, patients, 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. Side effects of inhaled therapies include dry mouth, thrush, dental cavities, and pneumonia. There may be less variability in drug delivery using nebulized devices; 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, which could affect disease control. Finally, pulmonary rehabilitation and regular exercise play important roles in helping individuals with COPD maintain quality of life.[29] However, pulmonary rehabilitation programs may be difficult to access, particularly in more rural areas, and maintenance of improvement after the program ends is challenging.

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 help mobility but patients may still be limited by battery life or having oxygen requirements that are too high for concentrators. Equipment malfunctions are common and challenging to manage, particularly when away from home. 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.

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 is and potential interventions when they are having increased symptoms (e.g., American Lung Association COPD Action Plan).

The caregiving burden for COPD falls mainly to unpaid caregivers. For patients with less severe disease, caregiving for COPD involves helping patients primarily with symptom 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.[30,31] 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, persons with COPD we interviewed cited the need for treatments with new mechanisms of action, particularly those which 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. Finally, we heard that lighter, more reliable oxygen systems need to be developed to ensure that people with COPD are able to fully participate in their daily lives with less burden, and without concern for running out of oxygen or equipment malfunctions while away from home.

Patient groups raised the concern that existing COPD quality of life measures focus only on physical symptoms and limitations caused by COPD, and that 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). Thus, current measures may underestimate the impact of COPD symptoms on a person's quality of life. Additionally, patient groups raised the concern that the FDA does not place enough emphasis on patient-centered quality of life outcomes when evaluating new treatments for COPD, which may impact drug development programs.

Patients and patient groups were also concerned about how the FDA evaluates potential new therapies for COPD. For example, there is an emphasis on lung function, exacerbations, and death, and thus treatments that do not affect one or more of those outcomes may be viewed less favorably, even if those treatments affect other domains such as quality of life or biomarkers of disease (e.g., CT imaging). We heard that these limitations may decrease innovation and discourage manufacturers from starting or continuing respiratory drug development programs.

Health Equity Considerations

Patients and patient groups reported that access to care could be extremely difficult in rural areas, particularly for patients who were dependent on oxygen that limited their mobility. Additionally, the high price of inhalers and coverage of nebulizers under the medical benefit may affect access and affordability of these treatments. Thus, patient groups advocated for flexibility in treatment choice to accommodate individual patient needs.

Finally, patient groups were concerned about the lack of diversity in COPD clinical trials. They highlighted that minority groups who are disproportionately affected with COPD (e.g., American Indian/Native Alaskan; never smokers) are not well reflected in either clinical trials or large cohort studies, including the SPIROMICS and COPDGene cohorts, which have collectively enrolled almost 13,000 participants.[32,33]

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Scope of Review

We evaluated the clinical effectiveness of ensifentrine as an add-on therapy to current maintenance therapy versus no additional treatment for adults with moderate to severe COPD. We sought and reviewed evidence on patient-important outcomes (e.g., changes in COPD exacerbations, respiratory symptoms, quality of life, etc.), changes in lung function (i.e., changes in forced expiratory volume in 1 second [FEV_1]), and harms. Data permitting, we reviewed evidence on treatment effect modification by subpopulations reported to be important in COPD research. The full protocol of the review is available in Section D1 of the Supplement.

Evidence Base

Evidence informing our review of ensifentrine for the treatment of moderate to severe COPD was derived from two Phase III randomized controlled trials (RCTs): ENHANCE-1 and ENHANCE-2.[10] Data on harms was supplemented by two Phase II RCTs; trial characteristics, including baseline characteristics and efficacy data from these trials are reported in Supplement Tables D3.1, 3.3, 3.9-12, 3.18-20. [34,35]

ENHANCE-1 and -2 were Phase III multicenter, randomized trials that evaluated nebulized ensifentrine 3 mg twice daily versus placebo for 24 weeks, with an additional 24-week safety extension in ENHANCE-1 only.[36] The trials ran concurrently between September 2020 and December 2022. Participants were randomized in a 5:3 ratio to ensifentrine:placebo over 24 weeks (3:1 ratio in the safety extension in ENHANCE-1). The primary outcome of the trials was a change in lung function as measured by FEV_1 at week 12. Participants were between 40 and 80 years of age, current or former smokers (i.e., ≥10 pack years), and had symptomatic moderate to severe COPD with an established diagnosis (i.e., score of ≥2 on the modified Medical Research Council [mMRC] Dyspnea Scale and post-bronchodilator FEV_1/FVC <0.70 [to confirm COPD] and FEV_1 ≥30% and ≤70% [to confirm moderate-severe COPD]). Exclusion criteria included: history of life-threatening COPD, recent COPD-related hospitalization, pneumonia, or COVID-19, history of another respiratory disorder, lung resection or reduction surgery in the last year, or long-term use of oxygen or pulmonary rehabilitation (unless stable for the last four weeks). Participants were allowed to continue with LAMA or LABA therapy (with or without ICS) if stable for 28 days prior to randomization; however, patients on dual LAMA+LABA therapy or triple LAMA+LABA+ICS therapy were excluded. Prohibited medications are reported in Supplement Table D3.1.

Baseline characteristics and key outcome measures are reported in Table 3.1. Participants were around 65 years of age, mostly White and non-Hispanic, and a substantial proportion of participants were not on background medication (31% in ENHANCE-1 and 45% in ENHANCE-2). See Supplement Table D3.2 for all baseline characteristics. Compared to real-world observational studies in COPD, participants in the ENHANCE-1 and -2 trials were younger, had more hypertension (60% vs. ~34%), and were less likely to have experienced a recent exacerbation.[37-39]

Trial withdrawal was high (ENHANCE-1 at week 48: 14.8%; ENHANCE-2 at week 24: 23.1%). See Supplement Table D3.17. Both trials were conducted during the COVID-19 pandemic; as such, many withdrew consent during the trial (of those who withdrew, 37-45% withdrew consent) and participants were required to withdraw from the trial if they tested positive for COVID-19 any time after enrollment (of those who withdrew, 13-15% had COVID-19). As a result, there were missing outcome data. The investigators noted that they used multiple imputation for missing values. However, it is unclear the percentage of missing data in each analysis.

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.[40] In general, ENHANCE-1 and -2 trials achieved "fair" diversity on most demographic categories evaluated. See Supplement D1 for full details of CDR methods and results.

Table 3.1. Baseline Characteristics and Key Measures in ENHANCE-1 and -2

Baseline Characteristics and Key Measures	ENHANCE-1 N=477 ensifentrine* N=283 placebo	ENHANCE-2 N=498 ensifentrine N=291 placebo
Age in Years, Mean (SD)	65 (7.4)	65.2 (7.4)
Sex, Female %	41.8	51.8
Race/Ethnicity, %		
White	89.8	94.7
Black or African American	3.3	4.3
Asian	3.3	0.3
Hispanic or Latino	2.6	5
Severity of Airflow Obstruction, %		
GOLD (moderate)	59.8	51.2
GOLD (severe)	39.8	48.7
Background Therapy, %		
Any	68.9	55.1
LAMA	29.3	32.3
LAMA+ICS	1.3	0.1
LABA	17.3	7.4
LABA+ICS	20.8	15.4
Exacerbation in the Last 15 Months, %	25.9	20.9
E-RS, mean (SD)	13.7 (6.5)	13.3 (6.5)
TDI, mean (SD)	5.9 (1.1)	5.9 (1.3)
SGRQ, mean (SD)	47.5 (17.7)	50.9 (16.9)
Rescue Medication Puffs per Day†, mean (SD)	1.53 (2.3)	1.9 (2.4)
Mean Baseline FEV_1, ml (SD)	1412 (478)	1282 (462)

E-RS: Evaluating Respiratory Symptoms, FEV_1: forced expiratory volume in 1 second, GOLD: Global Initiative for Chronic Obstructive Lung Disease, ICS: inhaled corticosteroid, LABA: long-acting β_2-agonist, LAMA: long-acting muscarinic antagonist, ml: milliliters, SD: standard deviation, SGRQ: St. George's Respiratory Questionnaire, TDI: Transition Dyspnea Index, %: percent.

* 48-week extension safety study included 228 participants in ensifentrine and 70 participants in placebo.

† Rescue medication included albuterol/salbutamol

3.2. Results

Clinical Benefits

In this main report, we describe changes in patient-important outcomes at week 24 (and week 48 where available for ENHANCE-1) and changes in lung function at week 12. As ENHANCE-1 and -2 were sufficiently similar in study design, baseline characteristics, and key outcome measures, we pooled data from ENHANCE-1 and -2 using pairwise fixed-effects meta-analyses. Our meta-analysis methods and model fit data are described in Section D1 of the Supplement. When there were discrepancies between the trial results, we also qualitatively report individual trial results. In Section A1 of the Supplement, we provide definitions of each outcome. To interpret changes in respiratory symptoms and quality of life measures, we examined whether the changes observed met criteria for minimal clinically importance differences (MCID) based on published thresholds.

Table 3.2. provides MCID thresholds in COPD. Finally, harms and discontinuation rates are summarized. Data from other outcomes and from two Phase II trials are available in Section D3 of the Supplement.

Table 3.2. Minimal Clinically Importance Differences for Patient-Reported Outcomes

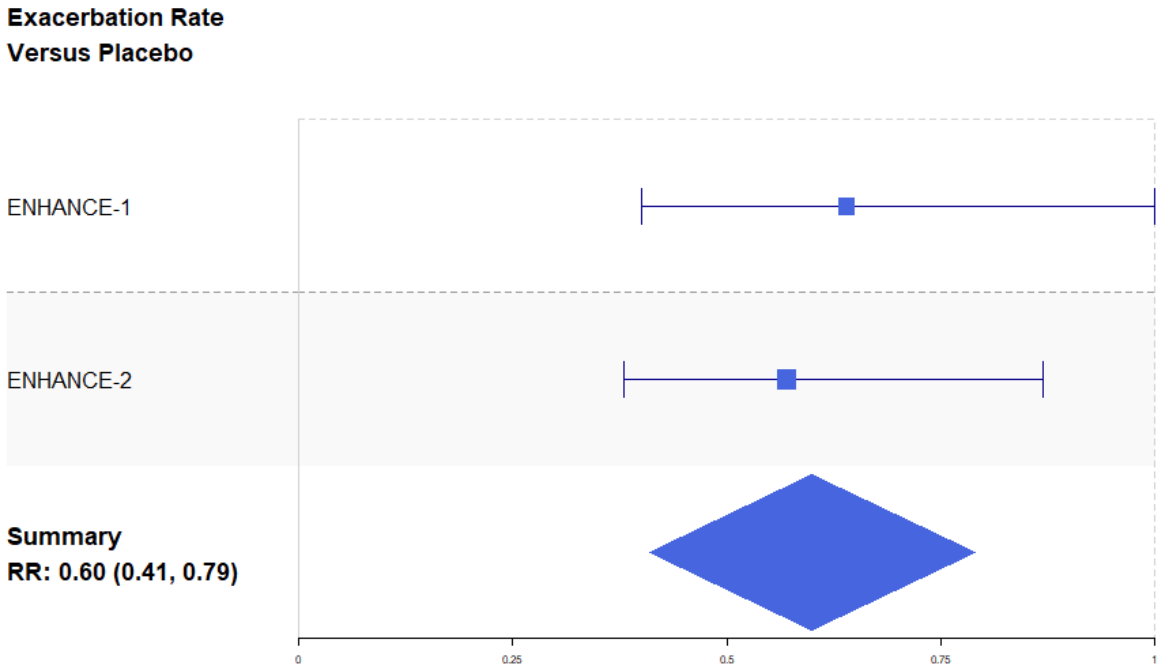
Outcome*	Score Range	Minimal Clinically Important Difference (MCID) in COPD
Respiratory Symptoms		
Evaluating-Respiratory Symptoms (E-RS)	0 to 40, higher score indicates more severe symptoms	≥2.0-point reduction in total score[41]
Transitional Dyspnea Index (TDI)	−9 to +9, negative score indicates more severe dyspnea	1-unit change[42]
Quality of Life		
St. George's Respiratory Questionnaire (SGRQ)	0 to 100, higher score indicates poorer health	≥4-point reduction, based upon data from patients with asthma and COPD.[43,44] Recent data suggest MCID for COPD should be at least 7 points.[45]
EuroQol-5-Domain Questionnaire (EQ-5D-5L) utility index	-0.59 to 1, with 1 being the best possible health state	0.037 to 0.063[46]

COPD: Chronic Obstructive Pulmonary Disease, MCID: Minimal Clinically Important Difference.
* There are no established MCID for rescue medication use and lung function.

Rate of Moderate to Severe Exacerbations

Moderate exacerbation was defined as worsening of COPD symptoms for >2 days requiring a minimum of three days of therapy with oral or systemic corticosteroids and/or antibiotics. Severe exacerbation was defined as worsening of symptoms and inpatient hospitalization.[10] Our meta-analysis that pooled data from ENHANCE-1 and -2 showed a statistically significant 40% decrease in the annualized event rate (based on 24 week data) of moderate or severe COPD exacerbations compared with placebo (rate ratio [RR]: 0.60; 95% CI: 0.41, 0.79; P<0.0001; I^2=0%) (Figure 3.1). Data presented at the American Thoracic Society 2024 conference reported that patients who received ensifentrine had a numerically, but not significantly, lower risk of transitioning from GOLD Category B (See Table 1.1.) to GOLD Category E (HR: 0.64; 95% CI: 0.41-1.01; P=0.058) and, in order to prevent one exacerbation on an annual basis, 6.25 patients needed to be treated.[47] Of note, although the RR estimates seen in ENHANCE-1 and -2 were numerically similar at week 24 (RR for ENHANCE-1: 0.64; 95% CI: 0.40, 1.00; P=0.05 and ENHANCE-2: 0.57; 95% CI: 0.38, 0.87; P=0.009), the ENHANCE-1 results were not statistically significant either at week 24 or week 48 (RR at week 48: 0.56; 95% CI: 0.32, 1.00; P=0.052).[10]

Figure 3.1. Forest Plot of Annualized Event Rate of Moderate or Severe COPD Exacerbations versus Placebo

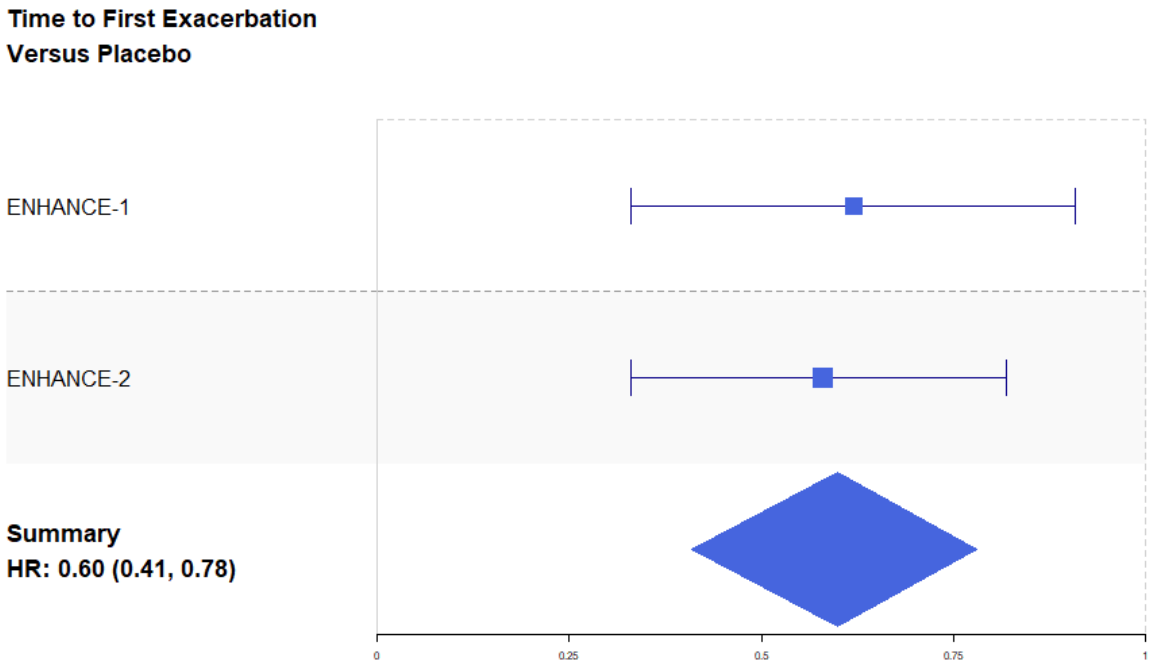


Legend: RR represents the rate ratio. Summary estimates with 95% confidence intervals that do not cross 1.0 are statistically significant.

Time to First Exacerbation

In both ENHANCE-1 and -2, there was a statistically significant longer time to first COPD exacerbation in those randomized to receive ensifentrine versus those randomized to placebo at week 24 (Figure 3.2). Our pooled estimate also showed an overall 40% delay in time to first exacerbation (HR: 0.60; 95% CI: 0.41, 0.78; P<0.0001; I^2=0%). This benefit was maintained at week 48 for participants in ENHANCE-1 (HR: 0.48; 95% CI: 0.28, 0.82; P=0.007).[10]

Figure 3.2. Forest Plot of Time to First COPD Exacerbation versus Placebo



Legend: HR represents the hazard ratio. Estimates with 95% confidence intervals that do not cross 1.0 are statistically significant.

Respiratory Symptoms

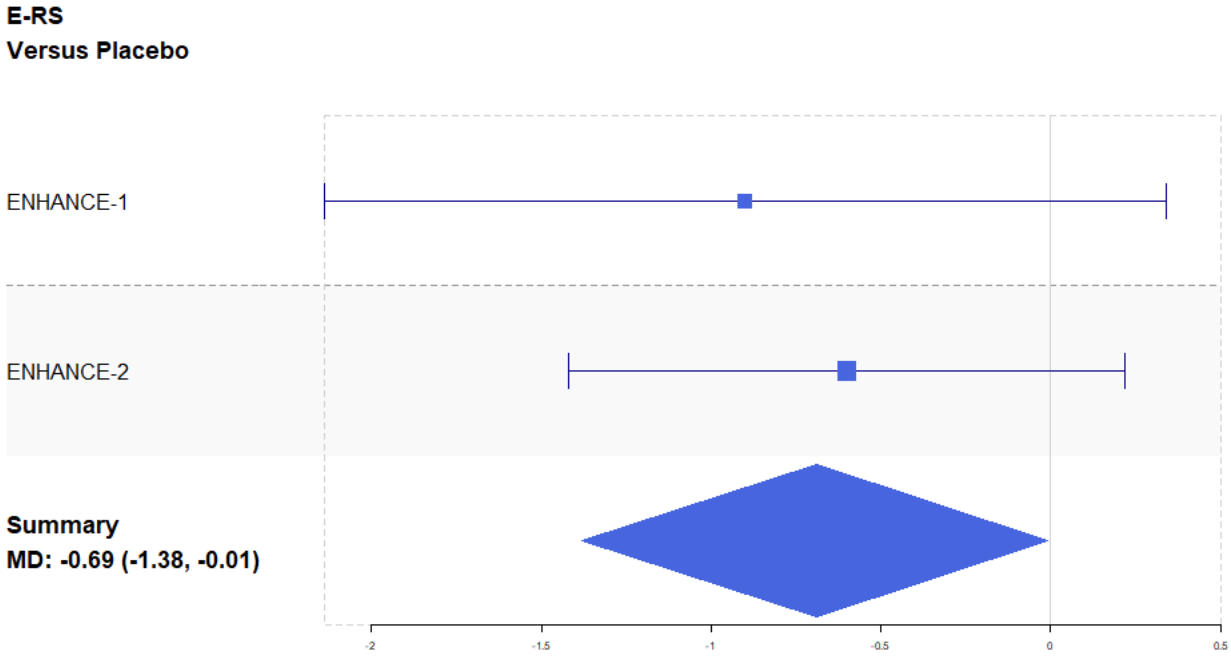
Evaluating Respiratory Symptoms (E-RS)

In ENHANCE-1, there was a statistically significant reduction in E-RS score in the ensifentrine group versus placebo at week 24, signifying improvement in respiratory symptoms in the ensifentrine group (mean difference [MD] versus placebo: -1.0; 95% CI: -1.7, -0.2; P=0.011).[10] Those in the ensifentrine group were also significantly more likely to achieve a ≥2.0-point reduction (MCID for E-RS[41]) at week 24 compared to the placebo group (48% vs. 39.4%, P≤0.05).[48] However, in ENHANCE-2, there was no statistically significant difference in E-RS scores at week 24 between the ensifentrine and placebo groups (MD versus placebo: -0.6; 95% CI: -1.4, 0.2; P=0.134).

Our pooled estimate showed a statistically significant reduction in E-RS score in the ensifentrine group (MD versus placebo: -0.69; 95% CI: -1.38, -0.01; P=0.047; I^2=0%) (Figure 3.3). However, the change from baseline in E-RS versus placebo did not exceed MCID. In both trials, there was symptom improvement from baseline to 6-week follow-up, and then the scores appear to plateau through 24 weeks. (Supplement Figure D2.1) Line charts representing the change in raw scores for patient-important outcomes from baseline to weeks 6, 12, and 24 are reported in Supplement Figures D2.1.-4.

The individual mean difference and 95% CIs estimated by our meta-analyses of E-RS (and other outcomes) may be slightly different to the estimates reported in the main trial publication.[10] See Supplement Tables D3.5-8 for all efficacy estimates. In our meta-analyses, we included the total number of participants reported to have been included in the trial. However, the published manuscript did not report the number of participants who contributed E-RS scores to the analysis. Thus, it is possible that the analyses in the manuscript are based upon a smaller pool of participants, and hence the difference in estimates.

Figure 3.3. Forest Plot of Change in E-RS versus Placebo

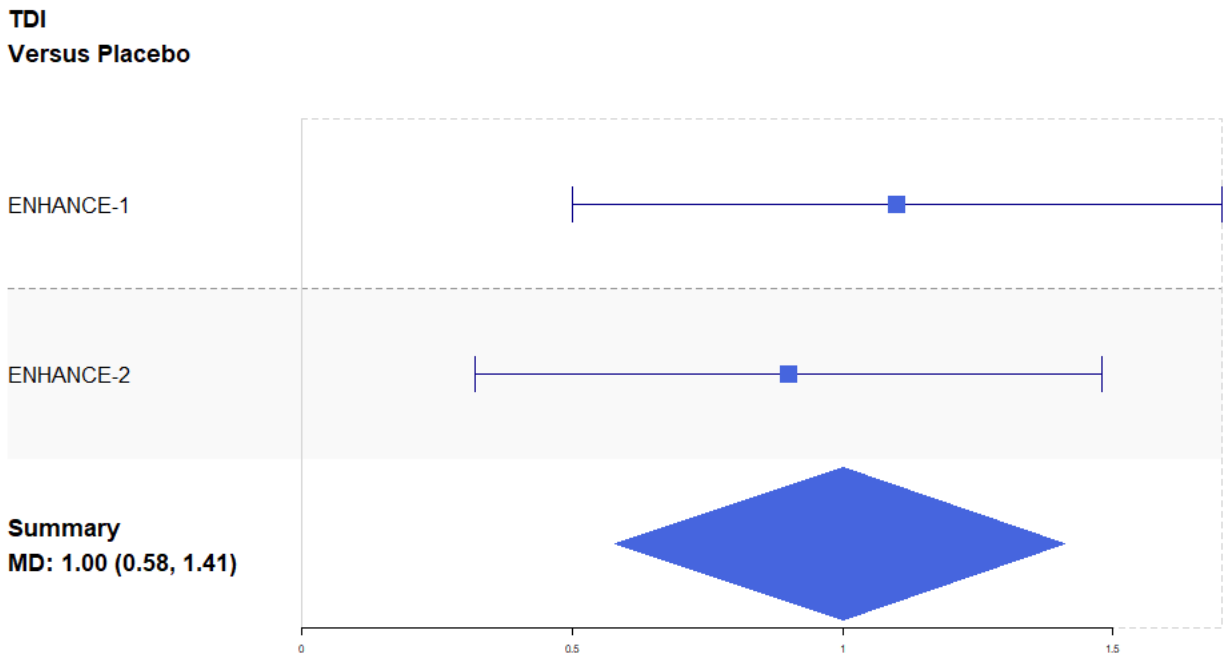


Legend: MD represents the mean difference versus placebo. Estimates with 95% confidence intervals that do not cross 0 are statistically significant.

Transition Dyspnea Index (TDI)

Both ENHANCE-1 and -2 trials reported a statistically significant improvement in TDI scores in the ensifentrine compared to the placebo groups at week 24 (MD versus placebo for ENHANCE-1: 1.0; 95% CI: 0.6, 1.5; P<0.001, and ENHANCE-2: 0.9; 95% CI: 0.4, 1.4; P<0.001).[10,49] Our pooled estimate was statistically significant (MD versus placebo: 1.00; 95% CI: 0.58, 1.41; P<0.001; I^2=0%). (Figure 3.4). This change from baseline in TDI versus placebo just meets the published MCID of a 1-unit change in the scale.[42] Again, the improvement seen in ENHANCE-1 was larger than in ENHANCE-2, though both were statistically significant.

Figure 3.4. Forest Plot of Change in TDI versus Placebo



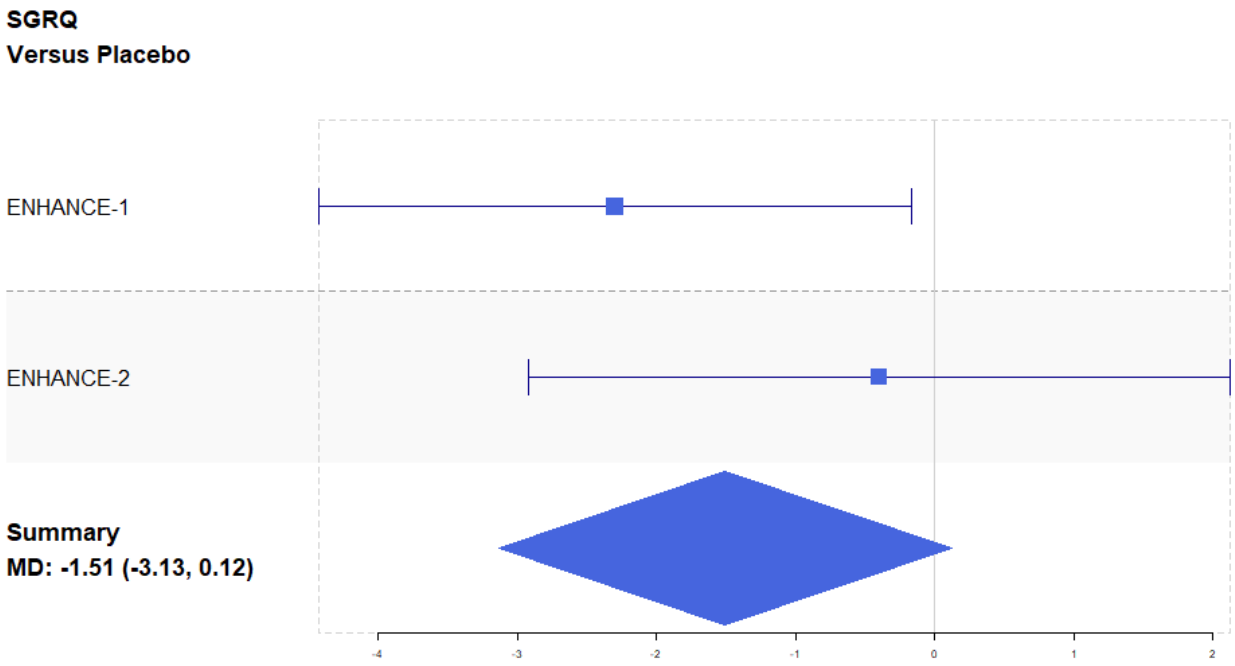
Legend: MD represents the mean difference versus placebo. Estimates with 95% confidence intervals that do not cross 0 are statistically significant.

Quality of Life

St. George's Respiratory Questionnaire (SGRQ)

The results from ENHANCE-1 reported a statistically significant improvement in quality of life in the ensifentrine group versus placebo at week 24 (MD versus placebo: -2.3; 95% CI: -4.3, -0.3; P=0.025) Those who were in the ensifentrine group were significantly more likely to achieve MCID (≥4-point reduction) at week 24 compared to those in the placebo group (58.2% vs. 45.9%, P≤0.05).[10, 43,44,48] See Supplement Table D3.6. On the other hand, ENHANCE-2 did not report a statistically significant improvement in quality of life in the ensifentrine group versus the placebo group at week 24 (MD versus placebo: -0.5; 95% CI: -2.7, 1.7; P=0.669) and, in fact, a greater proportion of participants in the placebo group were considered responders compared to the ensifentrine group (50% in the placebo group vs 45% in the ensifentrine group).[50] Our pooled estimate was not statistically significant and did not exceed MCID (MD versus placebo: -1.51; 95% CI: -3.13, 0.12; P=0.069; I^2=22%) (Figure 3.5).

Figure 3.5. Forest Plot of Change in SGRQ versus Placebo



Legend: MD represents the mean difference versus placebo. Estimates with 95% confidence intervals that do not cross 0 are statistically significant.

EuroQol-5-Domain Questionnaire (EQ-5D-5L)

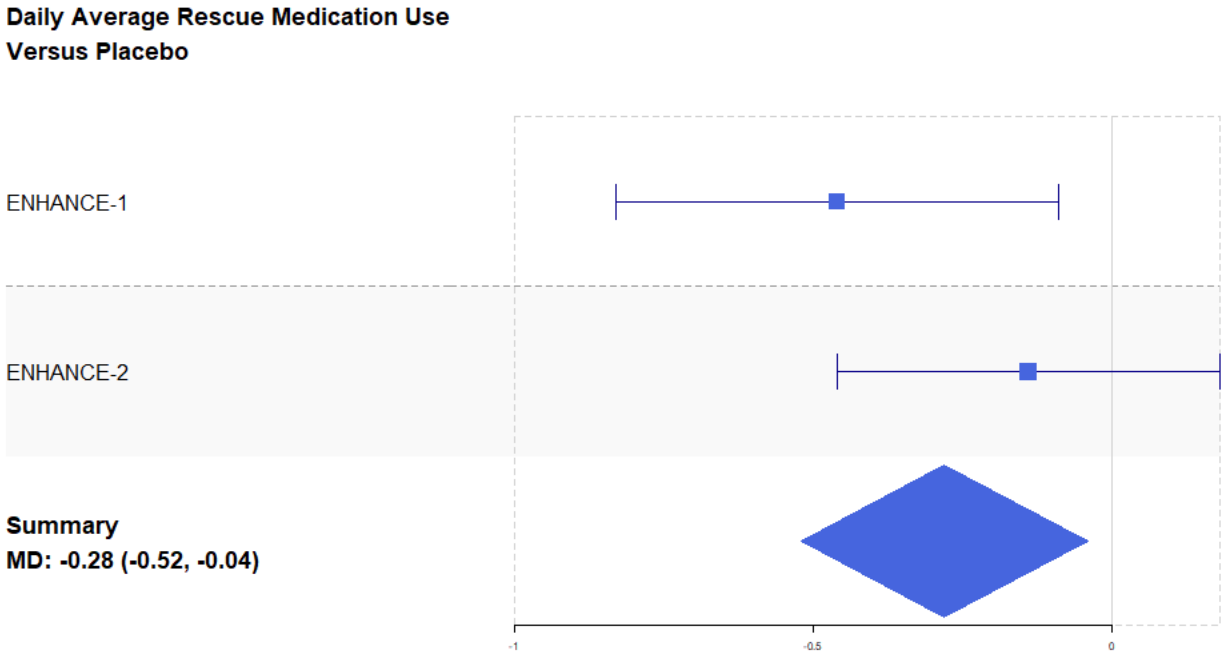
Measurements from the EQ-5D-5L were available only from ENHANCE-2. In this trial, those in the ensifentrine group reported a statistically significant increase in EQ-5D-5L at week 24 compared to placebo (MD versus placebo: 0.027; 95% CI: 0.004, 0.050; P=0.019).

Use of Rescue Medication

The investigators evaluated the use of rescue medication (albuterol/salbutamol) by calculating an average daily use across a seven-day period. ENHANCE-1 reported a statistically significant reduction in use of rescue medication in the ensifentrine group at week 24 compared to the placebo group (MD versus placebo: -0.45; 95% CI: -0.70, -0.20; P<0.001). However, in the ENHANCE-2 trial, there was no statistically significant difference between the groups at week 24 (MD versus placebo: -0.14; 95% CI: -0.41, 0.14; P=0.32).

Our pooled estimate was statistically significant (MD versus placebo: -0.28; 95% CI: -0.52, -0.04; P=0.02; I^2=39%). (Figure 3.6). Moderate heterogeneity was detected in the fixed-effects meta-analysis. We conducted a random-effects meta-analysis and the estimate remained stable, though the P value was no longer statistically significant (Supplement Table D2.1).

Figure 3.6. Forest Plot of Change in Daily Use of Rescue Medication versus Placebo

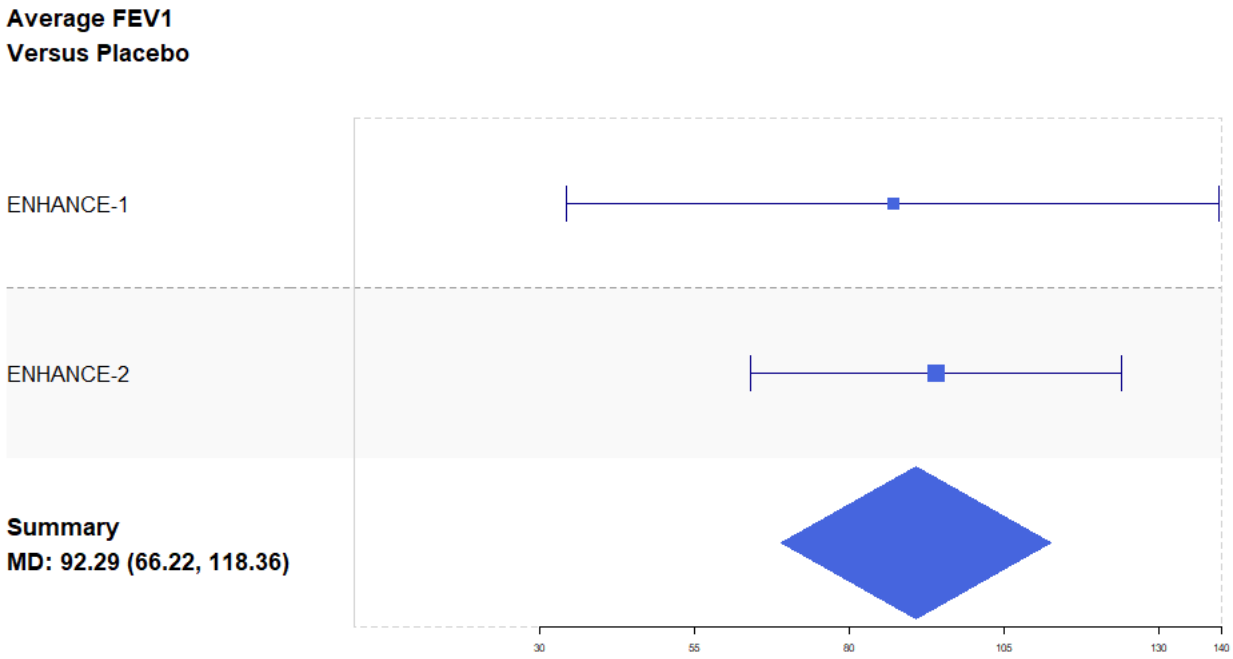


Legend: MD represents the mean difference versus placebo. Estimates with 95% confidence intervals that do not cross 0 are statistically significant.

Lung Function

Both ENHANCE-1 and -2 trials reported a statistically significant improvement in lung function in the ensifentrine versus placebo groups at week 12 (average FEV_1). See Supplement Table D3.4. Our pooled estimate was statistically significant (MD versus placebo: 92.29 ml; 95% CI: 66.22, 118.36; P<0.0001; I^2=0%). (Figure 3.7).

Figure 3.7. Forest Plot of Change in Average FEV_1 versus Placebo



Legend: MD represents the mean difference versus placebo. Estimates with 95% confidence intervals that do not cross 0 are statistically significant.

Additional lung function measures, as well as other outcome data, can be found in Section D2 of the Supplement and Supplement Tables D3.4.-8. No data for oxygen use nor functional capacity was reported in the trials.

Harms

The safety profile for ensifentrine was evaluated at week 24 for ENHANCE-1 and -2, and at week 48 for ENHANCE-1 only.[10] Across both trials, the risk of any treatment-emergent adverse events (TEAEs) was similar between ensifentrine and placebo groups (36.8% vs. 35.9%) at week 24. Events that occurred greater than 1% in the ensifentrine group at week 24 are reported in Table 3.4. TEAEs reported at 48 weeks in ENHANCE-1 were similar to those reported at 24 weeks.

Discontinuation overall was high in the trials, and higher in ENHANCE-2 compared to ENHANCE-1 (ENHANCE-1: 19.4% vs. ENHANCE-2: 28.5%). In our meta-analysis that removed COVID-19 cases, discontinuation rates due to TEAEs were similar between the ensifentrine and placebo groups (RR: 0.92; 95% CI: 0.6, 1.41; P=0.7) (Supplement Figure D2.5).

Adverse events of interest to our review (e.g., pneumonia, hypertension, cardiac disorder, gastrointestinal adverse events) were reported at a low frequency and similar in both ensifentrine and placebo groups. See Table 3.4 for rates of specific adverse events. In a Phase II trial, a higher proportion of those who received ensifentrine reported headache compared to placebo (9% vs.

4%).[35] However, this was not observed in the Phase III trials. Additional data on harms from Phase III and II can be found in Supplement Section D2 and Supplement Tables D3.13-20.

Table 3.4. Treatment-emergent Adverse Events Occurring in >1% in Ensifentrine Group at Week 24[10]

TEAEs, n (%)	ENHANCE-1		ENHANCE-2	
	Ensifentrine (N=477)	Placebo (N=283)	Ensifentrine (N=498)	Placebo (N=291)
Nasopharyngitis	13 (2.7)	16 (5.7)	9 (1.8)	3 (1.0)
Hypertension	12 (2.5)	4 (1.4)	5 (1.0)	1 (0.3)
Back Pain	10 (2.1)	1 (0.4)	8 (1.6)	5 (1.7)
COPD	7 (1.5)	6 (2.1)	11 (2.2)	5 (1.7)
Toothache	6 (1.3)	2 (0.7)	0 (0)	1 (0.3)
Pneumonia	6 (1.3)	2 (0.7)	4 (0.8)	5 (1.7)
Urinary Tract Infection	5 (1.0)	1 (0.4)	8 (1.6)	5 (1.7)
Diarrhea	2 (0.4)	2 (0.7)	8 (1.6)	2 (0.7)
Sinusitis	1 (0.2)	1 (0.4)	6 (1.2)	0 (0)

COPD: chronic obstructive pulmonary disease, N: total number, TEAE: treatment-emergent adverse event

Subgroup Analyses and Heterogeneity

In ENHANCE-1 and -2, subgroup analyses were conducted for some of the outcomes of interest. There was no evidence of effect modification by: age, sex, eosinophil count (e.g., <100 or ≤150 cells/µL versus ≥100 or >150 cells/µL), COPD exacerbation in the past 15 months, chronic bronchitis, background medication (e.g., any, LABA or LABA+ICS, LAMA or LAMA+ICS, LAMA only), smoking status, or whether the participant had moderate or severe COPD.[10,51-59] However, we note that the trials were not powered to detect subgroup differences. See Supplement Tables D3.20-25. Evidence for effect modification was not explored for: medical comorbidities (e.g., hypertension, osteoporosis, obesity, cardiovascular disease, diabetes, frailty), emphysema, nor people with frequent exacerbations.

Uncertainty and Controversies

The trials were largely conducted during the COVID-19 pandemic. This led to withdrawals both because of COVID infection (required by trial protocol) and, presumably, because patients did not wish to participate in a trial during the pandemic, which caused a significant number of withdrawals both related to participants testing positive for COVID and non-COVID withdrawals. Loss to follow-up of a large number of trial participants can threaten the validity of results. While this is unlikely to be a problem with withdrawals due to COVID infection, other withdrawals increase the risk of bias. We note, of course, that this is an expected, unfortunate outcome of a trial of a respiratory treatment being conducted during the pandemic and not a reflection on the overall quality of the ENHANCE trials.

The population recruited into the trials compared were generally younger and had fewer exacerbations than participants in real world observational studies. Additionally, the background therapy used in the trials does not reflect the most recent standards of care for treatment for moderate to severe COPD. Approximately 30% of participants in ENHANCE-1 and 45% of participants in ENHANCE-2 were on no background therapy at baseline. While participants taking dual LAMA+LABA therapy or triple LAMA+LABA+ICS background therapy, which has become standard of care in symptomatic patients and/or those with frequent exacerbations, were excluded from the Phase III trials, short-term data from a Phase IIb study suggests that ensifentrine (dosed at 1.5 mg or 6 mg) added on to LAMA+LABA therapy can improve FEV_1.[10] Additionally, there was no effect modification by background therapy in the trial results. Longer term and larger studies are needed to characterize the magnitude of the benefit of ensifentrine added on to dual and triple therapy, the patient population for whom the drug is most likely to be prescribed for in clinical practice.

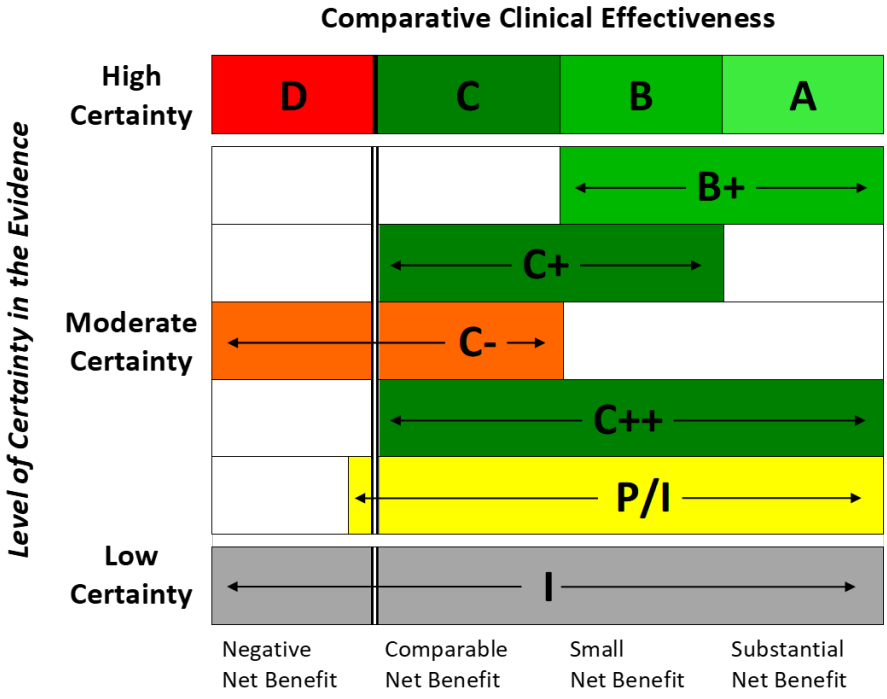
Our meta-analyses showed that, overall, ensifentrine improved lung function and decreased exacerbations. However, there were some inconsistencies in results on quality of life measures. For example, the overall differences in E-RS and SGRQ did not meet the MCID values defined in the literature, though analyses by responder status show that participants treated with ensifentrine in ENHANCE-1 were more likely to have clinically important improvements in quality of life compared with placebo. Additionally, changes in the E-RS and SGRQ in ENHANCE-2 were smaller than in ENHANCE-1. Study investigators pointed out that in ENHANCE-2, a higher proportion of COPD patients in the placebo group withdrew from treatment (41.9% vs. 23.4% in the ensifentrine group), leading to a less severe placebo group at week 24, as an explanation for why changes in ENHANCE-2 may have been smaller than in ENHANCE-1.[10] Finally, we did not have access to individual participant data, so we are unable to assess which patients may have had greater benefit from treatment. Given that a substantial portion of trial participants were on no maintenance therapy at baseline, understanding whether quality of life improvements differed between background therapy groups is important in understanding the magnitude of benefit that may be seen in real-world practice, where the vast majority of patients would be on some background therapy.

Both Phase III trials were relatively short, with the primary outcomes measured at 12 and 24 weeks. Although the differences in most outcomes appeared to be stable up to 24 weeks, longer-term data are needed to confirm the durability of ensifentrine's effects. For example, trials for roflumilast and dupilumab, which would similarly be add-on therapies for patients with symptomatic moderate-to-severe COPD, have some outcomes up to 52 weeks. Furthermore, the short duration of the trial may obscure seasonal effects, as exacerbations may be more prevalent in winter months when there are more respiratory viruses circulating. Long-term, real-world data are needed to confirm the magnitude of ensifentrine's benefits.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.8) is provided here.

Figure 3.8. 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*

ENHANCE-1 and ENHANCE-2 were parallel Phase III trials testing ensifentrine as an add-on therapy for patients with moderate to severe COPD. Results from these trials show overall benefit of ensifentrine in terms of lung function, exacerbation rate, and some parameters of quality of life; there were relatively few side effects. However, interpretation of the results must be done with caution, as there were some differences between trial participants and background therapy from real-world practice. In particular, more data are needed to assess the effect of ensifentrine in patients who are on dual LAMA+LABA therapy or triple LAMA+LABA+ICS therapy. Although such

patients were not included in the trial, there are some data to suggest that ensifentrine could add benefit in such populations without the potential side effects that limit use of roflumilast. There were also a large number of withdrawals from the trial. This may have biased the results for some outcomes. Finally, longer-term data are needed to assess the durability of effect.

While the results of ENHANCE-1 and -2 are promising, there remains some uncertainty about the magnitude of overall benefit in patients receiving the most optimized modern inhaler therapies for COPD, although there was no effect modification by background therapy type in the trials. We do not have significant concerns about harms with ensifentrine. For these reasons, we have high certainty that ensifentrine added to maintenance therapy, compared with maintenance therapy alone, results in at least a small net health benefit, and may result in substantial net health benefit (**"B+"**). We have somewhat greater certainty in the benefits when ensifentrine is added to the regimens studied than to regimens that combine LABA and LAMA therapy.

Table 3.5. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with Moderate to Severe COPD		
Ensifentrine + Maintenance Therapy	Maintenance therapy alone	B+

COPD: Chronic Obstructive Pulmonary Disease

Midwest CEPAC Votes

Table 3.5. Midwest CEPAC Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
***Patient Population for all questions**: Adults with Moderate to Severe COPD*		
Is the current evidence adequate to demonstrate that the net health benefit of ensifentrine added to maintenance therapy is superior to that of maintenance therapy alone?	11	4

The majority of the panel voted that the evidence is adequate to demonstrate that the net health benefit of ensifentrine added to maintenance therapy is superior to that of maintenance therapy alone in adults with moderate to severe COPD. The panel members expressed their uncertainty with the effectiveness of ensifentrine in patients taking dual or triple inhaler therapy, as well as in populations who were underrepresented in the clinical trials. They expressed their concerns of whether the trial resembles the real-world population and the inclusion and exclusion criteria of the study. The clinical experts and ICER staff expressed how trial withdrawals due to COVID-19 infection may have affected the results of the study. Patient experts expressed their experience with exacerbations and how there is a clear benefit to quality of life if there is any reduction with the number of exacerbations, as they may take three to six months to fully recover and risk their life and quality of life.

4. Long-Term Cost Effectiveness

4.1. Methods Overview

The primary aim of this analysis is to estimate the cost-effectiveness of ensifentrine added on to current maintenance therapy for the treatment of COPD relative to current maintenance therapy alone over a lifetime time horizon. The base-case took a health care sector perspective (i.e., focused on health care costs only). Patient and caregiver productivity impacts were considered in a modified societal perspective scenario analysis.

We developed a *de novo* decision analytic model in Microsoft Excel for this evaluation, informed by key clinical trials and prior relevant economic models.[60-64] Costs and outcomes were discounted at 3% per year.

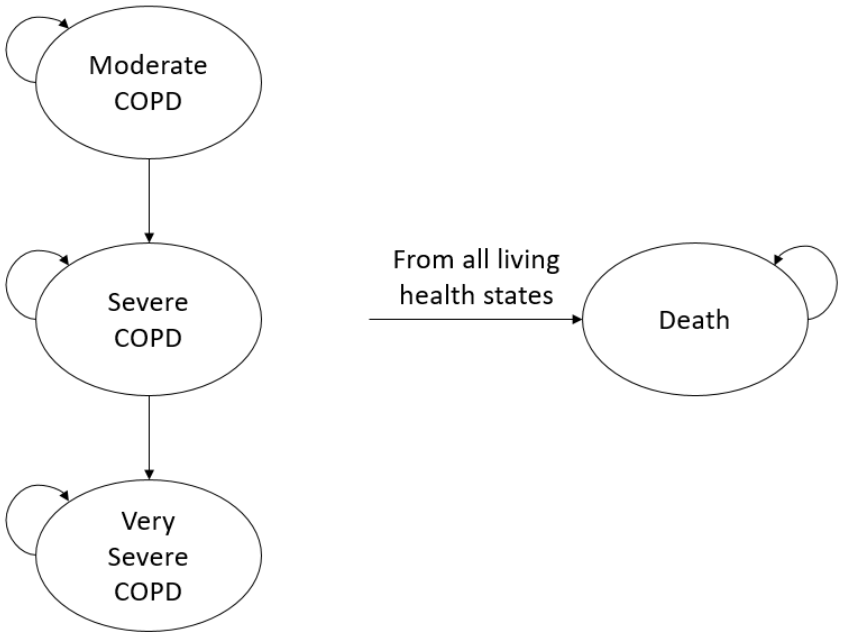
The Markov model focused on an intention-to-treat analysis, with a hypothetical cohort of patients with moderate to severe COPD being treated with either ensifentrine added on to current maintenance therapy or current maintenance therapy alone entering the model. The model cycle length was one year, and a lifetime time horizon was used.

The model had four primary health states (Figure 4.1), 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.[62] Members of the modeled cohort could only transition to more severe health states, and within each severity health state, exacerbations were tracked as events. Exacerbations were defined using an event-based definition based on the health care utilization required.[62] 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.[62] Exacerbations could have downstream implications on mortality, quality of life, and costs.

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

The findings within this report have been updated since the Evidence Report to now include the recently announced price for ensifentrine. The previously used placeholder price for ensifentrine has been replaced with the wholesale price announced by the manufacturer.

Figure 4.1. Model Structure



4.2. Key Model Assumptions and Inputs

Table 4.1 summarizes key model assumptions along with a rationale for each.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Members of the modeled cohort could only transition to more severe health states.	COPD is a progressive disease with irreversible effects on lung function.[64] Some economic models have allowed for transitions to a less severe health state in the first model cycle. We do not include this in our model due to the lack of evidence as well as concerns for double counting when assigning an effect for fewer exacerbations and an effect on moving to a less severe health state with fewer exacerbations.
Ensifentrine's effect on pulmonary function testing did not result in different health state transition probabilities between the intervention and the comparator.	Ensifentrine is not expected to be disease modifying, and thus it was not modeled to impact disease progression.

Assumption	Rationale
Ensifentrine's effect on improved quality of life was downstream of its effect on exacerbations. Ensifentrine's effect on pulmonary function testing did not result in daily improved quality of life in patients not experiencing exacerbations.	Data on the impact of ensifentrine on quality of life while patients were not experiencing an exacerbation was requested from the manufacturer to assess whether the differences in quality of life between the intervention and comparator arm of the trial was the result of ensifentrine's effect on exacerbations, pulmonary function, or both. However, these data were not provided and thus we assumed the improved quality of life associated with ensifentrine was the result of fewer exacerbations in alignment with other economic models. In a scenario analysis, we tested this assumption by assuming that ensifentrine results in higher health state utility estimates as compared to current maintenance therapy alone.
Individuals who discontinued ensifentrine due to adverse events discontinued at week 12. No subsequent discontinuation or treatment stopping was modeled.	Individuals who discontinued ensifentrine due to adverse events should be captured over the trial follow-up period. The ensifentrine effect size was not adjusted for discontinuation due to the intent to treat nature of the evidence source for the ensifentrine effect.
Adverse events associated with ensifentrine only impacted discontinuation. No costs or consequences were assigned to any specific adverse event.	Adverse events were comparable between the ensifentrine arm and the placebo arm of the trials.
Transition probabilities between COPD severity states do not differ by age, but they do depend on smoking status.	In past economic models that have incorporated age and smoking cessation into disease progression estimations, age and age^2 have not been statistically significant, but smoking cessation has been.[62]

COPD: Chronic obstructive pulmonary disease

Table 4.2 presents key model inputs, but greater detail on these inputs, along with a more comprehensive description of model inputs, can be found in the Supplement.

Table 4.2. Key Model Inputs

Parameter	Input	Source
Cohort with Moderate COPD at Baseline, %	78.1%	Mannino et al., 2022[65]
Cohort with Severe COPD at Baseline, %	21.9%	Mannino et al., 2022[65]
Exacerbations per Year, Moderate COPD,* Current Maintenance Therapy	1.17	Hoogendoorn et al., 2011[62]
Exacerbations per Year, Severe COPD,† Current Maintenance Therapy	1.61	Hoogendoorn et al., 2011[62]
Exacerbations per Year, Very Severe COPD,‡ Current Maintenance Therapy	2.10	Hoogendoorn et al., 2011[62]
Percent of Exacerbations that are Severe	13.7%	Hoogendoorn et al., 2011[62]
Percent of Exacerbations that are Moderate	86.3%	Hoogendoorn et al., 2011[62]
Ensifentrine Exacerbation Rate Ratio	0.60	ICER's meta-analysis of week 24 data from ENHANCE-1 and ENHANCE-2
Case-Fatality Rate per Severe Exacerbation	15.6%	Hoogendoorn et al., 2011[62]
Ensifentrine Adverse-Event Discontinuation	5.1%	ICER's combination of week 24 data from ENHANCE-1 and ENHANCE-2, excluding COVID cases
Ensifentrine Annual Cost	$35,400	Wholesale price of ensifentrine[66]
Current Maintenance Therapy Annual Cost	$3,453	Redbook, SSR Health
Health Care Cost per Moderate Exacerbation	$2,415	Bogart et al., 2020[67]
Health Care Cost per Severe Exacerbation	$26,047	Bogart et al., 2020[67]

COPD: Chronic obstructive pulmonary disease, %: percent

* 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

4.3. Results

Base-Case Results

Over a lifetime time horizon, treatment with ensifentrine is expected to result in fewer exacerbations, thus resulting in more QALYs, evLYs, and life years gained. The intervention costs (i.e., the costs to acquire ensifentrine) are greater with ensifentrine, but there are slightly fewer non-intervention costs (e.g., costs associated with exacerbations) in those treated with ensifentrine. Table 4.3 reports the base-case model outcomes for each arm of the model with incremental cost-effectiveness ratios reported in Table 4.4.

Table 4.3. Results for the Base-Case for Ensifentrine Added on to Current Maintenance Therapy as Compared to Current Maintenance Therapy Alone

Treatment	Intervention Cost	Total Cost	Total Exacerbations	QALYs	evLYs	Life Years
Ensifentrine + Current Maintenance Therapy	$284,000	$564,000	8.03	6.25	6.34	8.43
Current Maintenance Therapy Alone	$0	$284,000	12.26	5.68	5.68	7.71

evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case

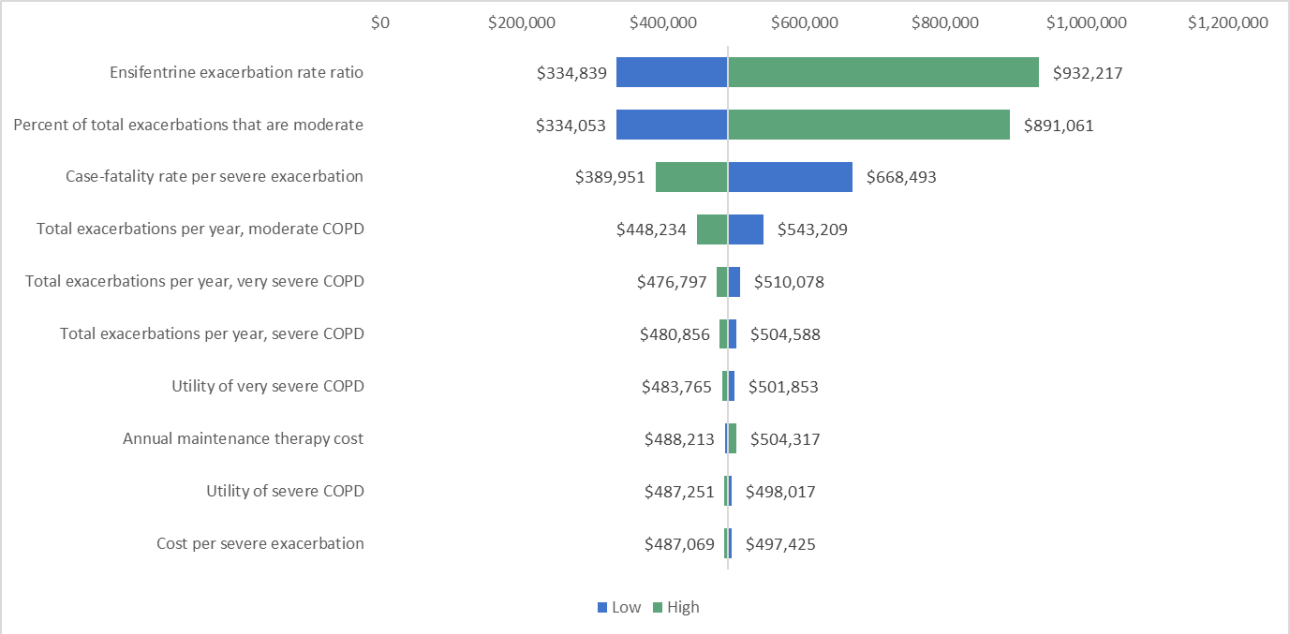
Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
Ensifentrine + Current Maintenance Therapy	**Current Maintenance Therapy Alone**	$492,000	$426,000	$387,000

evLYs: equal value of life years gained, QALY: quality-adjusted life year

Sensitivity Analyses

Figure 4.2 reports the inputs with the most influence on the incremental cost-effectiveness ratio. The parameters with the greater influence on the cost-effectiveness of ensifentrine were the ensifentrine exacerbation rate ratio, severity distribution of exacerbations, and the mortality risk associated with a severe exacerbation.

Figure 4.2. Tornado Diagram



COPD: Chronic obstructive pulmonary disease

Tables 4.5 and 4.6 present the probability of ensifentrine being cost-effective at common thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained, respectively. At the wholesale acquisition price for ensifentrine, 0% of the 1,000 iterations within the probabilistic sensitivity analysis resulted in incremental cost-effectiveness ratios beneath $150,000 per evLY gained.

Table 4.5. Probabilistic Sensitivity Analysis Cost per QALY Gained Results

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Ensifentrine	0%	0%	0%	0%

QALY: quality-adjusted life year

Table 4.6. 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
Ensifentrine	0%	0%	0%	1%

evLYs: equal value of life years gained

Additional sensitivity analysis result tables can be found in Section E of the Supplement.

Scenario Analyses

Table 4.7 reports the incremental cost per evLY gained for the base-case and three scenario analyses. Cost-effectiveness stayed nearly the same from the modified societal perspective. Cost-effectiveness improved in the scenario analysis that excluded future unrelated health care costs and in the scenario that assumed a positive effect of ensifentrine on quality of life.

Table 4.7. Scenario Analysis Results

Treatment	Base-Case ($/evLY)	Modified Societal Perspective ($/evLY)	Exclusion of Unrelated Costs ($/evLY)	Ensifentrine Effect on Quality of Life ($/evLY)
Ensifentrine	$426,000	$442,000	$402,000	$349,000

evLY: equal value of life year

Additional scenario analysis findings can be found in Section E of the Supplement.

Threshold Analyses

Tables 4.8 and 4.9 report the threshold prices at $50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained, respectively.

Table 4.8. QALY-Based Threshold Analysis Results

	WAC per Year	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Ensifentrine	$35,400	$3,900	$7,500	$11,000	$14,600

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Table 4.9. evLY-Based Threshold Analysis Results

	WAC per Year	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Ensifentrine	$35,400	$4,500	$8,600	$12,700	$16,800

evLYs: equal value of life years gained, WAC: wholesale acquisition cost

Uncertainty and Controversies

The health states in the model were defined by the GOLD classification which considers lung function to define disease severity and disease progression. There are newer classifications, such as the GOLD ABE classification, that factor in both symptoms and exacerbations to classify a patient's severity. These newer classifications are primarily used for guiding treatment recommendations,

but the underlying severity progression largely remains the same. We chose the GOLD classification to define our health states due to the vast amount of data for transitions, costs, and consequences stratified by the GOLD classifications. We do not anticipate dramatically different findings if a different classification was used for disease severity/progression due to the differential impact of the treatment that is primarily on exacerbations and not disease severity/progression.

Additionally, we did not assume that exacerbations impact disease progression. This assumption was aligned with the majority of economic models in COPD; however, a few models have incorporated a reduction in FEV_1 following an exacerbation. Most of those models were modeling FEV_1 decline over time, rather than modeling defined health states. We engaged with economic experts who had previously incorporated a link between an exacerbation and lung function and heard that the evidence to support this assumption is limited and it was not a key driver of the cost-effectiveness.

We also assumed that ensifentrine's effect on pulmonary function testing did not result in improved quality of life. Ensifentrine's effect on improved quality of life observed in the model was downstream of ensifentrine's effect on exacerbations. Data on the impact of ensifentrine on quality of life while patients were not experiencing an exacerbation was requested from the manufacturer to assess whether the differences in quality of life between the intervention and comparator arm of the trial was the result of fewer exacerbations, slower decline in lung function, or both. However, these data were not provided and thus we assumed the improved quality of life associated with ensifentrine was the result of fewer exacerbations in alignment with other economic models. In a scenario analysis, we tested this assumption by assuming that ensifentrine results in higher health state utility estimates as compared to current maintenance therapy alone. If data become available to suggest that ensifentrine improves quality of life outside of fewer exacerbations, the cost-effectiveness would improve.

There is variability, both in the regimens that are used and in the specific treatments within each regimen that are used, in the current maintenance therapy that people living with COPD use. Regimen- and treatment-specific evidence for the current maintenance therapy was only used to inform the cost of current maintenance therapy. We used the best available source (i.e., source with a large representative sample and estimates stratified by GOLD classification) to inform the basket of regimens and treatments within current maintenance therapy; however, the dates included in this source largely predated LABA/LAMA combination products. To account for this potential limitation, we varied the cost of current maintenance therapy across a very wide range in the sensitivity analyses. Variability in the cost of the current maintenance therapy had a very small impact on the overall findings given ensifentrine is added on to current maintenance therapy.

Finally, the findings from the modified societal perspective scenario analysis may not fully represent the impact of COPD on patients and caregivers. The current modified societal perspective includes

patient productivity and caregiver time spent caregiving. Data on other indirect impacts such as caregiver quality of life were not available for inclusion.

4.4 Summary and Comment

These analyses suggest that treatment with ensifentrine results in fewer exacerbations and in greater QALYs, greater evLYs, and greater life years. At a wholesale acquisition cost of $35,400 per year, the incremental cost-effectiveness ratio for ensifentrine exceeds commonly used thresholds. If ensifentrine is shown to increase the day-to-day quality of life of patients living with COPD, beyond quality of life improvements associated with fewer exacerbations, cost-effectiveness improves but still remains above commonly used thresholds.

5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There is substantial unmet need despite currently available treatments.	Almost half of persons with COPD report that symptoms affect their daily life at least 24 days out of the month and 54% of patients on triple therapy were dissatisfied with the current control of their COPD.[4,8] Additionally, side effects from current therapies can limit their use. Therefore, there is substantial need for new therapies. To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported below: evLY shortfalls: • Absolute evLY shortfall: 8.11 • Proportional evLY shortfall: 53.8% QALY shortfalls: • Absolute QALY shortfall: 7.50 • Proportional QALY shortfall: 51.8% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality-adjusted life expectancy, respectively, that would be lost due to untreated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system.	Rates of COPD are higher in the American Indian/Alaska Native populations compared with the general US population.[68] The Health Improvement Distribution Index (HIDI) for the American Indian/Alaska Native population is 1.7.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.	Ensifentrine is not thought to be disease-modifying and is not likely to have a large effect on caregivers' quality of life and/or their ability to pursue their own goals in the long-term.

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.	Although ensifentrine has a novel mechanism of action, its delivery is via standard nebulizer and thus it is not likely to have an effect on access.

evLY: equal value of life years, COPD: Chronic obstructive pulmonary disease, QALY: quality-adjusted life-year, HIDI: Health Improvement Distribution Index

Midwest CEPAC Votes

At the public meeting, the Midwest CEPAC deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements:

Table 5.3. Midwest CEPAC Votes on Benefits Beyond Health and Special Ethical Priorities - Condition

Benefits Beyond Health and Special Ethical Priorities	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
There is substantial unmet need despite currently available treatments	0	2	0	9	4
This condition is of substantial relevance for people from a health/ethnic group that have not been equitably served by the health care system.	0	0	5	8	2

The majority of the panel members voted that they "agree" or "strongly agree" there is substantial unmet need despite currently available treatments. Two panel members voted that they "strongly disagree." The patient experts spoke about the great possibility of this new therapy reducing their exacerbations. "They spoke about how each exacerbation can have long-lasting effects or end in death. They also spoke about how a reduction in exacerbation can lead to reduced stress on families, in part by decreasing costs and increasing the ability of the patient to participate in life activities. The clinical experts expressed that while they are always worried about potential side effects of a new therapy, this treatment has the potential to improve symptom burden and thus may be beneficial to some patients with COPD.

By a majority vote by one, eight panelists "agreed" that there is substantial relevance for people from a health/ethnic group that have not been equitably served by the health care system. Five panel members voted "neutral," while two panel voted that they "strongly agree." The panel members spoke about the inadequate representation of American Indian/Alaska Natives in the trials, as they are the most disproportionately affected based on population size. The panel spoke

about the possible effects of smoking and other environmental factors, access to health technology for testing, and access to formal diagnosis. While the panel remained unsure about the access to treatment for these racial/ethnic groups, they expressed their concerns for the various barriers to access.

To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements based on the relative effects of ensifentrine added to maintenance therapy versus maintenance therapy alone.

Table 5.4. Midwest CEPAC Votes on Benefits Beyond Health and Special Ethical Priorities - Treatment

Benefits Beyond Health and Special Ethical Priorities	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life	0	2	10	3	0
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery	0	4	8	3	0

The majority of the panel members voted "neutral" that ensifentrine added to maintenance therapy is likely to produce substantial improvement in caregivers' quality of life, while two panel members voted "disagree" and three panel members voted "agree." The panel heard from patient experts about how caregivers are necessary when dealing with exacerbations, as they are unable to proceed with their normal functions entirely. They expressed how a caregiver having to always be present when dealing with exacerbations brings a burden on the caregivers' mental health that also reflects on the patient themselves. However, panel members expressed their mixed feelings as they compared chronic effects to periodic effects of day-to-day life.

By a one-vote majority, eight panel members voted "neutral" that this treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery. Four panel members voted that they "disagree," while three panel members voted that they "agree." Many panelists expressed their hesitancy for the treatment's effects, claiming that it may have a marginal benefit for a small population. However, clinical and patient experts expressed how patients who have difficulty using inhalers properly could benefit from having this treatment, which is administered by nebulization.

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of ensifentrine are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained. The HBPB for ensifentrine is $7,500 to $12,700 per year.

Table 6.1. Annual Cost-Effectiveness Threshold Prices for Ensifentrine

Annual Prices Using…	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
QALYs Gained	$35,400	$7,500	$11,000	69%-79%
evLYs Gained	$35,400	$8,600	$12,700	64%-76%

evLY: equal value life year, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Midwest CEPAC Votes

Long-term value for money votes were not taken at the public meeting because a net price for ensifentrine was not available.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of ensifentrine as an add-on therapy to current maintenance therapy compared to current maintenance therapy alone for adults with moderate to severe COPD. In alignment with the cost-effectiveness analysis, current maintenance therapy was represented by a combination of treatments informed by retrospective administrative claims data.[69] We used an annual WAC price of $35,400 for ensifentrine, and the three threshold prices (at $50,000, $100,000, and $150,000 per evLYG) in our estimates of budget impact.

This potential budget impact analysis includes the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we used inputs for the size of the adult U.S. population 271,616,592 (average over 2024-2028), the prevalence of COPD in adults (5.6%), and the percentage of adult patients with moderate-to-severe COPD (63.3%).[12,65] Applying these sources results in estimates of 9,628,265 eligible patients in the US. For the purposes of this analysis, we will assume that 20% of these patients would initiate treatment in each of the five years, or 1,925,653 patients per year.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. The five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $735 million per year for new drugs. ICER's methods for estimating potential budget impact are described in detail in Section F of the Supplement.

7.2. Results

Figure 7.1 illustrates the cumulative annual per patient treated potential budget impact for ensifentrine as an add-on therapy to current maintenance therapy compared to current maintenance therapy alone. At ensifentrine's WAC price of $35,400 annually, the average annual budget impact per patient treated, per year, was $30,111 in Year 1 with cumulative net annual costs increasing to $143,468 in Year 5.

Figure 7.1. Cumulative Annual Per-Patient Treated Budget Impact of Ensifentrine as an Add-on Therapy to Current Maintenance Therapy Compared to Current Maintenance Therapy Alone for Adults with Moderate to Severe COPD

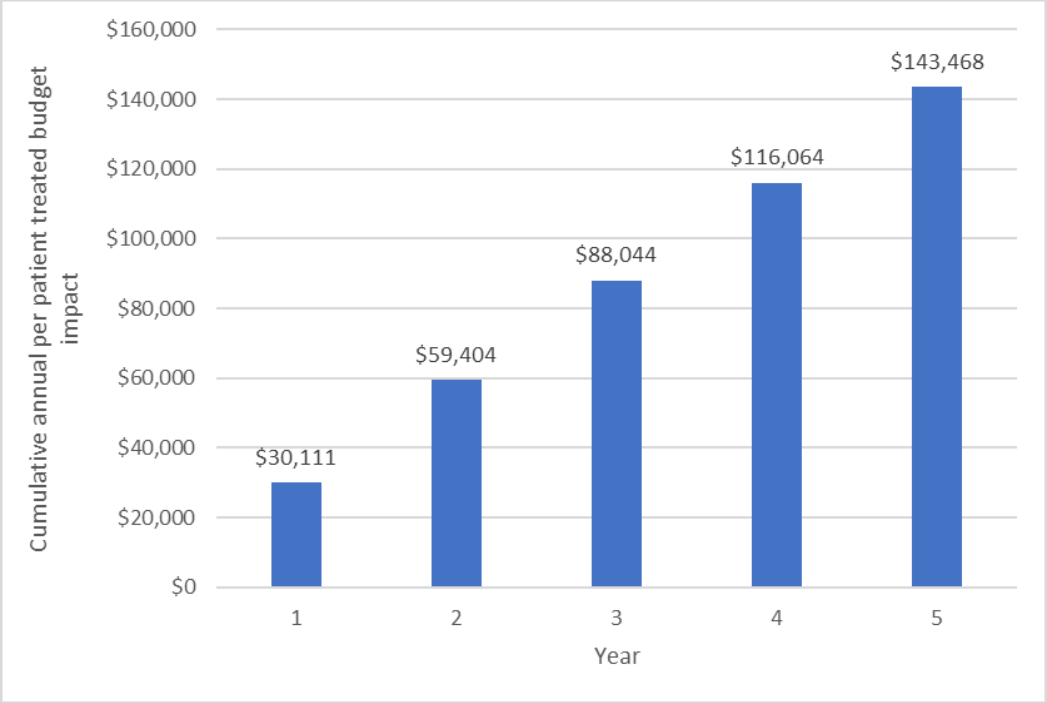
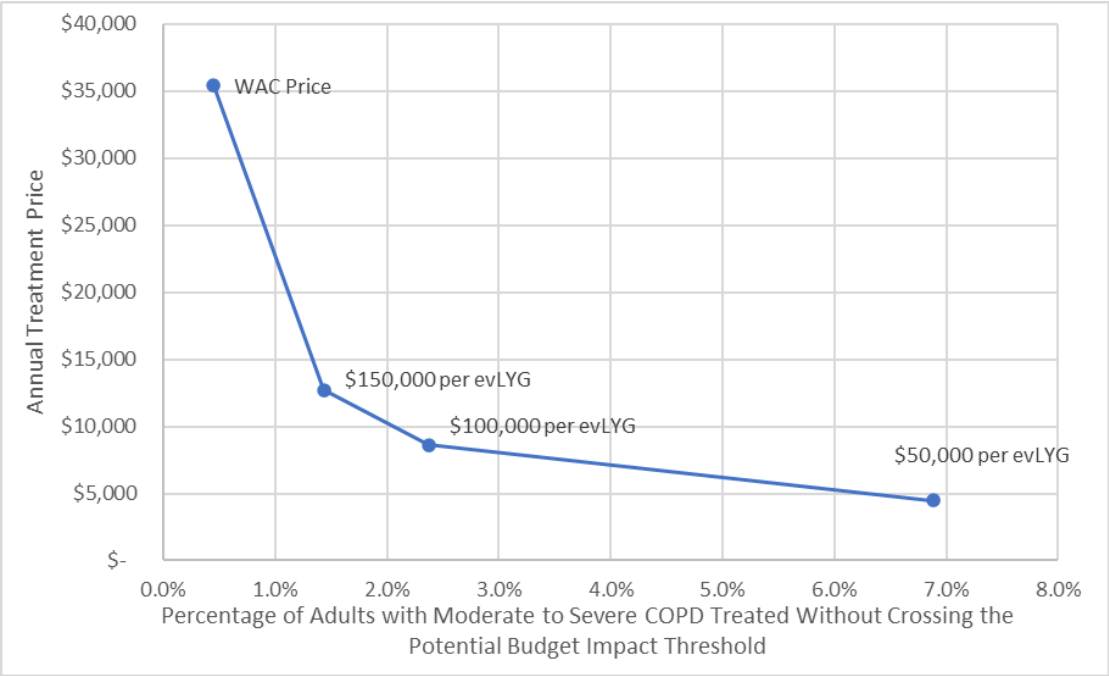


Figure 7.2 illustrates the potential budget impact of ensifentrine as an add-on therapy to current maintenance therapy. At the placeholder price, approximately 0.5% of adults living with moderate to severe COPD who are eligible for treatment could be treated with ensifentrine without crossing the ICER potential budget impact threshold of $735 million per year. At prices to reach thresholds of $150,000, $100,000, and $50,000 per evLYG ($12,706, $8,596, and $4,486), approximately 1.4%, 2.4%, and 6.9% of adults living with moderate to severe COPD, respectively, could be treated over five years without reaching the ICER potential budget impact threshold of $735 million per year.

Figure 7.2. Potential Budgetary Impact of Ensifentrine (at the WAC Price and three Threshold Prices) as an Add-on Therapy to Current Maintenance Therapy Compared to Current Maintenance Therapy Alone for Adults with Moderate to Severe COPD



COPD: chronic obstructive pulmonary disease, evLYG : equal-value life year gained

Access and Affordability Alert

Assuming ensifentrine's current wholesale acquisition cost ($35,400 annually), approximately 0.5% of the roughly 9.1 million US patients with moderate to severe COPD could be treated within five years without crossing the ICER potential budget impact threshold of $735 million per year. The percentage of patients with moderate to severe COPD who continue to have suboptimal control of their disease despite therapy is uncertain; however, one clinical expert indicated that 30 to 50% of patients would likely benefit from additional treatment. Even if the estimated potentially eligible patient population was reduced by 50%, the potential budget impact would remain substantial with less than 1% of the potentially eligible population treated without crossing the potential budget impact threshold. Additional efforts to achieve affordability and access must be considered, thus we are issuing an access and affordability alert.

The purpose of an ICER affordability and access alert is to signal to stakeholders and policymakers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients.

8. Policy Recommendations

Following the Midwest CEPAC's deliberation on the evidence, a policy roundtable discussion was moderated by Dr. Steve Pearson around how best to apply the evidence on the use of ensifentrine. The policy roundtable members included two patient advocates, two clinical experts, and two payers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found here.

Health Equity

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with chronic obstructive pulmonary disease (COPD) are introduced in a way that will help reduce health inequities.

There are important inequities today in the diagnosis and treatment of COPD. Disparities in smoking rates and socioeconomic factors contribute to increased prevalence and worse outcomes of COPD among American Indian/Alaska Native populations, yet their access to diagnosis and treatment lags many other groups.[70,71] African Americans diagnosed with COPD have a higher risk of exacerbations and worse disease status.[72] Women are more likely to report a delay in diagnosis, in part due to lower smoking rates (three-fourths of never smokers with COPD are women).[16,73] Finally, people who live in rural communities have greater age-adjusted mortality due to chronic lower respiratory disease, in part due to disparities in access to care.[74]

There is also documented widespread underuse of spirometry for the diagnosis of COPD across all populations.[75] Spirometry is important in achieving accurate diagnoses and in guiding management of COPD, yet data suggest that only around 15% of patients with COPD receive a spirometry test in the year prior to diagnosis, and only about one-third are tested in the year following diagnosis.[76] Numerous reasons have been documented for this underuse, including difficulties accessing lung function laboratories, lack of education about COPD and COPD guidelines, overburdened primary care visits, lack of access to pulmonary specialists, as well as age and comorbidities.[77] Patients who require supplemental oxygen have additional challenges. Due to issues with reimbursement, not all forms of supplemental oxygen are readily available, which may affect mobility and quality of life for people living with COPD.[78] Furthermore, there is low utilization of pulmonary rehabilitation programs, which have been shown to improve COPD disease outcomes, in part due to substantial geographic disparities in access to programs.[23,79] Thus, reducing inequities in COPD diagnosis and care will require multi-pronged efforts by multiple stakeholders.

To address these concerns:

Manufacturers should take the following actions:

- Include a more diverse patient population in clinical trials, including reflecting the racial and ethnic makeup of the affected population as closely as possible, and including never smokers, who make up an increasing proportion of the COPD population and who are often excluded from COPD clinical trials.

Payers should take the following actions:

- Work with provider groups to improve the basic infrastructure for the diagnosis and management of COPD, including expansion of access and reimbursement for spirometry (e.g., expansion of testing in primary care, pharmacist-led spirometry clinics[80]), and development of telemedicine networks to support primary care-specialist collaboration in the care of patients in areas where specialists are in short supply.

- Ensure that benefit designs developed in conjunction with employers and other plan sponsors do not create requirements for out-of-pocket spending that create major barriers to appropriate access for vulnerable patients.

- As the dominant payer for patients with COPD, Medicare should revise its reimbursement policies for supplemental oxygen. Currently, all forms of oxygen are reimbursed similarly and thus more expensive forms of oxygen, which allow patients with severe and very severe COPD more mobility and a better quality of life, are not easily accessible. To address this concern, Medicare should set differential reimbursement rates such that more expensive forms of oxygen (e.g., liquid oxygen) are accessible to patients who meet guideline-based criteria for use (e.g., patients who are mobile outside the home and who need >3 liters/minute of continuous flow oxygen during exertion).[81] Additionally, guidelines for oxygen coverage should ensure adequate coverage to maximize patients' ability to effectively carry out their daily activities with minimal burdens.

- Medicare also should take steps to improve access to and appropriate use of pulmonary rehabilitation.

Clinical specialty societies should take the following actions:

- Encourage evidence-based, appropriate use of spirometry for the diagnosis and management of COPD by all clinicians caring for people living with COPD. This effort will require educating physicians - particularly primary care physicians – to refer patients for spirometry to confirm diagnosis of COPD, and advocating for increased access and adequate reimbursement for spirometry.

- Clinical specialty societies should continue to use their voice to help advocate for better access to all effective therapies for COPD, including affordable inhalers and access to supplemental oxygen and pulmonary rehabilitation.

Patients and patient advocacy groups should take the following actions:

- Develop and disseminate educational materials to encourage persons with symptoms of COPD to have spirometry testing for an accurate diagnosis.

- Continue to advocate for better access to standard of care therapies (e.g., inhalers, pulmonary rehabilitation), as well as increased access to oxygen and better oxygen systems, as exemplified by the Four Pillars of Oxygen Reform and the Supplemental Oxygen Access Reform Act legislation introduced in the US Congress, and advocated by the COPD Foundation, among others.[82]

- Encourage patients from diverse populations to participate in clinical trials so that clinical trials can accurately reflect the real-world COPD population.

Policymakers/Regulators/Funders should take the following actions:

- State policymakers should extend COVID pandemic-era expansion of telemedicine policies and consider joining interstate compacts that allow for inter-state consultations and broader reimbursement. Many people with COPD will benefit from specialist care, but a shortage of pulmonologists in many areas leads to delays in timely diagnosis and treatment of COPD.

- The FDA and research funders should use all available mechanisms to increase enrollment of underrepresented populations (including never smokers) in clinical trials of COPD treatments, such that the populations being studied adequately reflect real-world COPD populations.

Payers

Recommendation 1

Payers should include coverage of effective smoking cessation therapies, including nicotine replacement products, pharmacologic therapies, cognitive behavioral therapy (CBT) and combinations thereof, as smoking cessation is a critical part of the treatment of COPD.

Given that many patients with COPD continue to smoke, and that continued smoking is associated with a greater risk of exacerbations and more rapid progression of disease, smoking cessation is a critical part of COPD treatment.[83-85] Effective smoking cessation interventions include nicotine

replacement products, pharmacologist therapies such as bupropion and varenicline, and cognitive behavioral therapy. Because the reasons for continued smoking and the efficacy of interventions vary amongst populations, payers should work to increase access to smoking cessation interventions, including over-the-counter products, to allow for tailoring of treatment to individual patient needs.[86] Furthermore, payers should work with clinicians to promote collecting accurate smoking histories in the medical record to ensure that patients who are smokers can be readily identified and receive appropriate treatment as part of their care for COPD.

Manufacturers

Recommendation 1

Manufacturers should set prices that will foster affordability and access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. For ensifentrine, the manufacturer has priced far above this level and therefore missed an opportunity to provide broad access and increased uptake of the drug.

Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatments, but also contribute to general health care cost growth that pushes families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful. For patients with moderate to severe COPD, particularly those with other medical comorbidities, the cost of multiple inhalers can be high and a substantial portion of patients report cost-related non-adherence.[29]

With a new mechanism of action to treat COPD and a favorable side effect profile, there is likely to be significant interest in using ensifentrine for many patients with COPD. Given the large COPD population, the manufacturer of ensifentrine has an important opportunity to support broad access by setting the price in fair alignment with the proven benefits for patients. With current evidence, the ICER report estimated an appropriate health benefit price benchmark to be between $7,500 and $12,700 per year. However, the manufacturer has set an initial launch price of $35,400 per year.[66] At this price, payers are likely to limit access to the drug by administering more stringent prior authorization criteria and/or by placing it on a more expensive pharmacy tier. As a result, it will be more difficult for patients to gain access to an effective drug.

Recommendation 2

The manufacturer of ensifentrine should set up broad distribution networks to limit barriers to access.

The manufacturer should work to ensure a wide distribution network as opposed to limiting access to specific pharmacy networks. Because ensifentrine is a nebulized drug and may be covered under either the medical (durable medical equipment [DME]) or pharmacy benefit, having a wide

distribution network (i.e., both pharmacies and DME suppliers) would simplify access for patients and minimize out-of-pocket costs.

Researchers/Regulators

Recommendation 1

Conduct research that directly compares real-world treatment options and sequential treatment effectiveness.

Once FDA approval is obtained, there is often little incentive for manufacturers to pursue head-to-head trials with current standard of care therapies. Appropriate head-to-head trials would inform decision-making by patients and clinicians, particularly as new agents come to market, and there is a role for funders such as NIH and PCORI to encourage and fund such studies. For example, in the case of ensifentrine, the ENHANCE trials were conducted at a time when the standard of care for COPD was different than current guidelines and so it was not tested in patients who were already on dual LAMA/LABA or triple LAMA/LABA/ICS therapy. Despite the lack of evidence, clinical experts indicated that they were most likely to use ensifentrine as add-on therapy to dual or triple therapy. Thus, comparative effectiveness trials are needed to help determine ensifentrine's effectiveness when added on to dual or triple therapy and the subgroups who would benefit most from therapy.

Recommendation 2

Develop new research programs on biomarkers to improve future diagnosis of COPD and to better target treatments to patients who would gain the greatest benefit from new therapies.

The diagnosis of COPD is currently spirometry-based, and as discussed above, there are barriers to accessing spirometry. As a result, some people with symptoms of COPD do not have a formal diagnosis while other people are told they have COPD when they do not actually have the disease.[75] Thus, other methods of diagnosing COPD are needed to both improve diagnostic accuracy and identify potentially untreated COPD patients.[1] For example, computed tomography (CT) scans are now readily available. With the increased use of CT scans for lung cancer screening, for example, developing imaging criteria of COPD could be helpful in securing diagnoses, particularly in more rural areas, where access to spirometry may be difficult.

Additionally, emerging evidence demonstrates that there are likely different subtypes of COPD, even beyond the traditional chronic bronchitis versus emphysema categories.[1] For example, the presence of high levels of eosinophils may represent a more inflammatory type of COPD, which may correspond to a greater response to anti-inflammatory medications such as inhaled corticosteroids. However, more research is needed to define which biomarkers are most useful to define subgroups and tailor treatment. With newer, more expensive treatments for COPD in the pipeline (e.g., ensifentrine, dupilumab), defining treatment subgroups will become increasingly important.

Additionally, as biomarkers are validated, the FDA should consider adding guidance to expand the number of biomarkers accepted as trial outcomes and encourage implementation of biomarker outcomes into drug development programs.[1]

Recommendation 3

Expand the set of outcome measures for studies of COPD interventions in order to capture the broader effects of treatment on patients' lives.

The FDA currently focuses on lung function (FEV1), exacerbations, and death for drug approvals. While these are core measures for COPD, they do not fully capture the ways that treatments may help patients. The FDA should seek to include additional outcome measures, including more patient-centered outcome measures, in developmental programs for interventions for people living with COPD.[1]

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Chronic Obstructive Lung Disease (COPD): A heterogenous group of lung conditions 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. Subtypes include emphysema and chronic bronchitis. The most common symptoms include dyspnea, cough, and sputum production.[87]

Long-acting muscarinic antagonists (LAMA): A bronchodilator treatment that works by blocking the bronchoconstriction effect of acetylcholine. This prevents the neurotransmitter from causing the muscles surrounding the lungs' airways to constrict, reducing symptoms of COPD.[88]

Long-acting beta-adrenoceptor agonists (LABA): A bronchodilator treatment option that induces smooth muscle relaxation by stimulating beta-adrenergic receptors.[88]

Inhaled corticosteroids (ICS): An anti-inflammatory therapeutic option for COPD that can be taken alone or in combination with LAMA and/or LABA treatment. Targeting lung inflammation with ICS can have clinical benefits on lung function, symptoms, and exacerbation risk, but it can also be associated with adverse effects including an increased risk of pneumonia.[89]

Dual bronchodilator therapy (dual therapy): A combination of LAMA and LABA therapies. These can either be delivered separately or as a fixed dose combination and are usually offered to patients who have had COPD exacerbations (see guidelines in Section C).

Triple bronchodilator therapy (triple therapy): A combination of LAMA, LABA, and ICS therapies. These are delivered in various combinations: LAMA+LABA+ICS, LABA/ICS + LAMA, LAMA/LABA + ICS, or LAMA/LABA/ICS as a fixed dose combination. Triple therapy is usually offered to patients who have a history of one or more recent moderate or severe exacerbations or those who continue to have exacerbations on monotherapy and have eosinophils count ≥300 cells/µL.

Eosinophil count: A measure of the number of eosinophils per microliter of blood. High blood eosinophil count (≥300 cells/µL) serves as a biomarker for response to ICS in preventing acute exacerbations.[90]

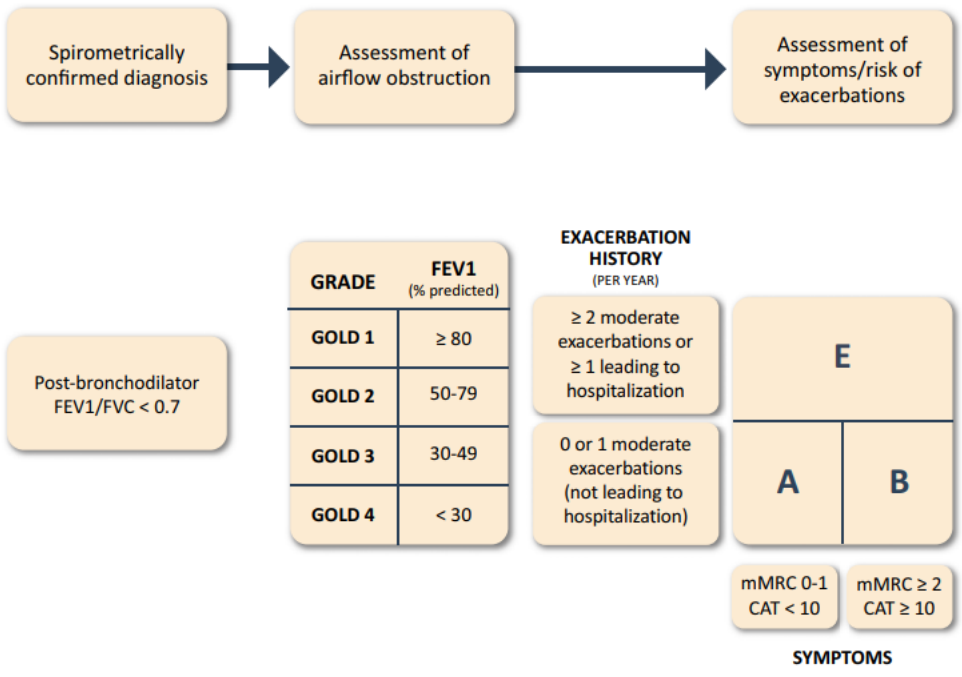
Rescue medication: A medicine used to quickly relieve symptoms of COPD when experiencing a sudden worsening of symptoms.

Assessments of Symptoms and Severity in COPD

The modified Medical Research Council (mMRC) dyspnea scale: The mMRC scale is a self-assessment tool used to measure the level of impairment caused by breathlessness during daily activities in respiratory diseases, such as COPD. Ratings on the scale ranges from 0 to 4, with 0 representing no breathlessness except during strenuous exercise; and 4 being too breathless to leave the house, or breathless when dressing.[91]

Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification: A measure of the severity of airflow obstruction, based on spirometry testing.[87] Patients have a spirometrically confirmed diagnosis (i.e., post-bronchodilator $FEV_1/FVC < 0.7$). Next, patients have an assessment of airflow obstruction and are categorized into different GOLD categories (GOLD 1, 2, 3, and 4) based on their FEV_1 % predicted. Finally, patients are assessed for their symptoms and risk of exacerbations are classified into three groups: group A (those with 0 or 1 moderate exacerbation, mMRC of 0-1, and COPD Assessment Test [CAT] <10), group B (those with 0 or 1 moderate exacerbation, mMRC ≥2, and CAT ≥10), and group E (≥2 moderate exacerbation or ≥1 severe exacerbation leading to hospitalization). See Figure A1 for a visual description of the categories.

Figure A1. GOLD ABE assessment tool from Agusti et al (2023)[87]



Lung Function Outcome Measures Definitions

Spirometry: A test used to measure the ability of a person to inhale and exhale air respective to time. Measurements from spirometry are used to help classify severity of disease (see GOLD classification above). Common measurements from spirometry include FEV_1, forced vital capacity (FVC), and forced expiratory volume (FEV_1).

Forced vital capacity (FVC): The maximal volume of air that can be expired following maximum inspiration.

Forced expiratory volume in 1 second (FEV_1): The volume of air (in liters) exhaled in the first second during forced exhalation after maximal inspiration.[10]

Patient-Important Outcomes Definitions

Minimal clinically important difference (MCID): The smallest change in an outcome that represents a meaningful change for the patient.

COPD exacerbations: Defined as worsening of COPD symptoms (two or more major symptoms or one major and one minor symptom).

- Moderate exacerbation: Worsening of COPD symptoms for >2 days requiring a minimum of 3 days of therapy with oral or systemic corticosteroids and/or antibiotics.
- Severe exacerbation: Worsening of COPD symptoms requiring inpatient hospitalization.[10] Major symptoms: Dyspnea, sputum volume, sputum purulence (color)[10]
- Minor symptoms: Sore throat, colds (nasal discharge and/or nasal congestion), fever (oral temperature >37.5 °C) without other cause, increased cough, increased wheeze[10]

EuroQol-5-Domain Questionnaire (EQ-5D-5L): A self-reported, standardized instrument designed to measure health utility in terms of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L scale ranges from 0-100, with higher scores representing better health. EQ-5D-5L utility index ranges from -0.59 to 1, with 1 being the best possible health state. The anchor-based minimal clinically important difference (MCID) for EQ-5D-5L utility index ranged from 0.037 to 0.063 in those with a COPD diagnosis.[46]

Transitional Dyspnea Index (TDI): Interviewer-administered rating used to measure change in dyspnea in 3 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 1-unit change has been determined to be MCID for those with a COPD diagnosis.[42]

Evaluating-Respiratory Symptoms (E-RS) Total Score: Patient-reported outcome that evaluates the effect of treatment on the severity of respiratory symptoms in stable COPD. This measure consists of 11 items which are specific to respiratory symptoms, including breathlessness, cough and sputum, and chest symptoms. Total score ranges from 0-40, MCID: ≥2.0-point reduction[41], based on three subscales:

- Severity of breathlessness subscale (RS-breathlessness): Score range from 0-17, MCID: ≥1.0-point reduction;
- Cough and sputum subscale (RS-cough and sputum): Score range 0-11, MCID: ≥0.7-point reduction;
- Chest symptoms subscale (RS-Chest symptoms): Score range 0-12, MCID: ≥ 0.7-point reduction.

In the ENHANCE trials, participants reported symptoms every evening and scores were calculated by taking the sum of the items for the total score. Higher values indicate more severe symptoms.[41]

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).[45] Scores range from 0 to 100, with higher scores indicating more health limitations. A mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment in COPD and asthma.[44] However, a recent thesis reported that for those with moderate to very severe COPD, the MCID should be at least 7 points.[45]

Health Care resource utilization: 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.[10]

Daily average rescue medication: The mean number of self-reported rescue medication puffs/day over 7 a day period.[10]

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.[92] 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.[93,94] 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 QALY and 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 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 HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

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 ensifentrine and did not receive any feedback on this topic.

B. Patient Perspectives: Supplemental Information

B1. Methods

To gather stakeholder perspectives for this report, we engaged with people living with COPD, patient advocacy groups, including representatives from COPD advocacy organizations, clinical experts, and two payers to gather information to better understand the experience and treatment of COPD.

We spoke with six people in the US living with moderate to severe COPD, referred to us by COPD Foundation. We spoke with people who were diagnosed at a variety of ages, lived in geographically disparate areas, and who were and were not oxygen-dependent. We also spoke with two patient advocacy groups, both general respiratory health and COPD specific.

We interviewed nine clinical experts with expertise diagnosing, treating, and/or researching COPD. All were pulmonologists practicing in academic and Veteran's Affairs settings throughout the US. Clinical experts were referred to us by the manufacturer, patient organizations, and other clinical experts.

We spoke with two payers from different parts of the US, a commercial health plan based in the northeast US and a Medicaid plan based in the southern US.

C. Clinical Guidelines

American Thoracic Society (ATS) 2020 Clinical Practice Guideline for the Pharmacologic Management of COPD[95]

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.[95]

The National Institute for Health and Care Excellence (NICE) 2019[96]

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 + LABA. 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 3 months of ICS use, then the patient should revert to LABA + LAMA. If the patient has asthmatic features or features suggesting steroid responsiveness, they should be offered LABA + ICS. If patients continue to have symptoms that impact quality of life or have one severe or two moderate exacerbations in a year, they should be offered triple therapy.[96]

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023[5]

The recommended pharmacological treatment for patients with COPD is based upon which group they would be best placed in. Patients with COPD group A should be offered a bronchodilator. Patients in group B should be offered LABA + LAMA, preferably as a single inhaler. Patients in group E should be offered LABA + LABA and consider offering triple therapy if eosinophils count is ≥300 cells/µL. 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 or treating other causes of dyspnea. Those with exacerbations on monotherapy should also receive LABA + LAMA, except those with eosinophils count is ≥300 cells/µL, who should be offered LABA + LAMA + ICS. For patients on LABA + LAMA and persistent exacerbations, they should be offered LABA + LAMA + ICS if their eosinophil count is ≥100 cells/µL. For patients who continue to have exacerbations on triple therapy, the addition of roflumilast or a macrolide antibiotic such as azithromycin may be considered. ICS should be used when: 1) there is a history of hospitalization for exacerbations of COPD; 2) ≥2 moderate exacerbations of COPD per year, 3) eosinophils ≥300 cells/µL; or 4) there is a history of asthma. ICS *could* be considered when: 1) there is 1 moderate exacerbation of COPD per year; or 2) eosinophil count is 100 to <300 cells/µL. However, ICS should not be used when: 1) there are repeated pneumonia events; 2) eosinophil count is <100 cells/µL; or 3) there is a history of mycobacterial infection.[5]

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for the review was adults with moderate to severe chronic obstructive pulmonary disease (COPD).

Data permitting, we evaluated the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors (e.g., sex, age [e.g., >75 years], socioeconomic status)
- Medical comorbidities (e.g., hypertension, osteoporosis, obesity, cardiovascular disease, diabetes, frailty)
- Eosinophil count (e.g., ≥300 cells/µl)
- People with frequent exacerbations (e.g., at least one exacerbation in the past year)
- Emphysema (i.e., destruction of alveoli causing difficulty with oxygen exchange) versus chronic bronchitis (i.e., airway inflammation that causes mucus production)
- Moderate versus severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] classification 2 versus 3)

Interventions

The intervention of interest for this review was:

- Ensifentrine (Verona Pharma)

Comparators

We examined ensifentrine as an add-on therapy to current COPD maintenance therapy versus no additional treatment.

- Current maintenance drug therapies may include:
    - Long-acting beta-agonists (LABAs)
    - LABA and inhaled corticosteroids (ICS)
    - Long-acting muscarinic antagonists (LAMAs)

- LAMA and ICS
- LABA and LAMA
- Triple therapy: LABA, LAMA, and ICS

Outcomes

The outcomes of interest are described in the list below.

- 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
- 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

Timing

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

Settings

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

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	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, organizations, 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	Item #	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	Item #	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 ensifentrine for treatment of moderate to severe COPD followed established best research methods.[97,98] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[99] 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 supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. 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. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data).

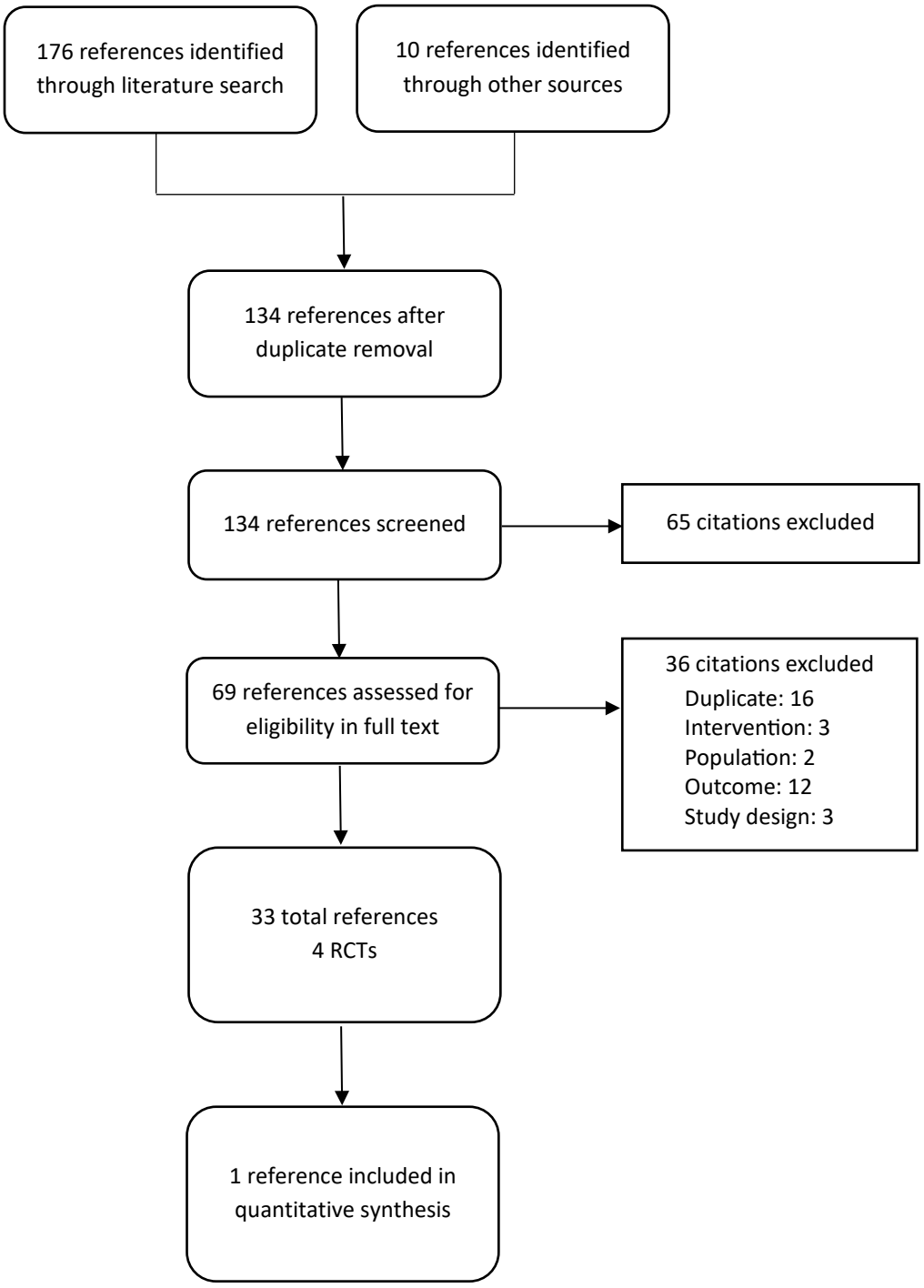
Table D1.2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

1	exp chronic obstructive pulmonary disease/
2	('Chronic Obstructive Lung Disease*' or 'COAD' or 'COPD' or 'Chronic Obstructive Airway Disease' or 'Pulmonary Disease, Chronic Obstructive' or 'Airflow Obstruction, Chronic' or 'Airflow Obstructions, Chronic' or 'Chronic Airflow Obstruction*').ti,ab.
3	1 or 2
4	('ensifentrine' or 'RPL 554' or 'RPL554' or 'RPL-554').ti,ab.
5	3 and 4
6	(animals not (humans and animals)).sh.
7	5 NOT 6
8	(addresses OR autobiography OR bibliography OR biography OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR guideline OR interactive tutorial).pt
9	7 NOT 8
10	limit 9 to English language
11	Remove duplicates from 10

Table D1.3. Search Strategy of EMBASE

1	'chronic obstructive pulmonary disease'/exp
2	'chronic airflow obstruction' OR 'chronic airway obstruction' OR 'chronic obstructive bronchopulmonary disease' OR 'chronic obstructive respiratory disease' 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' OR 'chronic obstructive lung dis*' OR 'chronic obstructive pulmonary dis*' OR 'chronic pulmonary obstructive dis*'
3	#1 or #2
4	'rpl 554' OR 'rpl554' OR 'vmx 554' OR 'vmx554' OR 'ensifentrine':ti,ab
5	#3 and #4
6	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
7	#5 NOT #6
8	#7 AND [english]/lim
9	#8 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it)
10	#8 NOT #9

Figure D1.4. PRISMA flow Chart Showing Results of Literature Search for Ensifentrine for COPD



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 (Nested Knowledge, Inc, St. Paul, MN); 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 exclusion of each excluded study.

Data Extraction

Data were extracted into Microsoft Word and Microsoft 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 published 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.[98,100] 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: annualized exacerbation event rate, lung function (average FEV_1, AUC 0-12h), and discontinuation due to adverse events. See Table D1.3.

Table D1.5. Risk of Bias Assessment: Annualized Exacerbation Event Rate

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias	Comment
Phase III							
ENHANCE-1	Low	Low	Low	Low	Low	Low	-
ENHANCE-2	Low	Low	Some Concerns	Low	Low	Some Concerns	Higher proportion of patients with severe COPD receiving placebo withdrew from treatment and trial.
Phase II							
Fergurson et al. 2021	NA	NA	NA	NA	NA	NA	-
Singh et al. 2020	NA	NA	NA	NA	NA	NA	-

Table D1.6. Risk of Bias Assessment: Lung Function (Average FEV1, AUC 0-12h)

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias	Comment
Phase III							
ENHANCE-1	Low	Low	Low	Low	Low	Low	-
ENHANCE-2	Low	Low	Low	Low	Low	Low	-
Phase II							
Fergurson et al. 2021*	Low	Low	Low	Low	Low	Low	-
Singh et al. 2020*	Low	Low	Low	Low	Low	Low	-

* Peak FEV1, not Average FEV1, was the primary outcome in this study. Though, average FEV1 was analyzed using the same approach as the primary outcome.

Table D1.7. Risk of Bias Assessment: Discontinuation due to Adverse Events

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias	Comment
Phase III							
ENHANCE-1	Low	Low	Low	Low	Low	Low	-
ENHANCE-2	Low	Low	Low	Low	Low	Low	-
Phase II							
Fergurson et al. 2021	Low	Low	Low	Low	Low	Low	-
Singh et al. 2020	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.[101] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.8. 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). Next, a representation score between 0 to 3 was assigned based on the PDRR estimate (See Table D1.9 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 D1.10.

Table D1.8. 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 D1.9. Representation Score

PDRR	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.10. 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 D1.11. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older adults)
ENHANCE-1	Fair	Fair	Fair
ENHANCE-2	Fair	Good	Fair

NE: Not Estimated, NR: Not Reported.

Table D1.11. presents the clinical trial diversity ratings on race and ethnicity, sex, and age (older adults) for ENHANCE-1 and -2. Given that ENHANCE-1 and -2 are multinational clinical trials, we requested information on the subpopulation of patients recruited in the US from the manufacturer for our evaluation of racial and ethnic diversity.

Race and Ethnicity: The manufacturer did not provide US-specific enrollment data; therefore, these trials were rated using the full sample. Both ENHANCE-1 and -2 trials, which we rated as "fair" on racial and ethnic diversity, had an adequate representation of White individuals compared to the disease prevalence; however, Black or African American individuals were underrepresented (3.8% of trial participants were Black or African American vs. 11.4% of patients with COPD).[102] In addition, Asian individuals were underrepresented in ENHANCE-2 (0.25% of trial participants vs. 1.4% of patients with COPD), while Hispanic individuals were underrepresented in ENHANCE-1 (2.6% of trial participants vs. 9.6% of patients with COPD). See Table D1.12.[102]

Sex: ENHANCE-2 adequately represented males and females. However, ENHANCE-1 underrepresented females and thus was rated as "fair." See Table D1.13.

Age: Both trials underrepresented older adults (50% of trial participants vs. 80% of patients with COPD) and were rated as "fair" based on pre-defined cut points. See Table D1.13.[103]

Table D1.12. Race and Ethnicity

	White	Black/ African American	Asian	Hispanic/ Latino	Total score	Diversity Rating	AIAN	NHPI
Prevalence[102]	71.3%	11.40%	1.40%	9.60%	-	-	1.50%	0.10%
ENHANCE-1	89.8%	3.3%	3.3%	2.6%	-	-	0%	0%
PDRR	1.26	0.29	2.36	0.27	-	-	0	0
Score	3	1	3	1	8	Fair	NC	NC
ENHANCE-2	94.7%	4.3%	0.25%	5.0%	-	-	0.1%	0%
PDRR	1.33	0.38	0.18	0.52	-	-	0.07	0
Score	3	1	1	2	7	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 D1.13. Sex and Age

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 years)	Score	Rating
Prevalence[103]	46.90%	53.10%	-	-	79.70%	-	-
ENHANCE-1	58.2%	41.8%	-	-	53.6%	-	-
PDRR	1.24	0.79	-	-	0.66	-	-
Score	3	2	6	Fair	2	2	Fair
ENHANCE-2	48.2%	51.8%	-	-	56.2%	-	-
PDRR	1.03	0.98	-	-	0.69	-	-
Score	3	3	6	Good	2	2	Fair

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).[104,105]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication 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: ensifentrine, RPL554, VMX554, chronic obstructive pulmonary disease, and COPD. We selected studies which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies

to ascertain whether there may be a biased representation of study results in the published literature.

Data Synthesis and Statistical Analyses

The studies were summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. 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 was noted in the text of the report. For each outcome of interest, we evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcome assessments.

If we had at least two studies comparing the same two interventions were sufficiently similar, we conducted pairwise meta-analyses. Two Phase III trials (ENHANCE-1 and -2) were included in a pairwise fixed-effects meta-analyses of primary and secondary endpoints (change from baseline in E-RS, TDI, SGRQ, and daily average rescue medication use at week 24, change in rate ratio in exacerbation rate at week 24, change in hazard ratio of time to first event at week 24, and change from baseline in lung function at week 12). Mean difference was chosen as the metric to analyze continuous outcomes (e.g., change in E-RS score). Risk or hazard ratios were chosen as the metric to analyze binary outcomes (e.g., annualized exacerbation event rate or time to first exacerbation). We used change from baseline, RR, or HR reported in the trials. We converted the 95% confidence intervals (CIs) to standard deviation to conduct the meta-analyses. As noted in the main report, the mean difference and 95% CIs estimated by our meta-analyses may be different to the estimates reported in the main trial publication. In our meta-analyses, because we were not able to obtain the exact number of participants who were included in each outcome, we included the total number of participants reported to have been included in the trial. The analyses in the manuscript may be based upon a smaller pool of participants and hence the difference in estimates. Model fit and heterogeneity were examined by reviewing AIC (Akaike Information Criterion), BIC (Bayesian Information Criterion), deviance, and I^2 (quantifies the degree of heterogeneity across studies). We also compared the fixed-effects model to a random-effects model to confirm model fit. (See Table D2.1.) The analyses were conducted in R using the metafor package. Results in terms of a point estimate and 95% confidence intervals were summarized graphically in forest plots in the main report or supplement.

Feasibility for indirect comparisons

We did not aim to compare ensifentrine to any other therapy than placebo.

Data Synthesis Limitations

There were two trials included in our meta-analysis. While the minimum number of trials for a fixed-effect meta-analysis is two, more studies would have increased the precision in our estimates.[106] While conducting our meta-analyses, we found one case of moderate heterogeneity - daily average rescue medication use. In this case, we examined the outcome measures and conducted random-effects analyses to compare model fit and determined that the fixed-effects models had the best fit to the data.

D2. Additional Clinical Evidence

Additional Methods

Evidence Base

Phase II Trials

We supplemented our evidence with two Phase II trials.[34,35] These two Phase II trials were included as they reported data from 3 mg ensifentrine versus placebo with a duration of at least four weeks. We specifically focused on harms data from the ensifentrine 3 mg arm of these two trials. We did not include data that examined other administrations of ensifentrine (e.g., dry powder inhaler, metered dose inhaler), as the data from those arms for lung function were only available at one week.

Singh et al. (2020) was a Phase IIb randomized, double-blind trial that evaluated four doses of nebulized ensifentrine twice daily versus placebo for four weeks in patients with moderate to severe COPD.[35] We only reviewed the 3 mg arm of ensifentrine. Participants were prohibited from using any maintenance COPD medication, e.g., steroids, antibiotics for lower respiratory tract infection, theophylline, and roflumilast, oral beta-blockers, LABAs, LAMAs, or oxygen therapy. The primary outcome was change in peak FEV_1 at week four. Participants were included if they were aged between 40-75 years of age, had a resting heart rate between 50-90 beats per minute (BPM), body mass index (BMI) between 18-35 mg/m2, and established COPD for at least one year (i.e., score of ≥2 on the mMRC Dyspnea Scale and post-bronchodilator FEV_1/FVC <0.70 [to confirm COPD] and FEV_1 ≥30 % and ≤70% [to confirm moderate-severe COPD]). Exclusion criteria included: life-threatening COPD, hospitalization due to COPD in the past 6 months, or exacerbation due to COPD in the last 3 months, history of another respiratory disorder, or had a cardiovascular disorder.

Ferguson et al. (2021) was a Phase IIb randomized, double-blind trial that evaluated four doses of nebulized ensifentrine twice daily versus placebo for four weeks in patients with moderate to severe COPD.[34] We only reviewed the 3 mg arm of ensifentrine. All participants also received open-label tiotropium (LAMA) once daily. The primary outcome was change in peak FEV_1 at week four.

Participants were included if they were aged between 40-80 years of age, had a resting heart rate between 45-90 BPM, BMI between 18-35 mg/m2, and established COPD (following the same criteria as Singh et al. 2020). Exclusion criteria included: life-threatening COPD, hospitalization due to COPD or pneumonia, lung resection or reduction surgery in the last year, history of another respiratory disorders, or had long-term use of oxygen. Baseline characteristics and key outcome measures for both Phase II trials are reported in Supplement Table D3.3. Baseline characteristics were similar to Phase III trials, with participants being around 63 years of age, mostly White and non-Hispanic, and the majority had chronic bronchitis. The key differences compared to Phase III trials were that participants in Singh et al. were not on any background medication, compared to 62% in the ENHANCE-1 and -2 trials. But, in Ferguson et al., around 19% of participants were on dual therapy (LAMA+LABA) and 3% were on triple therapy (LAMA+LABA+ICS), compared to none in the ENHANCE-1 and -2 trials.

Additional Results

Meta-Analysis Results

We conducted fixed-effects meta-analyses which are reported in the main report. To compare and confirm model fit, we also conducted random-effects meta-analyses for all outcomes. Based upon the model fit data reported in Table D2.1., the fixed-effects model was a better fit to the data and thus we used these results.

Table D2.1. Model Fit for Fixed- and Random-Effects Meta-Analysis Models.

	Estimate (95% CI)	P-Value	I^2	AIC	BIC	Deviance
Fixed-effects meta-analysis						
Evaluating Respiratory Symptoms (E-RS)	-0.69 (-1.38, -0.01)	0.047	0%	3.17	1.86	0.16
Transition Dyspnea Index (TDI)	1.00 (0.58, 1.41)	<0.001	0%	1.08	-0.22	0.22
St. George's Respiratory Questionnaire (SGRQ)	-1.51 (-3.13, 0.12)	0.069	22%	7.62	6.31	1.28
Daily average rescue medication use	-0.28 (-0.52, -0.04)	0.02	39.30%	0.36	-0.94	1.65
Exacerbation rate	0.60 (0.41, 0.79)	<0.0001	0%	-2.11	-3.42	0.13
Time to first exacerbation	0.60 (0.41, 0.78)	<0.0001	0%	-2.26	-3.57	0.04
Average FEV_1 (ml)	92.29 (66.22, 118.36)	<0.0001	0%	17.77	16.46	0.05
Random-effects meta-analysis						
Evaluating Respiratory Symptoms (E-RS)	-0.69 (-1.38, -0.01)	0.047	0%	5.17	2.56	0.16
Transition Dyspnea Index (TDI)	0.99 (0.58, 1.42)	<0.0001	0%	3.08	0.47	0.22
St. George's Respiratory Questionnaire (SGRQ)	-1.47 (-3.32, 0.37)	0.12	21.70%	9.83	7.23	1.5
Daily average rescue medication use	-0.29 (-0.60, 0.03)	0.07	39.30%	2.73	0.11	2.01
Exacerbation rate	0.60 (0.41, 0.79)	<0.0001	0%	-0.11	-2.73	0.13
Time to first exacerbation	0.60 (0.41, 0.78)	<0.0001	0%	-0.26	-2.88	0.04
Average FEV_1 (ml)	92.29 (66.22, 118.36)	<0.0001	0%	19.77	17.15	0.05

AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, CI: confidence interval, FEV_1: forced expiratory volume in 1 second, I^2: degree of heterogeneity across studies, ml: milliliters.

Subdomain Results

Evaluating Respiratory Symptoms (E-RS)

As noted in our main report, our pooled estimate for ensifentrine versus placebo on E-RS was statistically significant. Aligned with this, pooled data presented by the manufacturer reported greater improvements in those who received ensifentrine versus placebo in the chest symptoms and breathlessness subdomains at week 24.[48,107]

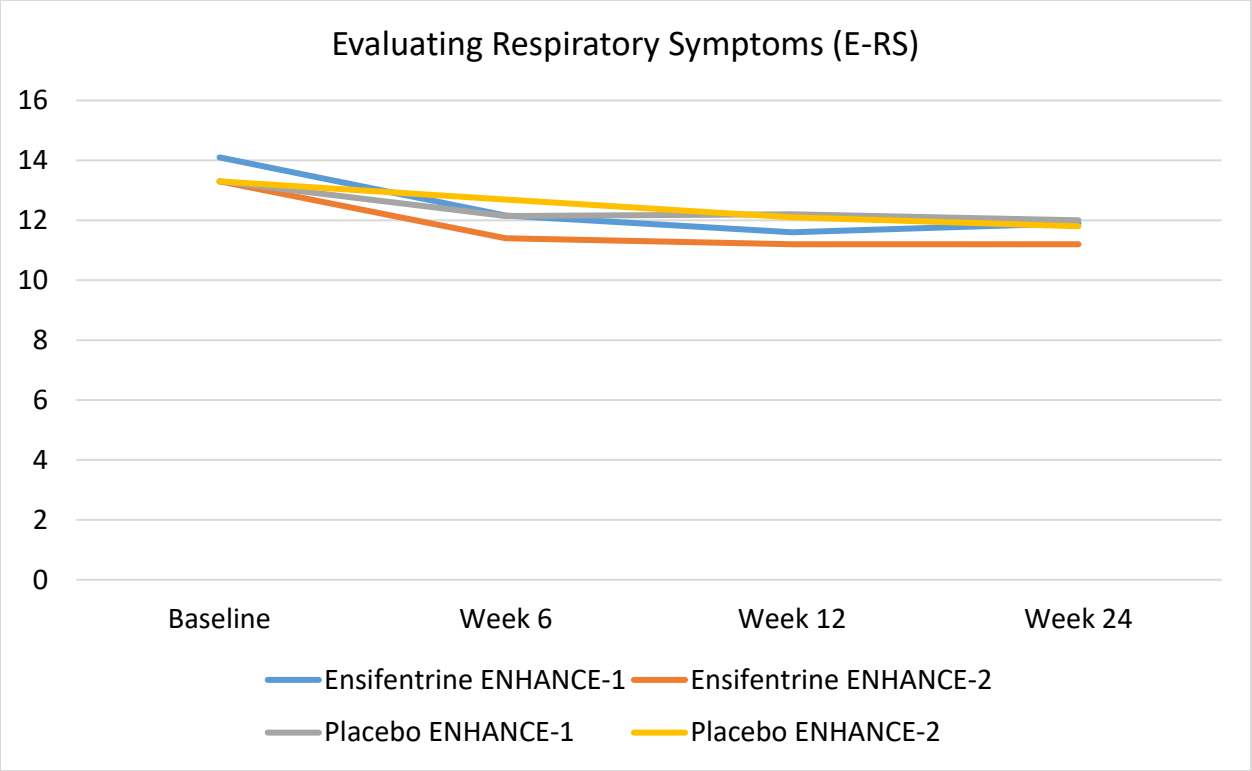
St. George's Respiratory Questionnaire (SGRQ)

As noted in our main report, our pooled estimate for ensifentrine versus placebo on SGRQ was not statistically significant. Pooled data presented by the manufacturer provides data from two of the SGRQ subdomains: symptoms and activity. The data shows significantly greater improvements in those who received ensifentrine versus placebo on the SGRQ symptom subdomain, but the difference between ensifentrine and placebo did not appear to meet statistical significance for the activity subdomain.[107]

Change in Raw Scores

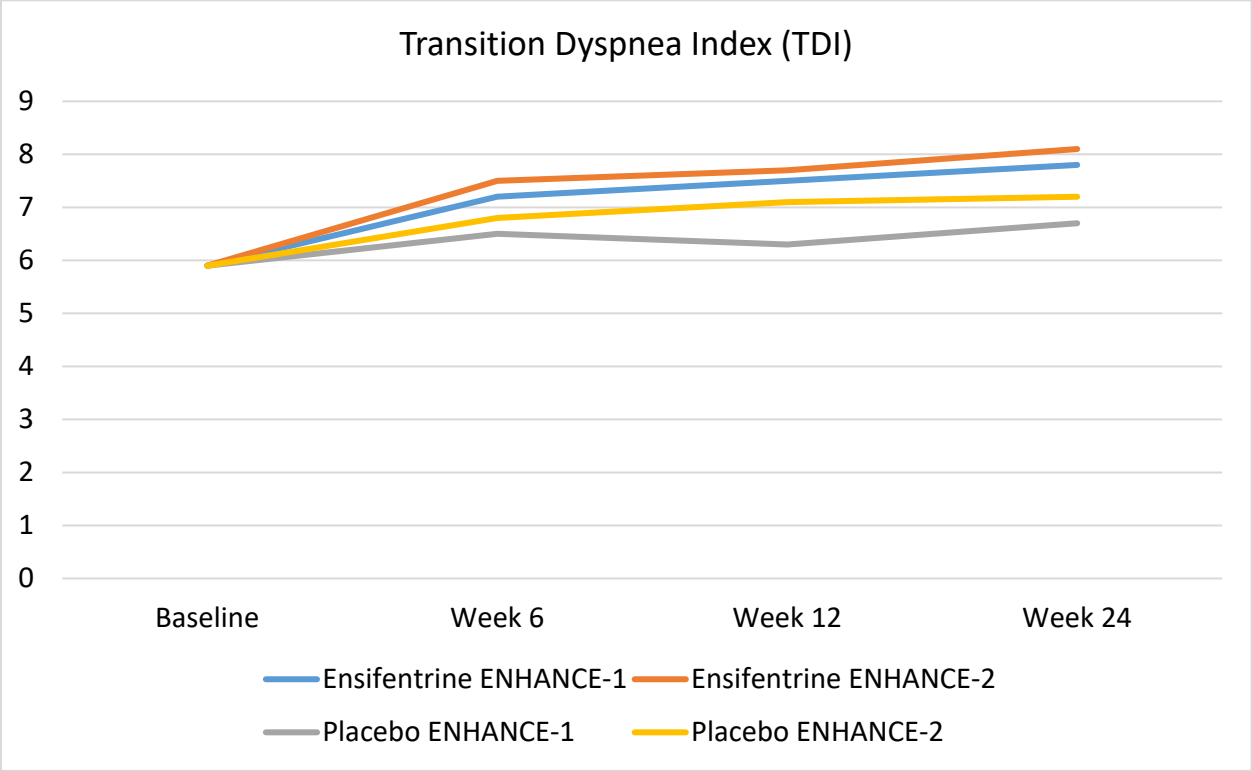
Figures D2.1.-4 represent the change in scores for the patient-important outcomes from baseline to week 6, 12, and 24. The data is based upon raw scores presented in the manuscript and thus the follow-up time points likely do not include data from all participants.

Figure D2.1. Line Chart Representing Change in Raw Scores for E-RS.



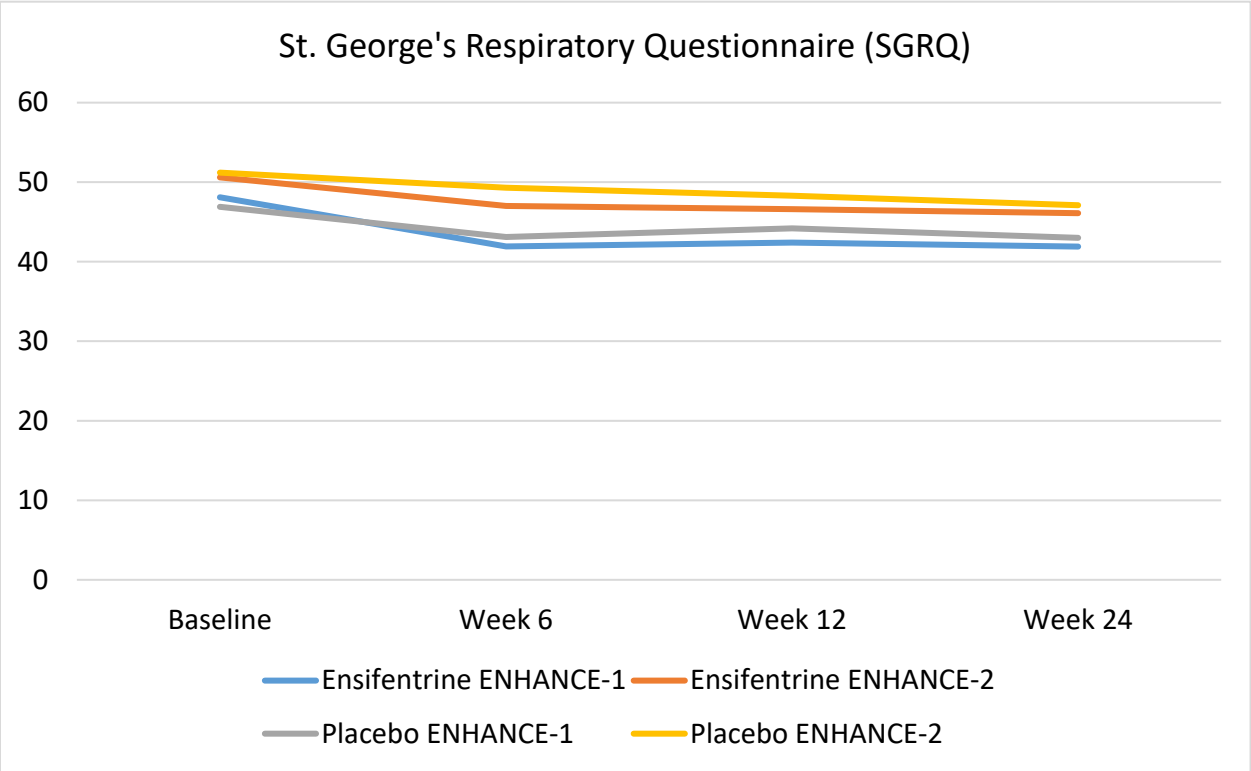
Legend: X-Axis represents the time point at which the assessment was taken by the participant and the Y-Axis represents the score on the E-RS.

Figure D2.2. Line Chart Representing Change in Raw Scores for TDI.



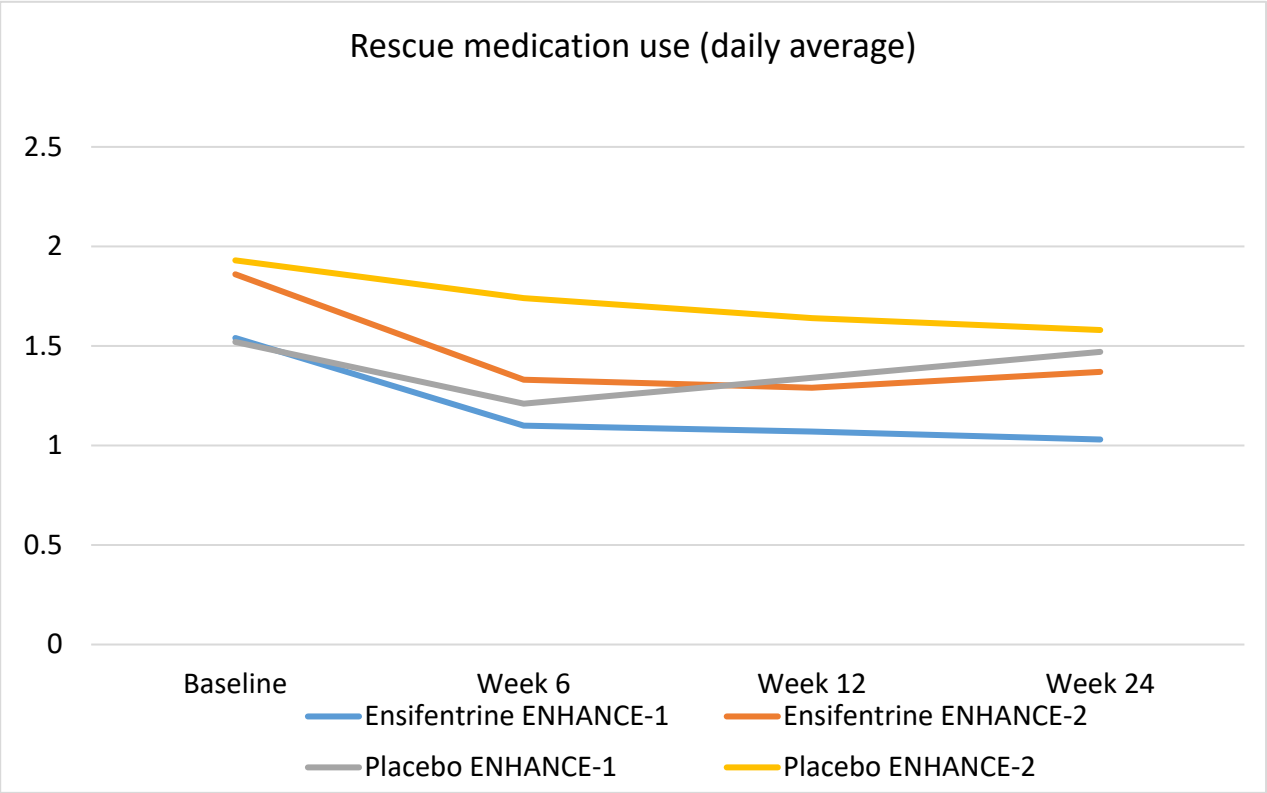
Legend: X-Axis represents the time point at which the assessment was taken by the participant and the Y-Axis represents the score on the TDI.

Figure D2.3. Line Chart Representing Change in Raw Scores for SGRQ.



Legend: X-Axis represents the time point at which the assessment was taken by the participant and the Y-Axis represents the score on the SGRQ.

Figure D2.4. Line Chart Representing Change in Raw Means for Daily Average Rescue Medication Use.



Legend: X-Axis represents the time point at which the assessment was taken by the participant and the Y-Axis represents the daily average rescue medication use (based on 7 day average).

Lung Function

Both ENHANCE-1 and -2 trials reported a statistically significant improvement in peak and morning trough FEV_1 in the ensifentrine groups versus placebo groups at week 12.[10] Data for evening trough FEV_1 were only available from a conference abstract for ENHANCE-1. The investigators reported that there was a statistically significant improvement in the ensifentrine versus placebo group at week 12.[48] See Supplement Table D3.4.

Health Care Resource Utilization

Data for health care resource utilization were only available from a conference abstract for ENHANCE-2. Participants in the ensifentrine group had fewer unplanned physician office visits and hospitalizations (11.8%), compared to those in the placebo group (15%).[108] Though, no statistical analyses were conducted or reported for these values.

Phase II Results

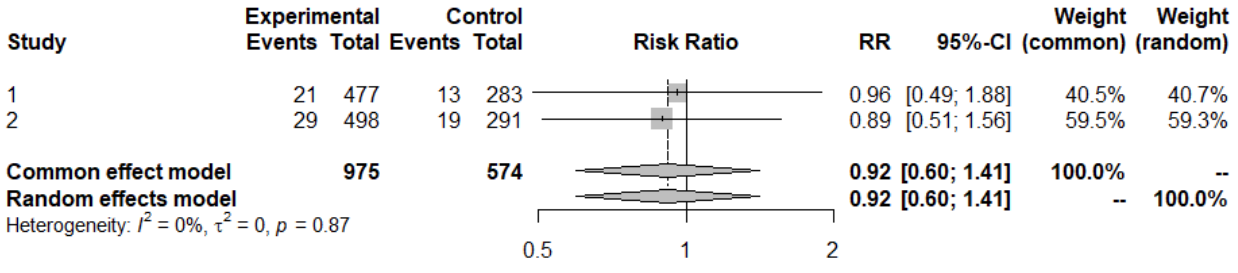
Efficacy data at week four for the two Phase II trials are reported in Supplement Tables D3.10-11.[34,35] In brief, Singh et al. (2020) reported statistically significant improvements in lung function (average FEV_1, peak FEV_1, and morning trough) respiratory symptoms (E-RS and TDI) and use of rescue medication in the ensifentrine (3 mg) group versus placebo at week 4.[35] However, there was no statistically significant difference in change in quality of life, as measured by SGRQ, between the groups at week 4. Ferguson et al. (2021) reported statistically significant improvements in lung function (average FEV_1 and peak FEV_1) in the ensifentrine (3 mg) group versus placebo at week 4, but not for morning trough FEV_1.[34] Unlike Singh et al., there were no statistically significant differences in change in respiratory symptoms (i.e., E-RS and TDI) or use of rescue medication between the ensifentrine (3 mg) and placebo groups at week 4. However, there was a statistically significant difference in change in SGRQ, with ensifentrine associated with greater improvement in quality of life compared to placebo. Caution should be taken when interpreting these results as these trials were not powered to detect significant differences between the groups. In addition, while Ferguson et al. included participants on dual and triple therapy, which would have been interest to our review as dual and triple therapy are now considered standard of care according to GOLD guidelines, the investigators did not conduct subgroup analyses that examined potential differences between those who were on dual or triple therapy, compared to those who were not.[5,34]

Additional Harms

Phase III Harms

As discussed in our main report, the pooled estimate for discontinuation rates due to TEAEs, excluding COVID-19 cases, was not statistically significant (RR: 0.92; 95% CI: 0.6, 1.41; P=0.7) (Figure D2.5) suggesting no difference in discontinuation between the two groups.

Figure D2.5. Forest Plot of Discontinuation due to Treatment-Emergent Adverse Events*



* Participants who received a COVID-19 diagnosis were removed

Phase II Harms

Two four-week Phase II trials were evaluated for harms.[34,35] In Singh et al. 2020, which evaluated ensifentrine in patients who received no background therapy, there was a low percentage of adverse events reported.[35] Participants who received ensifentrine were more likely to experience hypertension (5% vs. 1%), headache (9% vs. 4%), and cough (5% vs. 1%). Total adverse events and discontinuation due to adverse events were comparable between the ensifentrine and placebo groups (see Supplement Table 3.18). In Ferguson et al. 2021, which evaluated ensifentrine combined with tiotropium, total adverse events and discontinuation due to adverse events were comparable between the groups (see Supplement Table 3.18).[34] The safety profile observed in these Phase II trials of ensifentrine aligns with results seen in the Phase III trials, ENHANCE-1 and -2.

D3. Evidence Tables

Table D3.1. Study Design of Key Trials[10,34,35]

Trial/NCT	Study Design	Treatment Arms	Background Therapy	Inclusion/Exclusion Criteria	Primary Outcome [Timepoint]
Phase III trials					
ENHANCE-1 NCT04535986	Phase III randomized, double-blind, placebo-controlled Duration: 24 weeks (with a 48-week safety subset) N=760	Ensifentrine nebulized suspension; 3mg BID Placebo nebulized solution; BID	**Permitted** -Rescue medication of albuterol/salbutamol -Maintenance use of LAMA or LABA therapy if taken for at least 3 months prior to screening -Maintenance use of ICS if taken for at least 4 weeks prior to screening, taken with LAMA or LABA -Smoking cessation programs **Prohibited** -Oral, systemic or parenteral steroid therapies, antibiotics for lower respiratory tract infection, high doses of ICS, leukotriene inhibitors, theophylline and PDE4 inhibitor, terbutaline, ipratropium, beta2-agonists -Experimental drugs within 30 days or 5 half-lives of screening	**Inclusion** -Age 40 to 80 years -Current or former cigarette smoker (≥10 pack years) -Established COPD diagnosis with score of ≥2 on the mMRC Dyspnea Scale -Pre- and Post-albuterol/salbutamol FEV_1/FVC ratio of <0.70, and post-albuterol/salbutamol FEV_1 ≥30% and ≤70% of predicted normal **Exclusion** -History of life-threatening COPD, hospitalization due to COPD, pneumonia, COVID-19 in last 12 weeks, or COPD exacerbation requiring steroids in the last 3 months -Previous lung resection or lung reduction surgery in the last year, or pulmonary rehabilitation -Lower respiratory tract infection in the last 6 weeks	Least square mean change from baseline in average FEV_1 AUC0-12h [12 weeks]

Trial/NCT	Study Design	Treatment Arms	Background Therapy	Inclusion/Exclusion Criteria	Primary Outcome [Timepoint]
Phase III trials					
ENHANCE-2 NCT04542057	Phase III randomized, double-blind, placebo-controlled Duration: 24 weeks N=789	Ensifentrine nebulized suspension; 3mg BID Placebo nebulized solution; BID	Same criteria as ENHANCE-1	Same criteria as ENHANCE-1	Least square mean change from baseline in average FEV_1 AUC0-12h [12 weeks]
Phase II trials					
NCT03937479	Phase IIb, randomized, double-blind, placebo-controlled, 5-arm parallel group trial. Duration: 4 weeks N=166	Open-label tiotropium once daily plus blinded escalating doses of ensifentrine or placebo BID	**Prohibited** -Parenteral steroids, antibiotics for lower respiratory tract infection, oral steroids, theophylline, roflumilast, ICS therapy, or other antibiotics) -Experimental drugs within 30 days or five half-lives -Non-selective oral β-blockers -Use of oxygen therapy, even on an occasional basis	**Inclusion** -Age 40 and 80 years -Diagnosis of COPD as defined by the ATS/ERS guidelines -Post-bronchodilator spirometry at Screening demonstrating the following: FEV_1/FVC ratio of ≤0.70, FEV_1 ≥30% and ≤70% of predicted normal -Clinically stable COPD, score of ≥2 on mMRC dyspnea scale -Current and former smokers **Exclusion** -Life-threatening COPD including ICU admission and/or requiring intubation -A history of one or more hospitalizations for COPD or pneumonia -Pulmonary rehabilitation	Mean change from baseline in Peak FEV_1 0–3h [Week 4]

Trial/NCT	Study Design	Treatment Arms	Background Therapy	Inclusion/Exclusion Criteria	Primary Outcome [Timepoint]
NCT03443414	Phase IIb, randomized, double blind, placebo controlled, dose ranging study Duration: 4 weeks N=162	Nebulized formulation of ensifentrine 0.75mg, 1.5mg, 3mg, 6mg, or placebo	**Permitted** -ICS if the dose is stable for at least 4 weeks prior to visit 1 **Prohibited** -Oral, systemic or parenteral steroids, antibiotics for lower respiratory tract infection, theophylline, and roflumilast, oral beta-blockers, LABAs or LAMAs -Experimental drugs within 3 months or five half-lives, whichever is longer -Oxygen therapy	**Inclusion** -Aged 40 to 75 years -COPD diagnosis with symptoms compatible with COPD for at least 1 year -Clinically stable COPD -FEV_1/FVC ratio of ≤0.70 and FEV_1 must be ≥40 % to ≤80% of predicted normal -Current and former smokers **Exclusion** -A history of life-threatening COPD -COPD exacerbation requiring oral steroids in the previous 3 months -One or more hospitalizations for COPD in the previous 6 months -Pulmonary rehabilitation	Mean change from baseline in Peak FEV_1 (over 3 hours) [Week 4]

0-3h: over three hours, 0-12h: over twelve hours, ATS: American Thoracic Society, AUC: area under the curve, BID: twice daily, COPD: chronic obstructive pulmonary disease, ERS: European Respiratory Society, FEV_1: forced expiratory volume in 1 second, FVC: Forced vital capacity, ICS: inhaled corticosteroids, ICU: Intensive Care Unit, LABA: long-acting b2-agonist, LAMA: long-acting muscarinic antagonist, mg: milligram, mMRC: the modified Medical Research Council, N: number, %: percent

Table D3.2. Phase III Baseline Characteristics[10]

Study		ENHANCE-1		ENHANCE-2		ENHANCE-1&2	
Arms		Ensifentrine	Placebo	Ensifentrine	Placebo	Ensifentrine	Placebo
N		477	283	498	291	975	574
Age	Mean age, years (SD)	65.1 (7.1)	64.9 (7.7)	65 (7.4)	65.3 (7.3)	65	65
	≥65 years, n (%)	258 (54.1)	150 (53.0)	274 (55.0)	167 (57.4)	532 (54.6)	317 (55.2)
Sex, n (%)	Female	203 (42.6)	116 (41.0)	254 (51.0)	153 (52.6)	457 (47)	269 (47)
	Male	274 (57.4)	167 (59.0)	244 (49.0)	138 (47.4)	518 (53.1)	305 (53.1)
Race, n (%)	White	435 (91.2)	250 (88.3)	471 (94.6)	276 (94.8)	NR	NR
	Black or African American	16 (3.4)	9 (3.2)	24 (4.8)	11 (3.8)	NR	NR
	Asian	13 (2.7)	11 (3.9)	1 (0.2)	1 (0.3)	NR	NR
	American Indian or Alaska Native	0 (0)	0 (0)	1 (0.2)	0 (0)	NR	NR
	Other	0 (0)	1 (0.4)	1 (0.2)	3 (1.0)	NR	NR
	Not reported	13 (2.7)	12 (4.2)	0 (0)	0 (0)	NR	NR
Ethnicity, n (%)	Hispanic or Latino	15 (3.1)	6 (2.1)	26 (5.2)	14 (4.8)	NR	NR
	Not Hispanic or Latino	462 (96.9)	277 (97.9)	472 (94.8)	277 (95.2)	NR	NR
US participants, n (%)		87 (18.2)	58 (20.5)	281 (56.4)	174 (59.8)	NR	NR
mMRC score*, n (%)	Grade 2	333 (69.8)	197 (69.6)	275 (55.2)	162 (55.7)	NR	NR
	Grade 3	137 (28.7)	79 (27.9)	208 (41.8)	116 (39.9)	NR	NR
	Grade 4	7 (1.5)	7 (2.5)	15 (3.0)	13 (4.5)	NR	NR
Rescue medication puffs per day, mean (SD)		1.54 (2.40)	1.52 (2.23)	1.86 (2.35)	1.93 (2.43)	NR	NR
St. George's Respiratory Questionnaire (SGRQ), mean (SD)		48.1 (18.3)	46.9 (17.1)	50.6 (17.4)	51.2 (16.4)	NR	NR
Evaluating Respiratory Symptoms (E-RS), mean (SD)		14.1 (6.8)	13.3 (6.1)	13.3 (6.7)	13.3 (6.2)	NR	NR
Transition Dyspnea Index (TDI), mean (SD)		5.9 (1.1)	5.9 (1.1)	5.9 (1.3)	5.9 (1.2)	NR	NR
Mean baseline FEV_1, ml (SD)		1420 (487)	1403 (468)	1285 (451)	1279 (473)	NR	NR
Mean post-bronchodilator FEV_1	L (SD)	1.53 (0.46)	1.51 (0.47)	1.43 (0.44)	1.42 (0.45)	NR	NR
	% predicted (SD)	52.9 (10.3)	51.7 (10.5)	50.8 (10.7)	50.4 (10.7)	51.8 (10.6)	51.0 (10.6)

Study		ENHANCE-1		ENHANCE-2		ENHANCE-1&2	
Arms		Ensifentrine	Placebo	Ensifentrine	Placebo	Ensifentrine	Placebo
N		477	283	498	291	975	574
Severity of airflow obstruction (post-bronchodilator FEV_1), n (%)	GOLD 1 (mild)	1 (0.2)	0 (0)	1 (0.2)	0 (0)	NR	NR
	GOLD 2 (moderate)	294 (61.6)	164 (58.0)	265 (53.2)	143 (49.1)	559 (57)	307 (54)
	GOLD 3 (severe)	179 (37.5)	119 (42.0)	231 (46.4)	148 (50.9)	410 (42)	267 (46)
		ENHANCE-1		ENHANCE-2		ENHANCE-1&2	
	GOLD 4 (very severe)	3 (0.6)	0 (0)	1 (0.2)	0 (0)	NR	NR
Eosinophil count, n (%)	≤150 cells/µL	NR	NR	NR	NR	408 (42)	245 (43)
	>150 cells/µL	NR	NR	NR	NR	565 (57.9)	329 (57.3)
Concomitant maintenance COPD therapy use, n (%)	None used	146 (30.6)	91 (32.2)	223 (44.8)	131 (45.0)	369 (37.8)	222 (38.7)
	Maintenance therapy used	331 (69.4)	192 (67.8)	275 (55.2)	160 (55.0)	NR	NR
	LAMA†	151 (31.7)	76 (26.9)	168 (33.7)	90 (30.9)	319 (33)	166 (29)
	LAMA + ICS	4 (0.8)	5 (1.8)	1 (0.2)	0 (0)	5 (0.5)	5 (1)
	LABA†	89 (18.7)	45 (15.9)	34 (6.8)	23 (7.9)	123 (13)	68 (12)
	LABA + ICS	87 (18.2)	66 (23.3)	72 (14.5)	47 (16.2)	159 (16)	113 (20)
	ICS	NR	NR	NR	NR	164 (16.8)	118 (20.6)
Smoking history	Current smoker, n (%)	268 (56.2)	163 (57.6)	276 (55.4)	160 (55.0)	544 (56)	323 (56)
	Former smoker, n (%)	209 (43.8)	120 (42.4)	222 (44.6)	131 (45.0)	431 (44.2)	251 (43.7)
	Mean pack-years (SD)	41.1 (20.7)	41.8 (20.6)	42.7 (22.9)	41.9 (20.9)	NR	NR
	Mean years of smoking (SD)	39.3 (11.3)	39.0 (11.5)	38.9 (10.4)	39.9 (10.8)	NR	NR
COPD history	Chronic bronchitis‡, n (%)	385 (80.7)	215 (76.0)	322 (64.7)	190 (65.3)	707 (73)	404 (70)
	Emphysema, n (%)	195 (40.9)	146 (51.6)	303 (60.8)	179 (61.5)	NR	NR
	COPD exacerbations, ≤15 months prior to screening, n (%)	120 (25.2)	75 (26.5)	102 (20.5)	62 (21.3)	220 (23)	136 (24)

Cells/µL: cells per microliter, FEV_1: forced expiratory volume in 1 second, GOLD: Global Initiative for Chronic Obstructive Lung Disease, ICS: inhaled corticosteroids, L: volume, LABA: long-acting b2-agonist, LAMA: long-acting muscarinic antagonist, ml: milliliter, mMRC: the modified Medical Research Council, n: number, NR: not reported, SD: standard deviation, US: United States, %: percent

* mMRC scored from 0 (least out of breath) to 4 (most out of breath)

† The total number of patients receiving LAMAs excludes LAMA+ICS. The total number of patients receiving LABAs excludes LABA+ICS

‡ Defined as regular production of sputum for >3 months in two consecutive years (in the absence of other conditions that may explain it)

Table D3.3. Phase II Baseline Characteristics[34,35]

Study		Ferguson et al. 2021		Singh et al. 2020	
		NCT03937479		NCT03443414	
Arms		Ensifentrine	Placebo	Ensifentrine	Placebo
N		82	84	82	80
Age	Mean age, years (SD)	64.5 (7.92)	63.6 (8.41)	62.5 (6.51)	63.5 (6.44)
	≥65 years, n (%)	41 (50.0)	37 (44.0)	NR	NR
Sex, n (%)	Female	45 (54.9)	44 (52.4)	37 (45)	30 (38)
	Male	37 (45.1)	40 (47.6)	45 (55)	50 (63)
Race, n (%)	White	76 (92.7)	75 (89.3)	82 (100)	80 (100)
	Black or African American	6 (7.3)	9 (10.7)	0 (0)	0 (0)
Ethnicity, n (%)	Hispanic or Latino	2 (2.4)	3 (3.6)	0 (0)	0 (0)
	Not Hispanic or Latino	80 (97.6)	81 (96.4)	82 (100)	80 (100)
mMRC score, n (%)	<Grade 2	NR	NR	6 (7)	4 (5)
	≥Grade 2	NR	NR	76 (93)	76 (95)
Rescue medication puffs per day, mean (SD)		2.1 (0-10.6)*†	2.7 (0-13.6)*†	1.9 (2.14)	1.5 (1.88)
St. George's Respiratory Questionnaire (SGRQ), mean (SD)		52.9 (8.1-91.4)*	58.3 (21.2-99.5)*	42.1 (18.78)	42.3 (17.07)
Evaluating Respiratory Symptoms (E-RS), mean (SD)		12.2 (0-24.2)*‡	14.2 (1.2-30.3)*	12.0 (6.03)	11.5 (6.23)
Transition Dyspnea Index (TDI), mean (SD)		6.0 (1-12)*§	5.6 (0-9)*§	6.4 (1.43)	6.4 (1.38)
Concomitant maintenance COPD therapy use, n (%)	LAMA#	32 (39.0)	43 (51.2)	NA	NA
	LAMA + ICS	NR	NR	NA	NA
	LABA#	0 (0)	2 (2.4)	NA	NA
	LABA + ICS	5 (6.1)	13 (15.5)	NA	NA
	LABA + LAMA	16 (19.5)	16 (19.0)	NA	NA
	LAMA + LABA + ICS	3 (3.7)	2 (2.4)	NA	NA
	ICS	0 (0)	2 (2.4)	29 (35)	28 (35)
Smoking History	Current smoker, n (%)	43 (52.4)	53 (63.1)	47 (57)	43 (54)
	Former smoker, n (%)	39 (47.6)	31 (36.9)	35 (43)	37 (46)
	Mean pack-years (SD)	51.0 (20.56)	52.5 (27.37)	41.8 (19.05)	43.3 (20.21)
Chronic bronchitis¤, n (%)		42 (51.2)	47 (56.0)	56 (68)	46 (58)

COPD: chronic obstructive pulmonary disease, ICS: inhaled corticosteroids, LABA: long-acting b2-agonist, LAMA: long-acting muscarinic antagonist, mMRC: the modified Medical Research Council, n: number, NA: not applicable, NR: not reported, SD: standard deviation, %: percent

* range

† N= Ensifentrine: 71, Placebo: 76

‡ N= Ensifentrine: 74, Placebo: 77

§ N= Ensifentrine: 78, Placebo: 80

The total number of patients receiving LAMAs excludes LAMA+ICS. The total number of patients receiving LABAs excludes LABA+ICS

¤ Defined as regular production of sputum for >3 months in two consecutive years (in the absence of other conditions that may explain it)

Table D3.4. Phase III Changes in Lung Function[10,48,50,109]

Trial		Timepoint	ENHANCE-1		ENHANCE-2	
Study Arms			Ensifentrine	Placebo	Ensifentrine	Placebo
N			477	283	498	291
Average FEV_1, AUC 0-12h	**LS mean change from baseline, ml (95% CI)**	Week 12	61 (25, 97)	-26 (-64, 13)	48 (30, 66)	-46 (-70, -22)
	Vs. placebo (95% CI); P value		87 (55, 119); P<0.001		94 (65, 124); P<0.001	
Peak FEV_1	**LS mean change from baseline, ml (95% CI)**	Week 12	204 (165, 244)	57 (15, 100)	195 (175, 214)	48 (22, 75)
	Vs. placebo (95% CI); P value		147 (111, 183); P<0.001		146 (113, 179); P<0.001	
	LS mean change from baseline, ml (95% CI)		162 (21.2)*	46 (23.4)*	196 (11)*	43 (14.8)*
Morning trough FEV_1	**LS mean change from baseline, ml (95% CI)**	Week 12	8 (-30, 45)	-27 (-67, 13)	6 (-13, 24)	-44 (-68, -19)
	Vs. placebo (95% CI); P value		35 (1, 68); P=0.041		49 (19, 80); P=0.002	
	LS mean change from baseline, ml (95% CI)	Week 24	-24 (20.5)*	-37 (21.9)*	-7 (10.1)*	-32 (13.2)*
Evening trough FEV_1	**Vs. placebo (95% CI); P value**	Week 12	58 (24, 92); P<0.001		NR	

0-12h: over 12 hours, AUC: area under the curve, CI: confidence interval, FEV_1: forced expiratory volume in 1 second, N: number, NR: not reported, LS: least square, %: percent

* Standard error

† Average FEV_1, AUC 0-12h: FEV_1 is performed at various timepoints across a 12-hour period (pre dose and 30min and 1, 2, 4, 6, 8, and 12 hours post-dose). The FEV1 assessments are divided by 12 hours to provide an average measure of lung function over the 12-hour time period.[10]

‡ Peak FEV_1: Highest FEV_1 recorded across the post-dose assessments.[10]

§ Morning trough FEV_1: Morning, pre-dose FEV_1 assessment.[10]

Evening trough FEV_1: Evening FEV_1 assessment.[10]

Table D3.5. Phase III Changes in Respiratory Symptoms[10,49,50,107,109-111]

Trial		Timepoint	ENHANCE-1		ENHANCE-2		ENHANCE-1&2 Pooled	
Study Arms			Ensifentrine	Placebo	Ensifentrine	Placebo	Ensifentrine	Placebo
N			477	283	498	291	975	574
Evaluating Respiratory Symptoms (E-RS)	LS mean change from baseline, ml (95% CI)	Week 6	-1.94 (0.4)†	-1.16 (0.4)†	-1.9 (0.2)†	-0.61 (0.3)†	NR	NR
	Vs. placebo (95% CI); P value		-0.79 (-1.42, -0.16); P=0.015		-1.3 (-2.0, -0.7); P<0.001		NR	
	LS mean change from baseline, ml (95% CI)	Week 12	-2.5 (0.4)†	-1.1 (0.4)†	-2.1 (0.2)†	-1.2 (0.3)†	NR	NR
	Vs. placebo (95% CI); P value		-1.37 (-2.06, -0.68); P<0.001		-0.9 (-1.6, -0.2); P=0.016		NR	
	LS mean change from baseline, ml (95% CI)	Week 24	-2.2 (-3.1, -1.4)	-1.3 (-2.2, -0.4)	-2.1 (-2.6, -1.6)	-1.5 (-2.2, -0.9)	NR	NR
	Vs. placebo (95% CI); P value		-1.0 (-1.7, -0.2); P=0.011		-0.6 (-1.4, 0.2); P=0.134		NR	
E-RS Responders*	Odds ratio (95% CI); P value	Week 12	2.17 (1.55, 3.04); P<0.001		NR		NR	
	Odds ratio (95% CI); P value	Week 24	1.41 (1.01, 1.97); P=0.042		NR		NR	
E-RS symptom subdomain score†	Mean change vs. placebo (95% CI); P value	Week 6	-4.58 (-6.96, -2.21); P<0.001		NR		NR	
		Week 12	-6.84 (-9.29, -4.40); P<0.001		NR		NR	
		Week 24	-4.63 (-7.33, -1.93); P<0.001		NR		NR	
E-RS breathlessness subdomain score	LS mean change from baseline, ml (95% CI)	Week 24	NR	NR	NR	NR	-0.9 (-1.3, -0.5)	-0.6 (-1.0, -0.2)
Transition Dyspnea Index (TDI)	LS mean change from baseline, ml (95% CI)	Week 6	1.3 (0.2)‡	0.6 (0.2)†	1.6 (0.1)‡	0.9 (0.2)‡	NR	NR
	Vs. placebo (95% CI); P value		NR		0.7 (0.3, 1.1); P<0.001		NR	
	LS mean change from baseline, ml (95% CI)	Week 12	1.6 (0.2)‡	0.4 (0.2)†	1.8 (0.1)‡	1.2 (0.2)‡	NR	NR

	Vs. placebo (95% CI); P value		NR		0.6 (0.1, 1.0); P=0.010		NR	
	LS mean change from baseline, ml (95% CI)	Week 24	1.9 (1.4, 2.3)	0.8 (0.3, 1.4)	2.2 (1.9, 2.5)	1.3 (0.9, 1.7)	2.0 (1.5, 2.4)	0.9 (0.4, 1.4)
	Vs. placebo (95% CI); P value		1.0 (0.6, 1.5); P<0.001		0.9 (0.4, 1.4); P<0.001		P<0.05	
TDI Responders[§]	**Percent of participants**	Week 24	NR	NR	NR	NR	65%	45%
	Placebo-corrected odds ratio (95% CI); P value		NR	NR	NR	NR	1.9 (1.5, 2.7); P<0.05	

CI: confidence interval, LS: least square, MCID: Minimal Clinically Important Difference, N: number, %: percent

* Defined as those having a MCID (≥2-unit improvement) on the E-RS

† Included: breathlessness, cough and sputum, chest symptoms

‡ Standard error

§ Defined as those having a MCID (≥1-unit improvement) on the TDI

Table D3.6. Phase III Changes in Quality of Life[10,50,109-111]

Trial		Timepoint	ENHANCE-1		ENHANCE-2		ENHANCE-1&2 Pooled	
Study Arms			Ensifentrine	Placebo	Ensifentrine	Placebo	Ensifentrine	Placebo
N			477	283	498	291	975	574
St. George's Respiratory Questionnaire (SGRQ)	LS mean change from baseline, ml (SE)	Week 6	-6.18 (1.0)	-3.97 (1.1)	-3.60 (0.59)	-1.89 (0.77)	NR	NR
	LS mean change from baseline, ml (SE)	Week 12	-5.7 (1.0)	-2.7 (1.1)	-4 (0.6)	-2.9 (0.8)	NR	NR
	LS mean change from baseline, ml (95% CI)	Week 24	-6.2 (-8.4, -3.9)	-3.9 (-6.3, -1.5)	-4.5 (-5.9, -3.2)	-4.1 (-5.8, -2.3)	NR	NR
	Vs. placebo (95% CI); P value		-2.3 (-4.3, -0.3); P=0.025		-0.5 (-2.7, 1.7); P=0.669		NR	
SGRQ responders*	Odds ratio (95% CI); P value	Week 6	-4.58 (-6.96, -2.21); P<0.001		NR		NR	
	Odds ratio (95% CI); P value	Week 12	-6.84 (-9.29, -4.40); P<0.001		NR		NR	
	Odds ratio (95% CI); P value	Week 24	-4.63 (-7.33, -1.93); P<0.001		NR		NR	
SGRQ symptom subdomain	LS mean change from baseline, ml (95% CI)	Week 24	NR		NR		-8.0 (-11.1, -5.0)†	-4.9 (-8.1, -1.6)
SGRQ activity subdomain	LS mean change from baseline, ml (95% CI)	Week 24	NR		NR		-5.9 (-8.5, -3.3)	-4.5 (-7.3, -1.7)
EuroQol-5-Domain Questionnaire (EQ-5D-5L)	Vs. placebo (95% CI); P value	Week 12	NR		0.027 (0.004, 0.050); P=0.019		NR	
EQ-5D-5L VAS	Vs. placebo (95% CI); P value	Week 12	NR		0.8 (1.5, 3.0); P>0.05		NR	

CI: confidence interval, LS: least square, MCID: Minimal Clinically Important Difference, N: number, NR: not reported, SE: standard error, VAS: visual analogue scale, %: percent

* Defined as those having a MCID (≥4-unit improvement) in the SGRQ

† Reported as significant p<0.05

Table D3.7. Phase III Use of Rescue Medication[10,50,109,111]

Trial		Timepoint	ENHANCE-1		ENHANCE-2	
Study Arms			Ensifentrine	Placebo	Ensifentrine	Placebo
N			477	283	498	291
Average daily rescue med use over 7 days	LS mean change from baseline, ml (SE)	Week 6	-0.44 (0.11)	-0.31 (0.11)	-0.53 (0.09)	-0.19 (0.12)
	Vs. placebo (95% CI); P value		NR		-0.34 (-0.62, -0.06); P=0.017	
	LS mean change from baseline, ml (SE)	Week 12	-0.47 (0.1)	-0.18 (0.1)	-0.57 (0.07)	-0.29 (0.1)
	Vs. placebo (95% CI); P value		NR		-0.28 (-0.53, -0.04); P=0.021	
	LS mean change from baseline, ml (95% CI)	Week 24	-0.51 (-0.79, -0.22)	-0.05 (-0.36, 0.25)	-0.49 (-0.66, -0.31)	-0.35 (-0.57, -0.12)
	Vs. placebo (95% CI); P value		-0.45 (-0.70, -0.20); P<0.001		-0.14 (-0.41, 0.14); P=0.32	

CI: confidence interval, med: medication, LS: least square, N: number, NR: not reported, SE: standard error, %: percent

* Standard error

Table D3.8. Phase III Moderate or Severe COPD Exacerbations and COPD-related Hospitalization or Emergency Room Visits[10,47,51,108]

Trial		Timepoint	ENHANCE-1		ENHANCE-2		ENHANCE-1&2	
Study Arms			Ensifentrine	Placebo	Ensifentrine	Placebo	Ensifentrine	Placebo
N			477	283	498	291	975	574
Annualized exacerbation event rate	LS mean (95% CI)	Week 24	0.26 (0.17, 0.40)	0.41 (0.27, 0.63)	0.24 (0.18, 0.32)	0.42 (0.30, 0.57)	0.27 (0.19, 0.39)	0.45 (0.31, 0.65)
	Rate ratio (95% CI); P value		0.64 (0.40, 1.00); P=0.05		0.57 (0.38, 0.87); P=0.009		0.59 (0.43, 0.80); P<0.001	
	LS mean (95% CI)	Week 48	0.25 (0.13, 0.48)	0.44 (0.22, 0.87)	NR	NR	NR	NR
	Rate ratio (95% CI); P value		0.56 (0.32, 1.00); P=0.052		NR		NR	
Time to first event	Log-rank test vs. placebo	Week 24	P=0.041		P=0.011		NR	
	Hazard ratio (95% CI); P value		0.62 (0.39, 0.97); P=0.038		0.58 (0.38, 0.87); P=0.009		0.59 (0.44, 0.81); P<0.001	
	Log-rank test vs. placebo	Week 48	P=0.014		NR		NR	
	Hazard ratio (95% CI); P value		0.48 (0.28, 0.82); P=0.007		NR		NR	
Transition to GOLD Group E from Group B	Hazard ratio (95% CI); P value	Week 24	NR	NR	NR	NR	0.64 (0.41, 1.01); P=0.058	
COPD-related hospitalization or emergency room visit, n (%)		Week 24	NR	NR	59 (11.8)	44 (15.1)	NR	NR

CI: confidence interval, LS: least square, N: number, NR: not reported, %: percent

* Group B (0 or 1 moderate exacerbations in the prior year) to GOLD Group E (2 or more moderate or 1 serious exacerbation in the prior year)

Table D3.9. Phase II Changes in Lung Function[34,35]

Study		Timepoint	Ferguson et al. 2021		Singh et al. 2020	
			NCT03937479		NCT03443414	
Arms			Ensifentrine	Placebo	Ensifentrine	Placebo
N			82	84	82	79
Average FEV_1, AUC 0-12h	LS mean change from baseline, ml (95% CI)	Week 4	97 (49, 145)	10 (-38, 57)	NR	NR
	Vs. placebo (95% CI); P value		87 (20, 155); P=0.011		111 (51, 170)*; P<0.01	
Peak FEV_1	LS mean change from baseline, ml (95% CI)	Week 4	243 (191, 295)	119 (68, 170)	NR	NR
	Vs. placebo (95% CI); P value		124 (52, 197); P=0.001		199 (130, 270)*; P<0.001	
Morning trough FEV_1	LS mean change from baseline, ml (95% CI)	Week 4	5 (-40, 51)	-22 (-66, 23)	NR	NR
	Vs. placebo (95% CI); P value		27 (-36, 91); P=0.400		68 (4, 131)*; P<0.05	

0-12h: over 12 hours, AUC: area under the curve, CI: confidence interval, FEV_1: forced expiratory volume in 1 second, LS: least square, N: number, NR: not reported, %: percent

* Data has been digitized

Table D3.10. Phase II Changes in Respiratory Symptoms[34,35]

Study		Timepoint	Ferguson et al. 2021		Singh et al. 2020	
			NCT03937479		NCT03443414	
Arms			Ensifentrine	Placebo	Ensifentrine	Placebo
N			82	84	82	79
Evaluating Respiratory Symptoms (E-RS)	LS mean change from baseline, ml (95% CI)	Week 4	-1.1 (-1.93, -0.21)	-0.2 (-1.08, 0.62)	NR	NR
	Vs. placebo (95% CI); P value		-0.8 (-2.05, 0.37); P=0.171		-2 (-0.7, -3.3)*; P<0.01	
Transition Dyspnea Index (TDI)	LS mean change from baseline, ml (95% CI)	Week 4	2.1 (1.39, 2.74)	1.8 (1.1, 2.43)	1.55 (3.44)	0.37 (3.22)
	Vs. placebo (95% CI); P value		0.3 (-0.65, 1.25); P=0.538		1.19 (0.25, 2.14); P=0.014	

CI: confidence interval, LS: least square, N: number, NR: not reported, %: percent

* Data has been digitized

Table D3.11. Phase II Changes in Quality of Life[34,35]

Trial		Timepoint	Ferguson et al. 2021		Singh et al. 2020	
			NCT03937479		NCT03443414	
Study Arms			Ensifentrine	Placebo	Ensifentrine	Placebo
N			82	84	82	79
St. George's Respiratory Questionnaire (SGRQ)	LS mean change from baseline, ml (95% CI)	Week 4	-4.2 (-6.81, -1.51)	-0.1 (-2.71, 2.48)	40.1 (15.93)*	43.5 (16.99)*
	Vs. placebo (95% CI); P value		-4.1 (-7.76, -0.33); P=0.033		−2.29 (−5.96, 1.37); P=0.220	
SGRQ responders	Odds ratio (95% CI); P value	Week 4	NR		1.11 (0.53, 2.31); 0.791	
	Percentage of responders	Week 4	20.5	9.8	42	26

CI: confidence interval, VAS: visual analogue scale, LS: least square, N: number, %: percent

* St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)is a shorter version of the SGRQ, derived from the original version following detailed analysis of data from large studies in COPD.

Table D3.12. Phase II Use of Rescue Medication[34,35]

Trial		Timepoint	Ferguson et al. 2021		Singh et al. 2020	
			NCT03937479		NCT03443414	
Study Arms			Ensifentrine	Placebo	Ensifentrine	Placebo
N			71	76	82	81
Average daily rescue med use over 7 days	LS mean change from baseline, ml (95% CI)	Week 4	-0.5 (-0.86, -0.16)	-0.7 (-1.01, -0.33)	NR	NR
	Vs. placebo (95% CI); P value		0.2 (-0.33, 0.65); P=0.508		–0.49 (–0.91, –0.07); P=0.022	

CI:-confidence interval, LS: least square, N: number, NR: not reported, %: percent

Table D3.13. Phase III Treatment-Emergent Adverse Events[10]

Trial	ENHANCE-1		ENHANCE-1		ENHANCE-2	
Timepoint	Week 24		Week 48		Week 24	
Study Arms	Ensifentrine	Placebo	Ensifentrine	Placebo	Ensifentrine	Placebo
N	477	283	228	70	498	291
Any TEAE, n (%)	183 (38.4)	103 (36.4)	58 (25.4)	19 (27.1)	176 (35.3)	103 (35.4)
Serious TEAE, n (%)	32 (6.7)	19 (6.7)	11 (4.8)	5 (7.1)	28 (5.6)	17 (5.8)
Severe TEAE, n (%)	27 (5.7)	15 (5.3)	5 (2.2)	3 (4.3)	22 (4.4)	12 (4.1)
Leading to death, n (%)	2 (0.4)	4 (1.4)	2 (0.9)	1 (1.4)	4 (0.8)	1 (0.3)
TEAE causally related to treatment, n (%)	24 (5.0)	11 (3.9)	2 (0.9)	0	20 (4.0)	12 (4.1)
TEAE leading to discontinuation, n (%)	29 (6.1)	18 (6.4)	5 (2.2)	2 (2.9)	45 (9.0)	29 (10.0)
TEAE leading to discontinuation (minus COVID-19 cases), n (%)*	21 (4.4)	13 (4.6)	3 (1.3)	2 (2.9)	29 (5.8)	19 (6.5)
TEAE leading to withdrawal, n (%)	19 (4.0)	10 (3.5)	4 (1.8)	1 (1.4)	35 (7.0)	20 (6.9)
TEAE leading to withdrawal of trial (with COVID-19 diagnosis), n (%)	8 (1.7)	5 (1.8)	2 (0.9)	0	16 (3.2)	10 (3.4)
TEAE leading to withdrawal of trial (no COVID-19 diagnosis), n (%)	11 (2.3)	5 (1.8)	2 (0.9)	1 (1.4)	19 (3.8)	10 (3.4)

TEAE: treatment-emergent adverse event, N: number, %: percent

* Values for this outcome were estimated

Table D3.14. Phase III Select TEAEs[10,37,50,109,112]

Trial	ENHANCE-1		ENHANCE-1		ENHANCE-2	
Timepoint	Week 24		Week 48		Week 24	
Study Arms	Ensifentrine	Placebo	Ensifentrine	Placebo	Ensifentrine	Placebo
N	477	283	228	70	498	291
Nasopharyngitis, n (%)	13 (2.7)	16 (5.7)	6 (2.6)	0	9 (1.8)	3 (1.0)
Gastrointestinal, n (%)	NR	NR	NR	NR	26 (5.2)	15 (5.2)
Back pain, n (%)	10 (2.1)	1 (0.4)	NR	NR	8 (1.6)	5 (1.7)
COPD, n (%)	7 (1.5)	6 (2.1)	NR	NR	11 (2.2)	5 (1.7)
Toothache, n (%)	6 (1.3)	2 (0.7)	NR	NR	0	1 (0.3)
Pneumonia, n (%)	6 (1.3)	2 (0.7)	NR	NR	4 (0.8)	5 (1.7)
Urinary tract infection, n (%)	5 (1.0)	1 (0.4)	NR	NR	8 (1.6)	5 (1.7)
Diarrhea, n (%)	2 (0.4)	2 (0.7)	NR	NR	8 (1.6)	2 (0.7)
Sinusitis, n (%)	1 (0.2)	1 (0.4)	NR	NR	6 (1.2)	0
Upper respiratory tract infection, n (%)	6 (1.3)	5 (1.8)	4 (1.8)	0	NR	NR
Headache, n (%)	16 (3.4)	12 (4.2)	4 (1.8)	2 (2.9)	10 (2.0)	7 (2.4)

TEAE: treatment-emergent adverse event, N: number, NR: not reported, %: percent

Table D3.15. Phase III Cardiovascular Outcomes[10,50,109,112]

Trial		ENHANCE-1		ENHANCE-1		ENHANCE-2	
Timepoint		Week 24		Week 48		Week 24	
Study Arms		Ensifentrine	Placebo	Ensifentrine	Placebo	Ensifentrine	Placebo
N		477	283	228	70	498	291
Cardiovascular outcomes, n (%)	TEAEs	NR	NR	NR	NR	11 (2.2)	13 (4.5)
	TEAEs causally related to treatment	NR	NR	NR	NR	1 (0.2)	1 (0.3)
	Serious TEAEs	NR	NR	NR	NR	1 (0.2)	2 (0.7)
	Myocardial Infarction	0	0	1 (0.44)	0	NR	NR
Hypertension, n (%)		12 (2.5)	4 (1.4)	NR	NR	5 (1.0)	1 (0.3)

TEAE: treatment-emergent adverse event, N: number, NR: not reported, %: percent

Table D3.16. Phase III COVID-19[10,50,109,113]

Trial	ENHANCE-1		ENHANCE-1		ENHANCE-2	
Timepoint	Week 24		Week 48		Week 24	
Study Arms	Ensifentrine	Placebo	Ensifentrine	Placebo	Ensifentrine	Placebo
N	477	283	228	70	498	291
COVID-19 detected, n (%)	16 (3.4)	9 (3.2)	2 (0.9)	2 (2.9)	16 (3.2)	10 (3.4)
COVID-19 leading to study withdrawal (before week 12), n (%)			NR	NR		
Those with COVID-19 included in analysis, n (%)			NR	NR		
COVID-19 leading to study withdrawal (total duration), n (%)	8	6	NR	NR	16	11

N: number, NR: not reported, %: percent

Table D3.17. Phase III Trial Withdrawal from Trial[10]

Trial	ENHANCE-1		ENHANCE-2	
Timepoint	Week 48*		Week 24	
Study Arms	Ensifentrine	Placebo	Ensifentrine	Placebo
N	477	283	498	291
All cause, n (%)	77 (16.1)	38 (13.4)	105 (21.1)	73 (25.1)
Withdrew consent, n (%)	30 (39)	13 (34)	51 (49)	30 (41)
Positive COVID-19, n (%)	8 (10)	6 (16)	16 (15)	11 (15)
Adverse event, n (%)	10 (13)	1 (3)	15 (14)	6 (8)
Lost to follow-up, n (%)	5 (7)	3 (8)	8 (8)	11 (15)
COPD exacerbation withdrawal criteria, n (%)	7 (9)	5 (13)	5 (5)	6 (8)
Death, n (%)	4 (5)	5 (13)	3 (3)	1 (1)
Lack of efficacy, n (%)	3 (4)	2 (5)	2 (2)	5 (7)
Investigator discretion, n (%)	3 (4)	0	2 (2)	1 (1)
Other, n (%)	7 (9)	3 (8)	2 (2)	2 (3)
Sponsor discretion, n (%)	0	0	1 (1)	0

N: number, NR: not reported, %: percent

* Trial withdrawal data only available at week 48 of the ENHANCE-1 trial

Table D3.18. Phase II Treatment-Emergent Adverse Events[34,35]

Trial	Ferguson et al. 2021		Singh et al. 2020	
	NCT03937479		NCT03443414	
Timepoint	Week 4		Week 4	
Study Arms	Ensifentrine	Placebo	Ensifentrine	Placebo
N	83	84	82	79
Any TEAE, n (%)	18 (21.7)	17 (20.2)	12 (15)	10 (13)
Serious TEAE, n (%)	2 (2.4)	0 (0)	0	0
Severe TEAE, n (%)	NR	NR	2 (2)*	2 (3)*
Leading to death, n (%)	0	0	0	0
TEAE causally related to treatment, n (%)	2 (2.4)	4 (4.8)	NR	NR
TEAE Leading to discontinuation, n (%)	0 (0)	1 (1.2)	4 (5)*	2 (3)*

AE: adverse event, TEAE: treatment-emergent adverse event, N: number, %: percent

* AE not TEAE

Table D3.19. Phase II Select TEAEs[10,34,35]

Trial	Ferguson et al. 2021		Singh et al. 2020	
	NCT03937479		NCT03443414	
Timepoint	Week 4		Week 4	
Study Arms	Ensifentrine	Placebo	Ensifentrine	Placebo
N	83	84	82	79
Nasopharyngitis, n (%)	1 (1.2)	2 (2.4)	NR	NR
Hypertension, n (%)	NR	NR	4 (5)*	1 (1)*
COPD, n (%)	3 (3.6)	0 (0)	NR	NR
Diarrhea, n (%)	1 (1.2)	0 (0)	NR	NR
Cough, n (%)	NR	NR	4 (5)	1 (1)
Headache, n (%)	2 (2.4)	1 (1.2)	7 (9)*	3 (4)*

TEAE: treatment-emergent adverse event, N: number, %: percent

*Adverse event not TEAE

Table D3.20. Phase II Trial Withdrawal from Trial[34,35]

Trial	Ferguson et al. 2021		Singh et al. 2020	
	NCT03937479		NCT03443414	
Timepoint	Week 4		Week 4	
Study Arms	Ensifentrine	Placebo	Ensifentrine	Placebo
N	83	84	82	79
All cause, n (%)	6 (7.3)	5 (6)	6 (7.3)	4 (5)
Withdrew consent, n (%)	2 (2.4)	1 (1.19)	2 (2.53)	1 (1.2)
Adverse event, n (%)	0	1 (1.19)	4 (4.87)	3 (3.79)
Lost to follow-up, n (%)	1 (1.2)	0	0	0
Investigator discretion, n (%)	0	1 (1.19)	0	0
Protocol deviation, n (%)	3 (3.61)	2 (2.38)	0	0

N: number, NR: not reported, %: percent

Table D3.21. Phase III Background Medication Subgroup Data: Changes in Lung Function[54-57,114,115]

Trial	Subgroup	Arms	N	Average FEV_1, AUC 0-12h	Peak FEV_1 over 4h	Morning trough FEV_1
				LS mean change from baseline vs. placebo (95% CI); P value	LS mean change from baseline vs. placebo (95% CI); P value	LS mean change from baseline vs. placebo (95% CI); P value
				Week 12	Week 12	Week 12
ENHANCE-1	**Any background medication**	Ensifentrine	331	101.7 (66.2, 137.2); P<0.001	NR	NR
		Placebo	192			
ENHANCE-2		Ensifentrine	275	76 (39, 114); P<0.0001	NR	NR
		Placebo	160			
Pooled		Ensifentrine	606	NR	NR	NR
		Placebo	352			
ENHANCE-1	**LABA/LABA+ICS**	Ensifentrine	176	97 (50, 143)	154 (104, 204)	50 (5, 96)
		Placebo	111			
ENHANCE-2		Ensifentrine	106	75 (24, 126)	149 (93, 206)	66 (11, 121)
		Placebo	70			
Pooled		Ensifentrine	282	88 (53, 122); P<0.001	P<0.05	P<0.05
		Placebo	181			
Pooled	**LABA/ICS**	Ensifentrine	159	74; P<0.05	141; P<0.05	59; P<0.05
		Placebo	113			
ENHANCE-1	**LAMA/LAMA+ICS**	Ensifentrine	155	112 (57, 166)	155 (90, 220)	57 (-7, 121)
		Placebo	81			
ENHANCE-2		Ensifentrine	169	79 (27, 131)	122 (64, 180)	37 (-17, 90)
		Placebo	90			
Pooled		Ensifentrine	324	93 (55, 131); P<0.001	NR	NR
		Placebo	171			
Pooled	**LAMA**	Ensifentrine	319	92; P<0.05	135; P<0.05	44; P<0.05
		Placebo	166			

Trial	Subgroup	Arms	N	Average FEV_1, AUC 0-12h	Peak FEV_1 over 4h	Morning trough FEV_1
				LS mean change from baseline vs. placebo (95% CI); P value	LS mean change from baseline vs. placebo (95% CI); P value	LS mean change from baseline vs. placebo (95% CI); P value
				Week 12	Week 12	Week 12
ENHANCE-1	**No background medication**	Ensifentrine	146	60 (-3, 123); P=0.061	144 (72, 216)	6 (-60, 71)
		Placebo	91			
ENHANCE-2		Ensifentrine	223	115 (69, 161); P<0.001	161 (110, 212)	49 (0.9, 98)
		Placebo	131			
Pooled		Ensifentrine	369	NR	NR	NR
		Placebo	222			

CI: confidence interval, FEV_1: forced expiratory volume in 1 second, ICS: inhaled corticosteroids, LABA: long-acting b2-agonist, LAMA: long-acting muscarinic antagonist, N: number, NR: not reported, %: percent

Table D3.22. Phase III Background Medication Subgroup Data: Moderate or Severe COPD Exacerbations[54,57,114,115]

Trial	Subgroup	Arms	N	Annualized Exacerbation Rate Rate Ratio (95% CI); P Value Week 24	Time to First Event Hazard Ratio (95% CI); P value Week 24
ENHANCE-1	**Any background medication**	Ensifentrine	331	NR	NR
		Placebo	192		
ENHANCE-2		Ensifentrine	275	0.55 (0.32, 0.96); P=0.035	0.51 (0.29, 0.89); P=0.017
		Placebo	160		
Pooled		Ensifentrine	606	0.60 (0.41, 0.88)	0.55 (0.38, 0.81)
		Placebo	352		
ENHANCE-1	**LABA/LABA+ICS**	Ensifentrine	176	0.66 (0.34, 1.30)	0.59 (0.29, 1.17)
		Placebo	111		
ENHANCE-2		Ensifentrine	106	0.71 (0.31, 1.63)	0.58 (0.26, 1.32)
		Placebo	70		
Pooled		Ensifentrine	282	0.69 (0.41, 1.16)	0.58 (0.34, 0.99)
		Placebo	181		
Pooled	**LABA+ICS**	Ensifentrine	159	0.49 (0.24, 0.99); P<0.05	0.47 (0.23, 0.96); P<0.05
		Placebo	113		
ENHANCE-1	**LAMA/LAMA+ICS**	Ensifentrine	155	0.67 (0.29, 1.53)	0.61 (0.26, 1.43)
		Placebo	81		
ENHANCE-2		Ensifentrine	169	0.47 (0.23, 0.98)	0.47 (0.22, 0.98)
		Placebo	90		
Pooled		Ensifentrine	324	NR	NR
		Placebo	171		
Pooled	**LAMA**	Ensifentrine	319	0.54 (0.31, 0.94); P<0.05	0.51 (0.29, 0.90); p<0.05
		Placebo	166		
ENHANCE-1	**No background medication**	Ensifentrine	146	0.57 (0.22, 1.47)	0.66 (0.27, 1.62)
		Placebo	91		
ENHANCE-2		Ensifentrine	223	0.6 (0.32, 1.14); P=0.117)	0.69 (0.37, 1.29); P=0.244
		Placebo	131		
Pooled		Ensifentrine	369	0.60 (0.35, 1.01)	0.68 (0.41, 1.14)
		Placebo	222		

CI: confidence interval, ICS: inhaled corticosteroids, LABA: long-acting b2-agonist, LAMA: long-acting muscarinic antagonist, N: number, NR: not reported, %: percent

Table D3.23. Phase III Background Medication Subgroup Data: Changes in Respiratory Symptoms[10,54,58,59,114]

Trial	Subgroup	Arms	N	Evaluating Respiratory Symptoms (E-RS)	Transition Dyspnea Index (TDI)	TDI Responders*
				LS mean change from baseline vs. placebo (95% CI)	LS mean change from baseline vs. placebo (95% CI)	Placebo-corrected odds ratio (95% CI); P value
				Week 24	Week 24	Week 24
ENHANCE-1	**Any background medication**	Ensifentrine	331	NR	NR	NR
		Placebo	192			
ENHANCE-2		Ensifentrine	275	NR	NR	NR
		Placebo	160			
Pooled		Ensifentrine	606	NR	NR	NR
		Placebo	352			
ENHANCE-1	**LABA/LABA +ICS**	Ensifentrine	176	-0.8 (-1.9, 0.3)	0.8 (0.2, 1.5)	NR
		Placebo	111			
ENHANCE-2		Ensifentrine	106	-0.7 (-2.3, 0.9)	0.7 (-0.3, 1.7)	NR
		Placebo	70			
Pooled		Ensifentrine	282	-0.8 (-1.7, 0.1)	NR	NR
		Placebo	181			
Pooled	**LABA+ICS**	Ensifentrine	159	NR	1.4 (0.5, 2.3)†	1.6 (0.9, 2.8)
		Placebo	113		0.6 (-0.3, 1.6)†	
ENHANCE-1	**LAMA/LAMA +ICS**	Ensifentrine	155	-1.4 (-2.7, -0.1)	1.0 (0.1, 1.8)	NR
		Placebo	81			
ENHANCE-2		Ensifentrine	169	-0.5 (-1.9, 0.8)	1.4 (0.7, 2.2)	NR
		Placebo	90			
Pooled		Ensifentrine	324	-0.9 (-1.9, 0.0)	NR	NR
		Placebo	171			
Pooled	**LAMA**	Ensifentrine	319	NR	2.4 (1.8, 3.0)†	2.4 (1.6, 3.8); P<0.05
		Placebo	166		1.2 (0.6, 1.9)†	

Trial	Subgroup	Arms	N	Evaluating Respiratory Symptoms (E-RS)	Transition Dyspnea Index (TDI)	TDI Responders*
				LS mean change from baseline vs. placebo (95% CI)	LS mean change from baseline vs. placebo (95% CI)	Placebo-corrected odds ratio (95% CI); P value
				Week 24	Week 24	Week 24
ENHANCE-1	**No background medication**	Ensifentrine	146	-0.7 (-2.2, 0.7)	1.2 (0.4, 1.9)	NR
		Placebo	91			
ENHANCE-2		Ensifentrine	223	-0.6 (-1.9, 0.6)	0.7 (-0.1, 1.4)	NR
		Placebo	131			
Pooled		Ensifentrine	369	NR	NR	NR
		Placebo	222			

CI: confidence interval, ICS: inhaled corticosteroids, LABA: long-acting b2-agonist, LAMA: long-acting muscarinic antagonist, N: number, NR: not reported, %: percent

* Defined as those having a MCID (≥1-unit improvement) on the TDI

† Least-squares mean change from baseline

Table D3.24. Phase III Background Medication Subgroup Data: Changes in Quality of Life and Rescue Medication use[10,54,58,59,114]

Trial	Subgroup	Arms	N	St. George's Respiratory Questionnaire (SGRQ)	Average daily rescue medication use over 7 days
				LS mean change from baseline vs. placebo (95% CI)	LS mean change from baseline vs. placebo (95% CI)
				Week 24	Week 24
ENHANCE-1	**Any background medication**	Ensifentrine	331	NR	NR
		Placebo	192		
ENHANCE-2		Ensifentrine	275	NR	NR
		Placebo	160		
Pooled		Ensifentrine	606	NR	NR
		Placebo	352		
ENHANCE-1	**LABA/LABA+ICS**	Ensifentrine	176	-1.6 (-4.7, 1.5)	-0.17 (-0.61, 0.26)
		Placebo	111		
ENHANCE-2		Ensifentrine	106	-0.7 (-5.5, 4.1)	0.01 (-0.55, 0.57)
		Placebo	70		
Pooled		Ensifentrine	282	-1.2 (-3.9, 1.4)	NR
		Placebo	181		
Pooled	**LABA+ICS**	Ensifentrine	159	-2.8 (-7.2, 1.6)*	NR
		Placebo	113	-1.2 (-5.7, 3.3)*	
ENHANCE-1	**LAMA/LAMA+ICS**	Ensifentrine	155	-2.4 (-6.1, 1.4)	-0.42 (-0.78, -0.05)
		Placebo	81		
ENHANCE-2		Ensifentrine	169	-2.2 (-5.9, 1.5)	0.00 (-0.36, 0.36)
		Placebo	90		
Pooled		Ensifentrine	324	-2.3 (-4.9, 0.3)	NR
		Placebo	171		
Pooled	**LAMA**	Ensifentrine	319	-8.0 (-10.8, -5.3)*	NR
		Placebo	166	-5.6 (-8.7, -2.5)*	

Trial	Subgroup	Arms	N	St. George's Respiratory Questionnaire (SGRQ)	Average daily rescue medication use over 7 days
				LS mean change from baseline vs. placebo (95% CI)	LS mean change from baseline vs. placebo (95% CI)
				Week 24	Week 24
ENHANCE-1	**No background medication**	Ensifentrine	146	-2.9 (-6.6, 0.8)	-0.74 (-1.16, -0.32)
		Placebo	91		
ENHANCE-2		Ensifentrine	223	0.9 (-2.4, 4.1)	-0.32 (-0.80, 0.15)
		Placebo	131		
Pooled		Ensifentrine	369	NR	NR
		Placebo	222		

CI: confidence interval, ICS: inhaled corticosteroids, LABA: long-acting b2-agonist, LAMA: long-acting muscarinic antagonist, N: number, NR: not reported, %: percent

* Least-squares mean change from baseline

Table D3.25. Phase III Other Subgroup Data[55,56,114,116]

Trial	Subgroup	Arms	N	Changes in lung function	Moderate or severe COPD exacerbations	
				Average FEV_1, AUC 0-12h	Annualized exacerbation rate	Time to first event
				LS mean change from baseline vs. placebo (95% CI); P value	Rate ratio (95% CI); P value	Hazard ratio (95% CI); P value
				Week 12	Week 24	Week 24
ENHANCE-1	**Female**	Ensifentrine	203	90.6 (50.8, 130.4); P<0.001	NR	NR
		Placebo	116			
ENHANCE-2		Ensifentrine	254	75 (39, 112); P<0.001	NR	NR
		Placebo	153			
Pooled		Ensifentrine	457	NR	0.58 (0.38, 0.89)	0.56 (0.36, 0.86)
		Placebo	269			
ENHANCE-1	**Male**	Ensifentrine	274	85 (39.2, 130.8) P<0.001	NR	NR
		Placebo	167			
ENHANCE-2		Ensifentrine	244	114 (68, 161); P<0.001	NR	NR
		Placebo	138			
Pooled		Ensifentrine	518	NR	0.64 (0.41, 0.98)	0.63 (0.41, 0.97)
		Placebo	305			
ENHANCE-1	**<65 years**	Ensifentrine	219	70 (14.9, 125.1); P=0.013	NR	NR
		Placebo	113			
ENHANCE-2		Ensifentrine	224	87 (39, 135); P<0.001	NR	NR
		Placebo	124			
Pooled		Ensifentrine	443	NR	0.63 (0.39, 1.01)	0.59 (0.37, 0.93)
		Placebo	257			

Trial	Subgroup	Arms	N	Changes in lung function	Moderate or severe COPD exacerbations	
				Average FEV_1, AUC 0-12h	Annualized exacerbation rate	Time to first event
				LS mean change from baseline vs. placebo (95% CI); P value	Rate ratio (95% CI); P value	Hazard ratio (95% CI); P value
				Week 12	Week 24	Week 24
ENHANCE-1	**≥65 years**	Ensifentrine	258	102.3 (67.1, 137.6); P<0.001	NR	NR
		Placebo	150			
ENHANCE-2		Ensifentrine	274	100 (63, 136); P<0.001	NR	NR
		Placebo	167			
Pooled		Ensifentrine	532	NR	0.57 (0.38, 0.85)	0.60 (0.40, 0.90)
		Placebo	317			
ENHANCE-1	**Current smoker**	Ensifentrine	268	94.4 (50, 138.7); P<0.001	NR	NR
		Placebo	163			
ENHANCE-2		Ensifentrine	276	83 (42, 124); P<0.001	NR	NR
		Placebo	160			
Pooled		Ensifentrine	544	NR	0.57 (0.37, 0.87)	0.58 (0.38, 0.89)
		Placebo	323			
ENHANCE-1	**Former smoker**	Ensifentrine	209	75.8 (31.9, 119.7); P<0.001	NR	NR
		Placebo	120			
ENHANCE-2		Ensifentrine	222	107 (66, 149); P<0.001	NR	NR
		Placebo	131			
Pooled		Ensifentrine	431	NR	0.64 (0.41, 1.00)	0.62 (0.40, 0.96)
		Placebo	251			
ENHANCE-1	**ICS use**	Ensifentrine	386	64.4 (-0.5, 129.2); P=0.052	NR	NR
		Placebo	212			
ENHANCE-2		Ensifentrine	73	92 (28, 156); P=0.005	NR	NR
		Placebo	47			
Pooled		Ensifentrine	164	NR	0.57 (0.29, 1.12)	0.49 (0.25, 0.97)
		Placebo	118			

Trial	Subgroup	Arms	N	Changes in lung function	Moderate or severe COPD exacerbations	
				Average FEV_1, AUC 0-12h	Annualized exacerbation rate	Time to first event
				LS mean change from baseline vs. placebo (95% CI); P value	Rate ratio (95% CI); P value	Hazard ratio (95% CI); P value
				Week 12	Week 24	Week 24
ENHANCE-1	**No ICS use**	Ensifentrine	386	95.3 (559.4, 131.3); P<0.001	NR	NR
		Placebo	212			
ENHANCE-2		Ensifentrine	425	94 (62, 127); P<0.001	NR	NR
		Placebo	244			
Pooled		Ensifentrine	811	NR	0.62 (0.44, 0.88)	0.63 (0.45, 0.89)
		Placebo	456			
ENHANCE-1	**Chronic bronchitis**	Ensifentrine	385	75.5 (39.8, 111.2); P<0.001	NR	NR
		Placebo	215			
ENHANCE-2		Ensifentrine	322	78 (42, 114); P<0.001	NR	NR
		Placebo	190			
Pooled		Ensifentrine	707	NR	0.63 (0.44, 0.92)	0.65 (0.45, 0.94)
		Placebo	405			
ENHANCE-1	**Not known chronic bronchitis**	Ensifentrine	92	122.1 (53.4, 190.8); P<0.001	NR	NR
		Placebo	68			
ENHANCE-2		Ensifentrine	176	121 (73, 170); P<0.001	NR	NR
		Placebo	101			
Pooled		Ensifentrine	268	NR	0.56 (0.32, 0.96)	0.51 (0.30, 0.88)
		Placebo	169			
ENHANCE-1	**Baseline eosinophils ≤150 cells/µL**	Ensifentrine	NR	NR	NR	NR
		Placebo	NR			
ENHANCE-2		Ensifentrine	NR	NR	NR	NR
		Placebo	NR			
Pooled		Ensifentrine	408	NR	0.69 (0.42, 1.13)	0.69 (0.43, 1.13)
		Placebo	245			

Trial	Subgroup	Arms	N	Changes in lung function	Moderate or severe COPD exacerbations	
				Average FEV_1, AUC 0-12h	Annualized exacerbation rate	Time to first event
				LS mean change from baseline vs. placebo (95% CI); P value	Rate ratio (95% CI); P value	Hazard ratio (95% CI); P value
				Week 12	Week 24	Week 24
ENHANCE-1	**Baseline eosinophils >150 cells/µL**	Ensifentrine	NR	NR	NR	NR
		Placebo	NR			
ENHANCE-2		Ensifentrine	NR	NR	NR	NR
		Placebo	NR			
Pooled		Ensifentrine	565	NR	0.55 (0.37, 0.81)	0.54 (0.36, 0.80)
		Placebo	329			
Pooled	**Baseline eosinophils <100 cells/µL**	Ensifentrine	182	69; P<0.05	0.59 (0.24, 1.43)	0.56 (0.23, 1.35)
		Placebo	107			
Pooled	**Baseline eosinophils ≥100 cells/µL**	Ensifentrine	791	94; P<0.05	0.61 (0.44, 0.84); P<0.05	0.60 (0.43, 0.83); P<0.05
		Placebo	467			
ENHANCE-1	**Previous exacerbation (15 months)**	Ensifentrine	NR	NR	NR	NR
		Placebo	NR			
ENHANCE-2		Ensifentrine	NR	NR	NR	NR
		Placebo	NR			
Pooled		Ensifentrine	220	NR	0.70 (0.43, 1.17)	0.69 (0.41, 1.18)
		Placebo	136			
ENHANCE-1	**No previous exacerbation (15 months)**	Ensifentrine	NR	NR	NR	NR
		Placebo	NR			
ENHANCE-2		Ensifentrine	NR	NR	NR	NR
		Placebo	NR			
Pooled		Ensifentrine	755	NR	0.57 (0.39, 0.84)	0.57 (0.39, 0.83)
		Placebo	438			

Trial	Subgroup	Arms	N	Changes in lung function	Moderate or severe COPD exacerbations	
				Average FEV_1, AUC 0-12h	Annualized exacerbation rate	Time to first event
				LS mean change from baseline vs. placebo (95% CI); P value	Rate ratio (95% CI); P value	Hazard ratio (95% CI); P value
				Week 12	Week 24	Week 24
ENHANCE-1	**Moderate COPD**	Ensifentrine	294	88.3 (46.2, 130.3); P<0.001	NR	NR
		Placebo	164			
ENHANCE-2		Ensifentrine	265	140 (98, 181); P<0.001	NR	NR
		Placebo	143			
Pooled		Ensifentrine	NR	NR	NR	NR
		Placebo	NR			
ENHANCE-1	**Severe COPD**	Ensifentrine	179	84.4 (36.7, 132); P<0.001	NR	NR
		Placebo	119			
ENHANCE-2		Ensifentrine	231	45 (4, 87); P=0.034	NR	NR
		Placebo	148			
Pooled		Ensifentrine	NR	NR	NR	NR
		Placebo	NR			

Cells/µL: cells per microliter, CI: confidence interval, FEV_1: forced expiratory volume in 1 second, ICS: inhaled corticosteroids, LABA: long-acting b2-agonist, LAMA: long-acting muscarinic antagonist, N: number, NR: not reported, %: percent

D4. Ongoing Studies

Table D4.1. Ongoing Studies

Trial/ NCT	Study Design	Treatment Arms	Background Therapy	Inclusion/Exclusion Criteria	Key Primary Outcomes [Timepoints]
ENHANCE-CHINA NCT05743075	Phase III, randomized, double-blind, placebo-controlled, parallel-group Duration: 24 weeks N= 488 (estimated)	Ensifentrine 3 mg BID or placebo BID will be administered by aerosol inhalation	**Permitted** -Maintenance use of LAMA or LABA therapy **Prohibited** -Long term of oxygen use -Pulmonary rehabilitation -Use of an experimental drug within 30 days or 5 half-lives prior to screening, -Use of traditional Chinese medicine with antispasmodic and anti-asthmatic effects that would interfere with the study within 2 weeks prior to first dose	**Inclusion** -40 to 80 years -Current or former cigarette smokers with a history of cigarette smoking ≥ 10 pack-years -Patients with moderately to severe COPD -Pre- and Post- salbutamol FEV_1/FVC ratio < 0.70; and Post-salbutamol FEV_1 ≥ 30% and ≤ 70% of predicted -Score of ≥2 on the mMRC Dyspnea Scale **Exclusion** -History of life-threatening COPD -Hospitalizations for COPD, pneumonia, or COVID-19 in the 12 weeks prior to Screening and/or COPD exacerbation, -Patients with lower respiratory tract infection occurred and not resolved within 6 weeks prior to screening	Change from baseline in average FEV_1 AUC 0-12h [Week 12]

0-12h: over twelve hours, AUC: area under the curve, BID: twice daily, COPD: chronic obstructive pulmonary disease, FEV_1: forced expiratory volume in 1 second, FVC: Forced vital capacity, LABA: long-acting b2-agonist, LAMA: long-acting muscarinic antagonist, mMRC: the modified Medical Research Council
Source: www.ClinicalTrials.gov

D5. Previous Systematic Reviews and Technology Assessments

We identified several previously conducted systematic literature reviews and report summaries of two in this supplement: one with a network meta-analysis and one with a meta-analysis. No health technology assessments were found. The reviews are briefly summarized below.

Axson EL, Lewis A, Potts J, et al. Inhaled therapies for chronic obstructive pulmonary disease: a systematic review and meta-analysis. *BMJ Open*. 2020.[117]

This systematic review and network meta-analysis (NMA) aimed to investigate the effectiveness of inhaled therapies for COPD using data from RCTs and observational studies. The primary focus was to compare different inhaled therapy strategies, particularly triple bronchodilator therapy (LAMA+LABA+ICS) versus dual bronchodilator therapy (LAMA+LABA), to reduce exacerbation risk, improve lung function, enhance health-related quality of life, and minimize adverse events. Three databases were searched for RCTs, cohort studies, and case-control studies comparing interventions with each other or placebo for individuals with COPD. The primary outcome was the number of moderate-to-severe exacerbations in the short-term (<20 weeks of treatment) and long-term (≥20 weeks of treatment). The researchers included 231 studies (212 RCTs and 19 observational studies). Network meta-analyses were conducted for exacerbations, lung function (FEV_1), health-related quality of life (SGRQ), mortality, adverse events, and pneumonia. Observational studies were narratively summarized. The NMA found that triple therapy was more effective than dual therapy in reducing moderate-to-severe exacerbations, both in the short-term and long-term. There was no significant difference between triple and dual therapy in improving peak or trough FEV_1 nor health-related quality of life improvement, as measured by SGRQ. Triple therapy was associated with a significant reduction in all-cause mortality, but increased risk of pneumonia compared to dual therapy. Observational studies generally supported the findings from RCTs, favoring triple therapy in reducing exacerbations and improving health-related quality of life. Overall, triple therapy proved most effective in reducing moderate-to-severe exacerbations but has the potential of increasing pneumonia risk in individuals with COPD. The study acknowledges limitations, such as heterogeneity in patient characteristics and outcome reporting across studies and emphasizes the need for more studies to identify patient subgroups that may benefit more from specific therapies.

Koarai A, Sugiura H, Yamada M, et al. Treatment with LABA versus LAMA for stable COPD: a systematic review and meta-analysis. *BMC Pulm Med*. 2020.[118]

This systematic review and meta-analysis aimed to compare the efficacy and safety of LAMA and LABA in the treatment of stable COPD using studies evaluated outcomes of interest for at least 12 weeks. Key outcomes of interest were exacerbations, SGRQ score, TDI score, trough FEV_1, and adverse events. Of 1023 search results, a total of 19 RCTs with over 19,000 participants were included after screening. The meta-analysis found that LAMA treatment resulted in a significantly

lower incidence of exacerbations and total adverse events compared to LABA. Additionally, LAMA led to a slightly higher trough FEV_1. No significant differences in SGRQ and TDI scores between the two treatments were reported. Overall, LAMA treatment appears to be more beneficial than LABA for patients with stable COPD due to its lower incidence of exacerbations and adverse events. Subgroup findings from two studies suggest that LAMA treatment is significantly superior to LABA in patients with COPD with a history of exacerbations, but further studies in patients with an exacerbation history are needed to confirm this result. The study highlights the importance of considering both efficacy and safety outcomes when selecting bronchodilators for COPD management. However, the authors acknowledged that there was an insufficient number of trials for certain drugs which prevented subgroup analyses from being conducted.

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	X	X	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	X	
	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[119]

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. 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.[120]
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 evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. 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.

Target Population

The population for the economic evaluation included adults with moderate to severe COPD at baseline. Table E1.2 reports the baseline population characteristics that defined the cohort at the start of the model.

Table E1.2. Base-Case Model Cohort Characteristics

	Value	Source
Mean Age, years	67	Pace et al., 2022[121]
Female, %	56.4%	Pace et al., 2022[121]
Moderate COPD* at Baseline, %	78.1%	Mannino et al., 2022[65]
Severe COPD† at Baseline, %	21.9%	Mannino et al., 2022[65]
Current Smokers, %	41.2%	Pace et al., 2022[121]

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

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The intervention of interest for this review is ensifentrine (Verona Pharma). Ensifentrine was modeled as an add-on therapy to current COPD maintenance therapy versus current maintenance therapy alone.

E2. 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.

Disease Progression

COPD disease progression was modeled by way of transitioning to more severe health states in the economic model. Table E2.1 reports the transition probabilities between each of the alive health states. These transition probabilities are 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.

Table E2.1. Health State Transition Probabilities

Smoking Status	Moderate COPD* to Severe COPD†	Severe COPD† to Very Severe COPD‡	Source	Notes
Past Smoker	7.0%	6.1%	Atsou et al., 2011[122]	Average of the transition probabilities between ages 67 and 100 to align with the ages of the modeled population
Current Smoker	11.2%	9.4%		

* 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

Within each of the alive health states, the frequency and severity of exacerbations was tracked as events. Exacerbations were defined using an event-based definition based on the health care utilization required.[62] 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.[62] Subsequent sections of this report describe how exacerbations impact mortality, quality of life, and costs.

Table E2.2 reports the exacerbation parameters that were used in the economic model for current maintenance therapy alone, including the total number of exacerbations per model cycle and the severity distribution of the exacerbations, stratified by health state.

Table E2.2. Exacerbation Parameters, Current Maintenance Therapy Alone

Health State	Exacerbations§ per Year	Severe Exacerbations per Year#	Moderate Exacerbations per Year¤	Source	Notes
Moderate COPD*	1.17 (0.93, 1.44)	0.16	1.01	Hoogendoorn et al., 2011	13.7% of the total exacerbations are severe, 86.3% of the total exacerbations are moderate
Severe COPD†	1.61 (1.49, 1.74)	0.22	1.39		
Very Severe COPD‡	2.10 (1.46, 2.86)	0.29	1.81		

* 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

§ Either a moderate or 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 and/or antibiotics.

Table E2.3 reports the effectiveness of ensifentrine on reducing exacerbations. The ensifentrine rate ratio was applied to the total exacerbations per year as reported in Table E2.2. The relative percentage of total exacerbations that are severe versus moderate did not differ between the intervention and comparator arm.

Table E2.3. Ensifentrine Treatment Effect

Treatment	Exacerbation Rate Ratio (95% Confidence Interval)	Source	Notes
Ensifentrine	0.60 (0.41, 0.79)	ENHANCE-1 & ENHANCE-2	From ICER's meta-analysis of trial data at week 24

Mortality

All patients can transition 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.[123]

Standardized mortality ratios for COPD patients not due to exacerbations were applied to the all-cause mortality estimates. Table E2.4 reports these standardized mortality ratios stratified by health state.

Table E2.4. COPD Standardized Mortality Ratios

Health State	Standardized Mortality Ratio	Source	Notes
Moderate COPD*	1.6	Atsou et al., 2011[122]	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%).[62]

Discontinuation

Members of the modeled cohort could discontinue ensifentrine due to adverse events. Table E2.5 reports the adverse event-related discontinuation rate that was used in the economic model. Individuals that discontinued ensifentrine due to adverse events discontinued at week 12. No subsequent discontinuation or treatment stopping was modeled. Discontinuation impacted the model by reducing the percent of the cohort in the ensifentrine arm of the model who received the cost of ensifentrine. The ensifentrine effect size was not adjusted for discontinuation due to the intent to treat nature of the evidence source for the ensifentrine effect. Members of the modeled cohort who discontinued due to adverse events only received the cost of ensifentrine for the first 12 weeks of the model.

Table E2.5. Discontinuation Parameters

Discontinuation Reason	Ensifentrine	Source	Notes
Adverse Event, Excluding COVID	5.1%	ENHANCE-1 & ENHANCE-2[10]	ICER combined trial data at 24 weeks

Adverse Events

Adverse events associated with ensifentrine only impacted discontinuation. No costs or consequences were assigned to any specific adverse event because adverse events in the trial were comparable between the ensifentrine arm and the placebo arm.

Smoking Cessation

Because the transition probabilities for disease progression are dependent on smoking status, smoking status was tracked in the model. The percentage of the cohort that are current smokers at baseline is described in Table E1.2. During each model cycle, a current smoker had a 4.5% probability of smoking cessation.[124] 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.[125] Therefore, we modeled that 3.51% (4.5% * (100%-22%)) of the cohort would permanently stop smoking each model cycle.

Utility Inputs

Health state utility estimates are reported in Table E2.6 and were from a source that elicited utility estimates using the EQ-5D from patients with COPD. Differences in health state utility values between the intervention and comparator arm were modeled in a scenario analysis.

Table E2.6. Health State Utility Values

Health State	Utility	Source/Notes	Notes
Moderate COPD*	0.787 (0.77, 0.80)	Fenwick et al., 2021[126]	Elicited using the EQ-5D from patients with COPD
Severe COPD†	0.750 (0.73, 0.77)		
Very Severe COPD‡	0.647 (0.60, 0.70)		

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 an additional disutility. The disutilities per exacerbation are presented in Table E2.7. Exacerbations are modeled as an event, rather than as health states, and thus these disutilities are applied per event.

Table E2.7. Disutility Values, Per Exacerbation

Health State	Moderate Exacerbation§	Severe Exacerbation#	Source/Notes	Notes
Moderate COPD*	-0.0131	-0.0379	Hoogendoorn et al., 2011[62]	The annual disutility was 1.66% and 4.82% of the health state utility value for a moderate or severe exacerbation, respectively.
Severe COPD†	-0.0125	-0.0362		
Very Severe COPD‡	-0.0107	-0.0312		

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

§ A moderate exacerbation was defined as an exacerbation leading to a prescription of systemic corticosteroids and 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 2023 US dollars.

Drug Utilization

Table E2.8 reports the treatment regimen for ensifentrine.

Table E2.8. Ensifentrine Treatment Regimen

Treatment Regimen Parameter	Ensifentrine
Dose per Administration	3 mg
Frequency of Administration	Twice daily
Route of Administration	Nebulized

mg: milligram

For the purposes of estimating treatment costs, Table E2.9 details the current maintenance therapy basket that defined the comparator as well as what ensifentrine was added on to. The specific treatments within each maintenance therapy regimen included those with generic equivalents. If no generic equivalents existed for a maintenance therapy regimen, an average across all of the branded drugs within that maintenance therapy regimen was included in the cost estimation. If multiple generic equivalents existed for a maintenance therapy regimen, an average across all of the generic equivalents within that maintenance therapy regimen was included in the cost estimation.

Table E2.9. Current Maintenance Therapy Basket

Maintenance Therapy Regimens	Percent	Treatments in Regimen	Source
LAMA only	34%	Tiotropium bromide (100%)	Calculated the values in the percent column based on the number of patients in the GOLD 2, GOLD 3, and GOLD 4 groups on each maintenance therapy regimen as reported in Wallace et al., 2019.[69] Included maintenance therapy regimens that at least 10% of the population reported being on.
LABA + ICS	51%	Budesonide/formoterol fumarate (33.3%), Fluticasone propionate/salmeterol xinafoate (33.3%), Vilanterol trifenatate/fluticasone furoate (33.3%)	
LABA + LAMA + ICS	15%	Budesonide/glycopyrrolate/formoterol fumarate (50%), Fluticasone furoate/ umeclidinium/vilanterol (50%)	

ICS: inhaled corticosteroid, LABA: long-active beta-agonist, LAMA: long-acting muscarinic antagonist

Drug Acquisition Costs

For ensifentrine, we used the wholesale acquisition cost at launch of $2,950 per month ($35,400 per year).[66] For drugs within the current maintenance therapy basket that had a generic equivalent available, the lowest cost wholesale acquisition cost (WAC) was used. For drugs within the current maintenance therapy basket that did not have a generic equivalent available (e.g., Budesonide/glycopyrrolate/formoterol fumarate, Fluticasone furoate/ umeclidinium/vilanterol), we obtained net pricing estimates from SSR Health, LLC, which combines data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, patient assistance programs, and concessions to wholesalers and distributors, to derive a net price. We estimated net prices by comparing the four-quarter averages of both net prices and WAC per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the WAC from Redbook (accessed January 31, 2024) to arrive at an estimated net price per unit.

Table E2.10 reports the drug cost parameters for the drugs within current maintenance therapy.

Table E2.10. Current Maintenance Therapy Drug Costs

Treatment	Package Size	Strength	WAC per Package	Mean Discount from WAC*	Net Price per Package	Net Price per Year
Tiotropium bromide (LAMA only)	60 puffs/30 days	18 mcg	$460.82	N/A	$460.82	$5,607
Budesonide/formoterol fumarate (LABA+ICS)	120 puffs/30 days	80-160 mcg/4.5 mcg	$218.77	N/A	$218.77	$2,662
Fluticasone propionate/salmeterol xinafoate (LABA+ICS)	60 puffs/30 days	250 mcg/50 mcg	$116.44	N/A	$116.44	$1,417
Vilanterol trifenatate/fluticasone furoate (LABA+ICS)	60 blisters/30 days	100-200 mcg/25 mcg	$249.50	N/A	$249.50	$3,036
Budesonide/glycopyrrolate/formoterol fumarate (LABA + LAMA + ICS)	120 puffs/30 days	160 mcg/9 mcg/4.8 mcg	$645.14	71%	$187.74	$2,284
Fluticasone furoate/ umeclidinium/vilanterol (LABA + LAMA + ICS)	30 blisters/30 days	100 mcg/62.5 mcg/25 mcg	$657.60	72%	$181.50	$2,208

ICS: inhaled corticosteroid, LABA: long-active beta-agonist, LAMA: long-acting muscarinic antagonist, WAC: wholesale acquisition cost

* Calculated using net price data from SSR Health

Table E2.11 reports the drug costs used in the model. The current maintenance therapy annual cost was calculated by weighting the percentages in Table E2.9 by the costs in Table E2.10.

Table E2.11. Treatment Costs

Drug	Annual Cost	Source	Notes
Ensifentrine	$35,400	Jain, 2024[66]	Wholesale acquisition price
Current Maintenance Therapy	$3,453	Redbook, SSR Health	Calculated by weighting the percentages in Table E2.9 by the costs in Table E2.10

Administration Costs

Administration costs for ensifentrine included the purchase of a nebulizer at an assumed price of $125 per nebulizer.[127] The lifespan of the nebulizer was assumed to be five years, and thus a new nebulizer was purchased every five years for those individuals receiving ensifentrine.[128]

Additionally, the tubing and mouthpiece was replaced every six months.[129] The purchase of new tubing and a mouthpiece was $14.95 every six months.[130]

Health Care Utilization Costs

Table E2.12 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 were included elsewhere in the model but include office visits and other outpatient costs which includes oxygen therapy. 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 E2.12 will be added on to the non-COPD health care costs experienced by patients with COPD which are $22,113 per year.[131]

Table E2.12. Health State Costs

Health State	Annual Cost	Source	Notes
Moderate COPD*	$1,509	Wallace et al., 2019[69]	Inflated from 2015 US dollars to 2023 US dollars
Severe COPD†	$2,683		
Very Severe COPD‡	$3,432		

* 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 E2.13 reports the costs associated with a moderate and a severe exacerbation.

Table E2.13. Exacerbation Costs

Exacerbation Severity	Cost per Event	Source	Notes
Moderate Exacerbation*	$2,415	Bogart et al., 2020[67]	Inflated from 2017 US dollars to 2023 US dollars
Severe Exacerbation†	$26,047		

* A moderate exacerbation was defined as an exacerbation leading to a prescription of systemic corticosteroids and 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.[132] Lost productivity time was monetized using an average hourly wage of $34.27 as reported by the Bureau of Labor Statistics.[133]

Caregiver Costs

On average, caregivers of patients with COPD provide 20 hours of care per week.[134] This estimate was equally applied to all members of the modeled cohort residing in any of the alive health states due to the lack of evidence available to suggest a differential in caregiver time based on exacerbation status. Caregiver time was monetized using an average hourly wage of $34.27 as reported by the Bureau of Labor Statistics.[133]

E3. Results

Table E3.1. Results for the Base-Case for Ensifentrine Added on to Current Maintenance Therapy as Compared to Current Maintenance Therapy Alone

Treatment	Intervention Cost	Maintenance Therapy Costs	Administration Costs	Health State Costs	Exacerbation-Related Costs	Unrelated Health Care Costs
Ensifentrine + Current Maintenance Therapy	$284,000	$29,000	$500	$19,000	$45,000	$187,000
Current Maintenance Therapy Alone	$0	$27,000	$0	$17,000	$69,000	$171,000

E4. Sensitivity Analyses

Table E4.1. Tornado Diagram Inputs and Results

Input	Lower Input CE Ratio ($/QALY)	Upper Input CE Ratio ($/QALY)	Lower Input	Upper Input
Ensifentrine exacerbation rate ratio	$335,000	$932,000	0.41	0.79
Percent of total exacerbations that are moderate	$334,000	$891,000	77%	94%
Case-fatality rate per severe exacerbation	$668,000	$390,000	10%	22%
Total exacerbations per year, moderate COPD	$543,000	$448,000	0.93	1.44
Total exacerbations per year, very severe COPD	$510,000	$477,000	1.46	2.86
Total exacerbations per year, severe COPD	$505,000	$481,000	1.49	1.74
Utility of very severe COPD	$502,000	$484,000	0.60	0.70
Annual maintenance therapy cost	$488,000	$504,000	$87	$12,738
Utility of severe COPD	$498,000	$487,000	0.73	0.77
Cost per severe exacerbation	$497,000	$487,000	$21,193	$31,394

CE: cost-effectiveness

Table E4.2. Results of Probabilistic Sensitivity Analysis

	Intervention Arm	Comparator Arm
Costs	$565,400,000	$285,000
QALYs	6.25 (5.4, 6.8)	5.68 (4.7, 6.5)
evLYs	6.35 (5.6, 6.9)	5.71 (4.7, 6.5)
Incremental CE Ratio ($/QALY)	$493,000	
Incremental CE Ratio ($/evLY)	$427,000	

CE: cost-effectiveness, evLY: equal-value life year, QALY: quality-adjusted life year

E5. Scenario Analyses

Scenario Analysis 1: Modified Societal Perspective

In a scenario analysis, we expanded the perspective to the modified societal perspective. In this perspective, we included productivity losses attached to exacerbations and caregiver time spent caregiving. Table E5.1 reports the model outcomes for this scenario analysis and Table E5.2 reports the incremental cost-effectiveness ratios.

Table E5.1. Model Outcomes for the Modified Societal Perspective Scenario Analysis

Treatment	Total Cost	QALYs	evLYs	Life Years
Ensifentrine + Current Maintenance Therapy	$894,000	6.25	6.34	8.43
Current Maintenance Therapy Alone	$603,000	5.68	5.68	7.71

evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.2. Incremental Cost-Effectiveness Ratios for the Modified Societal Perspective Scenario Analysis

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
Ensifentrine + Current Maintenance Therapy	**Current Maintenance Therapy Alone**	$511,000	$442,000	$401,000

evLYs: equal value of life years gained, QALY: quality-adjusted life year

Scenario Analysis 2: Unrelated Health Care Costs Excluded

In a scenario analysis, we excluded unrelated health care costs. Table E5.3 reports the model outcomes for this scenario analysis and Table E5.4 reports the incremental cost-effectiveness ratios.

Table E5.3. Model Outcomes for the Scenario Analysis Excluding Unrelated Health Care Costs

Treatment	Total Cost	QALYs	evLYs	Life Years
Ensifentrine + Current Maintenance Therapy	$378,000	6.25	6.34	8.43
Current Maintenance Therapy Alone	$113,000	5.68	5.68	7.71

evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.4. Incremental Cost-Effectiveness Ratios for the Scenario Analysis Excluding Unrelated Health Care Costs

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
Ensifentrine + Current Maintenance Therapy	**Current Maintenance Therapy Alone**	$464,000	$402,000	$365,000

evLYs: equal value of life years gained, QALY: quality-adjusted life year

Scenario Analysis 3: Ensifentrine Effect on Quality of Life

In a scenario analysis, we assumed that ensifentrine would result in higher utility estimates for moderate COPD, severe COPD, and very severe COPD due to the slower decline in lung function. We assumed that health state utility estimates would be 0.019 higher in ensifentrine-treated patients in this scenario analysis. To arrive at this estimate, we calibrated the first cycle difference in utility between the ensifentrine arm and comparator arm to be equivalent to the difference in EQ-5D-5L between the ensifentrine arm and the placebo arm reported in Rheault et al., 2023.[111] Table E5.5 reports the model outcomes for this scenario analysis and Table E5.6 reports the incremental cost-effectiveness ratios.

Table E5.5. Model Outcomes for the Scenario Analysis Assuming an Ensifentrine Effect on Health State Quality of Life

Treatment	Total Cost	QALYs	evLYs	Life Years
Ensifentrine + Current Maintenance Therapy	$564,000	6.41	6.48	8.43
Current Maintenance Therapy Alone	$284,000	5.68	5.68	7.71

evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.2. Incremental Cost-Effectiveness Ratios for the Scenario Analysis Assuming an Ensifentrine Effect on Health State Quality of Life

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
Ensifentrine + Current Maintenance Therapy	**Current Maintenance Therapy Alone**	$384,000	$349,000	$387,000

evLYs: equal value of life years gained, QALY: quality-adjusted life year

E6. Model Validation

Model validation followed standard practices in the field. First, we provided the preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. As part of ICER's efforts in acknowledging modeling transparency, we also offer to share the model with the manufacturer for external verification shortly after publishing this draft report. 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.

Prior Economic Models

This is the first cost-effectiveness analysis of ensifentrine that we are aware of; however, there have been numerous cost-effectiveness analyses within COPD.[60,63,122,126 61,62,64] Additionally, this model closely follows existing models and uses key learnings from a cross-model comparison exercise.[61] Based on the cross-model comparison exercise conducted previously by Hoogendoorn and colleagues, there has been between model variability in the disease progression framework and subgroup specifications and in the mortality framework and subgroup specifications.[61] For the disease progression framework, our model used transition probabilities adapted from Atsou et al.[122] with transition rates specified by COPD disease severity and smoking status. This approach is most closely similar to the approach taken by Hansen and colleagues.[63] Exacerbations were modeled as events rather than health states, which is similar to the approach taken by Wacker and colleagues.[60] For the mortality framework and subgroup specifications, our model programmed mortality as a function of all-cause mortality from life tables, exacerbation-related mortality, and COPD-attributable mortality excluding exacerbation-related mortality specified by age and disease severity. This is most closely similar to the approach taken by Hoogendoorn and colleagues and by Wacker and colleagues.[60,62]

To validate the model, we updated our model inputs to the inputs used in the standard reference scenario from the published cross-model comparison exercise and updated the treatment inputs specific to the hypothetical intervention two in the published cross-model comparison exercise.[61] After doing this, our model outcomes were nearly identical to the ones reported by Wacker in the cross-model comparison exercise.[60,61] Our model produced an incremental €860 and 0.077 incremental QALYs when using these standard reference inputs. Wacker reported an incremental €844 and 0.075 incremental QALYs when using these standard reference inputs. It is not surprising that our findings most closely mirrored the findings reported by Wacker due to the similar way exacerbations and mortality were modeled. We then removed exacerbation-specific mortality, and our estimates were nearly identical to those reported by Rutten-van Mölken in the cross-model replication exercise that did not include any increased risk of mortality associated with an exacerbation.[135]

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with ensifentrine.

The potential budget impact analysis includes the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we used inputs for the size of the adult U.S. population 271,616,592 (average over 2024-2028), the prevalence of COPD in adults (5.6%), and the percentage of adult patients with moderate-to-severe COPD (63.3%).[12,65] Applying these sources results in estimates of 9,628,265 eligible patients in the US. For the purposes of this analysis, we assume that 20% of these patients would initiate treatment in each of the five years, or 1,925,653 patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[136,137] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact were calculated, we compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2023-2024, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $735 million per year for new drugs.

G. Supplemental Policy Recommendations

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: https://icer.org/wpcontent/uploads/2020/11/Cornerstones-of-Fair-Drug-Coverage-_-September-28-2020.pdf

Drug-Specific Coverage Criteria: Ensifentrine

Although ensifentrine was shown to be effective as add-on therapy for moderate to severe COPD, it was not tested head-to-head against dual LAMA/LABA or triple LAMA/LABA/ICS therapy. Thus, the efficacy of ensifentrine in addition to dual or triple therapy is not known and this will lead payers to develop prior authorization criteria and to consider other limits on utilization, particularly if the launch price is high.

None of these limits, however, should undermine the tenets of fair access to which all patients have a fundamental right.[12] To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for ensifentrine.

Coverage Criteria Considerations for Ensifentrine

- **Age:** This treatment will likely be covered for all adult patients with COPD without age thresholds.
- **Clinical eligibility**:
    - **Diagnosis:** Some payers may wish to consider diagnostic spirometry to confirm a diagnosis of COPD, in line with GOLD guidelines and clinical trial eligibility criteria.
    - **Severity:**
        - Although pivotal trial eligibility criteria included that patients should have a score of ≥2 on the mMRC Dyspnea Scale, clinical experts noted that these scales are not necessarily used routinely in clinical practice and did not see a reason to require a measure of severity as a condition of coverage.
        - Clinical experts did not believe it is reasonable for plans to require a specific minimum number of exacerbations per year or other time frame in order to

qualify for coverage since documentation of exacerbations may be variable, particularly among patients who have switched insurers within the past year. However, it is expected that payers will require that patients have "exacerbations" while on adequate LAMA/LABA or other standard of care. The definition of exacerbations should be broad, including any hospitalization or emergency department visit or need for a new prescription for oral steroids or antibiotics. Because some exacerbations will not be easily documentable (e.g., patients and clinicians may have pre-set plans for exacerbations including having oral steroids and antibiotics at home for use for exacerbations), payers should consider allowing clinician attestation regarding exacerbation history.

  - **Step Therapy:** The pivotal clinical trial included patients on no maintenance therapy, LAMA or LABA monotherapy, or LAMA or LABA with ICS. However, clinical experts suggested that ensifentrine's role in therapy would be as an add-on to guideline-based dual LAMA/LABA or triple LAMA/LABA/ICS therapy. Therefore, it is not unreasonable for payers to require patients to be on dual LAMA/LABA or triple LAMA/LABA/ICS therapy prior to trying ensifentrine. However, payers should be aware that some patients may not be able to tolerate dual or triple therapy due to side effects or difficulties with inhaler use, and thus there should be a clear and efficient process for requesting exceptions.

  - **Smoking status:** Although the ENHANCE trials were restricted to only smokers with COPD, clinical experts did not believe there was any reason to limit use of ensifentrine to current smokers.

- **Exclusion criteria**: There are no special medical comorbidities at this time that would serve as exclusion criteria for ensifentrine. Clinical experts did not believe that the exclusion criteria from the pivotal trials were appropriate for inclusion in insurance coverage criteria.

- **Dose:** Ensifentrine is delivered by standard jet nebulizer at a dose of 3 mg twice daily.

- **Duration of coverage and renewal criteria**: Initial coverage will likely be for a period of six to 12 months, which is long enough for assessment of efficacy and side effects.

- **Provider restrictions**: Given the importance of optimization of background therapy, clinical experts agreed that it is reasonable to restrict initial prescriptions for ensifentrine to pulmonary specialists or to clinicians in consultation with pulmonary specialists.

H. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on Friday, June 14th, 2024. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. One speaker did not submit a summary of their public comment.

A video recording of all comments can be found here, beginning at minute 00:10. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Tonya Winders, MBA
President and CEO, Global Allergy and Airways Patient Platform

Imagine being unable to walk to the mailbox without stopping to catch your breath. Imagine not attending your grandchild's wedding or weekly gathering of church friends due to your dependence on oxygen. Imagine speaking to a lawmaker who has no clue that COPD is a lung disease even though it is the third leading cause of death in the United States. Unfortunately, this is the reality for more than 16 million Americans today. COPD is a chronic progressive disease that changes lives forever.

10 years ago, my mother began to demonstrate symptoms of shortness of breath and cough. She never smoked, had no occupational exposures and does not live in a highly polluted area of the country. As the years went by, she dismissed the breathlessness, as simply getting older and being out of shape. After years of suffering in silence, she finally shared with her family, and we begin pushing her to see a pulmonologist. It took almost 3 years for her to get spirometry and referral to a specialist. That is when she heard the words for the first time, COPD. She was soon put on more aggressive treatments, and thankfully has maintained control of her disease. She has only been hospitalized one time, but limits her activities and interaction with others as a "necessary means "to staying well. She struggles with anxiety and depression due to the isolation & daily limitations. I wish her story was rare however it is not.

Let me introduce you to my dear friend Carolee who is living with advanced COPD. She is oxygen dependent and can no longer travel, spend time with her church friends, or even do her grocery shopping. She has been hospitalized, 2-3 times each year & now has a full-time caregiver living in her home. She experienced several cardiovascular events post exacerbation, resulting in longer hospital stays & more complicated recoveries. Yes she smoked for about twenty years but has been smoke free for forty years & yet still struggles with shame & guilt. She cannot afford her medication

and often has to make the decision between paying the rent, eating, or breathing. A choice no one should ever have to make.

Despite the availability of good treatments, many patients remain symptomatic and need new options. While COPD-specific quality of life instruments exist – – these tools are designed to focus on physical symptoms and limitations. They do not fully address the psychosocial aspects that affect a patient's ability to engage in meaningful life activities. They also fail to recognize the burden on the caregivers as this disease progresses.

Each year COPD directly costs our society more than $24 billion. When you consider indirect costs, the total is more than $49 billion per year. Among patients who are employed, COPD often leads to substantial income losses, estimated at $7,365 due to missed work. Moreover, approximately 40% of patients are forced into premature retirement, resulting in lifetime income losses of $316,000.11Today, there is limited data on the absenteeism, presenteeism, or impact on physical, mental, emotional, financial, social, and sexual health of caregivers.

The health risks associated with exacerbations are significant, with patients facing an almost fourfold increase in the risk of cardiovascular events, such as heart attacks, within 30 days after exacerbation. Experiencing two or more exacerbations can increase a patient's risk of a future severe exacerbation by 61%. In fact, up to 20% of patients require at least one hospital admission each year & COPD-related hospitalizations increase mortality risk,6

The annual economic impact associated with COPD is expected to rise to $4.8 trillion globally by 2030. The high unmet need for patients with COPD is evident. It is imperative during value assessments like today that we acknowledge the full spectrum of its impact – from the direct costs of medical care to the indirect costs borne by patients and their families. As we consider future health care policy and resource allocation in COPD, access to a new drug class with a novel mechanism of action will provide hope and health for people whose COPD is not adequately managed with the current treatments available….the quality of life for families like mine & millions more depend on it. We need more options! Thank you.

Tonya has acted as a paid advisor for unbranded disease awareness, education and advocacy for AZ, Chiesi, GSK, Roche, MSD, and Sanofi Regeneron and has received <25% of overall funds from these health care companies.

I. Conflict of Interest Disclosures

Tables I1 through I3 contain conflict of interest (COI) disclosures for all participants at the Friday, June 14th, 2024 Public meeting of Ensifentrine for Maintenance of Chronic Obstructive Pulmonary Disease.

Table I1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants*	
Sarah Emond, MPP, President and CEO, ICER	**Grace Ham, MSc**, Program and Events Coordinator, ICER
Grace Lin, MD, Medical Director for Health Technology Assessment, ICER	**Avery McKenna, BS,** Research Lead, ICER
Steve Pearson, MD, MSc, Special Advisor, ICER	**Finn Raymond, BS**, Research Assistant, ICER
David Rind, MD, MSc, Chief Medical Officer, ICER	**Liis Shea, MA**, Senior Program Director, ICER
Mel Whittington, PhD, MS, Senior Fellow Center for the Evaluation of Value and Risk in Health (CEVR), Tufts Medical Center	**Abigail Wright, PhD, MSc**, Research Lead, ICER

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table I2. Midwest CEPAC Panel Member Participants and COI Disclosures

Participating Members of Midwest CEPAC*	
Eric Armbrecht, PhD, Professor, Saint Louis University	**Bijan Borah, PhD**, Professor of Health Services Research, Mayo Clinic College of Medicine and Science
Kurt Vanden Bosch, PharmD, System Formulary Lead, St. Luke's Health System	**Don Casey, MD, MPH, MBA, MACP, FAHA**, Associate Professor of Internal Medicine, Rush Medical College
Yngve Falck-Ytter, MD AGAF, Case Western Reserve University	**Elbert Huang MD**, Professor of Medicine and Public Health Sciences, University of Chicago
Jayani Jayawardhana, PhD, Associate Professor, University of Kentucky	**Jill Johnson, PharmD,** Professor, UAMS College of Pharmacy
David D Kim, PhD, Assistant Professor, University of Chicago	**Bradley Martin, PharmD, PhD**, Professor, Division of Pharmaceutical Evaluation and Policy, University of Arkansas for Medical Sciences College of Pharmacy
Tim McBride, PhD, Professor, Washington University in St. Louis	**Jimi Olaghere**, Patient Advocate
Rachel Sachs, JD, MPH, "Professor of Law, Washington University in St. Louis"	**Timothy J. Wilt, MD, MPH**, Professor of Medicine and Public Health, University of Minnesota Schools of Medicine and Public Health and the Minneapolis VA Health Care System
Stuart Winston, DO, Patient Experience Consultant, Trinity-Health IHA Medical Group	

* No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table I3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Mindy Bauer, PharmD, Pharmacist, IPD Analytics	Mindy Bauer is a full-time employee at IPD Analytics.
Valerie Chang, BA, JD, Executive Director, Hawaii COPD Coalition, Vice Chair of Board, COPD Foundation	Hawaii COPD Coalition receives annual sponsorships from a BCBS insurer and exhibit fees from pharmaceutical companies for the annual COPD Education Day. The COPD Foundation also receives greater than 25% of funding from health care companies.
Stephanie Christenson, MD, MAS, Associate Professor, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, UCSF	Dr. Christenson reports grant support from the NIH, American Lung Association, COPD Foundation, and Department of Defense; consulting and advisory board fees from AstraZeneca, Sanofi, Regeneron, GSK, Verona Pharma, Glenmark Pharmaceuticals, Axon Advisors, Apogee Therapeutics, Amgen, Devpro Pharma, Kymera Therapeutics, and Genentech; Non-branded speaking fees from AstraZeneca, GSK, Sanofi, Regeneron, Amgen, Medscape, Horizon CME; writing fees from UpToDate.
Phyliss DiLorenzo, COPD Foundation Board Member	No personal conflicts to disclose. The COPD Foundation receives greater than 25% of funding from health care companies.
David Dohan, MD, Medical Director for Pharmacy and Appeals, Point34Health	Dr. Dohan is a full-time employee at Point34Health.
Juan Rojas, MD, MS, Director of Clinical Informatics & Data Science, Division of Translational & Precision Medicine, and Assistant Professor, Department of Internal Medicine, Division of Pulmonary, Critical Care, & Sleep Medicine, Rush University	No conflicts to disclose.