

Ensifentrine Added on to Dual Bronchodilator or Triple Therapy Demonstrates Clinically Meaningful Improvement in CAT Score in Symptomatic Patients with Chronic Obstructive Pulmonary Disease

Thomas M Siler¹, Tara Rheault², Daniel Reyner², Margot MacDonald-Berko², John Davidson³, Kathleen Rickard²

¹Midwest Chest Consultants, PC, Saint Charles, MO, USA; ²Verona Pharma, a Subsidiary of Merck & Co., Inc., Rahway, NJ, USA; ³Stat One LLC, Cary, NC, USA

Correspondence: Thomas M Siler, Midwest Chest Consultants, PC, Saint Charles, MO, USA, Tel +1 636 946-1650, Fax +1 636 947-6621, Email thomas.siler.md@midwestchest.com

Background: Many patients with chronic obstructive pulmonary disease (COPD) remain symptomatic despite the use of available maintenance therapies. Ensifentrine is a novel, selective, dual inhibitor of phosphodiesterase (PDE)3 and PDE4 approved for use as a maintenance therapy in adult patients with COPD. This study evaluated the effect of ensifentrine added on to dual or triple therapy on symptoms and health status in symptomatic patients with COPD using the COPD Assessment Test™ (CAT).

Methods: In this single-center, Phase 3b, open-label study, patients aged 40 to 80 years with symptomatic (modified Medical Research Council Dyspnea Scale ≥ 2 ; CAT ≥ 10), moderate to severe COPD on stable dual bronchodilator or triple therapy received 3 mg twice-daily nebulized ensifentrine for 12 weeks. CAT scores were assessed at baseline, week 6, and week 12.

Results: Twenty eligible patients received ensifentrine. Patients with ≥ 1 postdose assessment ($n=18$) were analyzed. After 12 weeks, ensifentrine improved CAT scores by ≥ 2 units in 67.0% (95% CI, 38.0%, 100.0%) of patients. Mean change from baseline was -2.3 units (95% CI, -4.0 , -0.6), exceeding the clinically important difference of -2 units. At week 6, 44.4% (95% CI, 22.0%, 89.5%) of patients were CAT responders; the mean change from baseline in CAT score was -1.5 units (95% CI, -4.0 , 1.1). No adverse events were reported.

Conclusion: Ensifentrine provided clinically meaningful improvement in health status measured by CAT score in two-thirds of symptomatic patients with COPD taking dual bronchodilator or triple therapy in a real-world setting.

Clinical Trial Registration Number: Clinical trial registered on June 10, 2024, with Clinicaltrials.gov (Identifier: NCT06460493).

Keywords: chronic obstructive pulmonary disease, ensifentrine, quality of life, phosphodiesterase inhibitor, COPD Assessment Test

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition characterized by chronic respiratory symptoms and persistent airflow limitation. COPD is a leading cause of morbidity and mortality, with a prevalence that continues to increase worldwide.¹⁻³ The aim of COPD management is to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status.¹ Current standard-of-care treatment regimens for patients with COPD include long-acting bronchodilators (long-acting muscarinic antagonists [LAMA] or long-acting β -agonists [LABA]), which can be used together (dual therapy) and combined with inhaled corticosteroids (ICS; triple therapy).⁴ Despite routine maintenance treatment with LAMA/LABA and LAMA/LABA/ICS therapy, many patients with COPD continue to experience persistent daily symptoms, particularly dyspnea (or shortness of breath) that can be disabling,

cough, and impaired mucus clearance, resulting in reduced quality of life. Validated tools used to assess treatment effectiveness include patient-reported questionnaires such as the St. George's Respiratory Questionnaire (SGRQ), Evaluating-Respiratory Symptoms (E-RS), Chronic Respiratory Questionnaire, and Clinical COPD Questionnaire to facilitate communication between the patient and physician. Although these tools are often used in clinical trials, they are not practical for use in routine clinical practice, given that they are complex, often time-consuming to complete, and may require additional specialized software.^{5–7}

The COPD Assessment Test™ (CAT) is a validated, short, and simple patient-completed questionnaire developed for use in a clinical setting to assess COPD symptoms over time and their effect on a patient's well-being.⁵ The CAT consists of 8 items selected to capture the wide range of COPD symptoms and impacts (ie, Cough, Mucus, Chest Tightness, Breathlessness, Limited Activities, Confidence, Sleep, and Energy), with each item presented on a 6-point scale from 0 (no impairment) to 5 (maximum impairment). Total CAT scores range from 0 to 40 and correlate closely with the SGRQ.^{1,8} The total score corresponds to the impact of COPD on daily life (mild, 0–9; moderate, 10–20; severe, 21–30; very severe, 31–40). The CAT is advantageous over other health status questionnaires because it takes 2 to 3 minutes to complete, its results can be viewed immediately and, by utilizing the score, improvement can be tracked to provide a holistic assessment of the patient's health status.⁸

The minimum clinically important difference (MCID) is defined as the smallest change in an outcome score that an individual patient perceives as beneficial.⁸ The MCID is useful for interpretation of patient-reported outcome data over time and to determine whether a clinically meaningful improvement in symptoms occurs from one visit to the next, particularly in response to treatment or intervention.^{6,8} For CAT scores, a decrease from baseline of ≥ 2 units over 2 to 3 months suggests a meaningful improvement based on the determined reliable estimate of the MCID.^{8,9} The effect of COPD treatment regimens on CAT scores has been evaluated previously. Treatment with dual umeclidinium (UMEC)/vilanterol (VI; LAMA/LABA) over 12 weeks and triple therapy with fluticasone furoate/UMEC/VI (LAMA/LABA/ICS) have demonstrated clinically meaningful improvements in CAT scores.^{10–13} However, despite symptom improvements observed and multiple variations and combinations of dual and triple therapies used within these classes, many patients in routine clinical practice continue to report moderate to severe symptoms with a substantial effect on daily activities and emotional well-being.^{11,12,14–16} For example, Chen et al reported that 64% of patients taking dual or triple therapy for approximately 6 months reported a substantial burden of symptoms (CAT score >20) and that their COPD affected their work (55.9% of respondents) and leisure time (69.8% of respondents).¹⁴ Moreover, in a 2025 survey of approximately 2000 patients with COPD conducted during a visit with a healthcare provider, 64% reported that COPD had a moderate to great impact on their daily lives, with nearly half (50%) of patients reporting a moderate to great impact on their emotional well-being.¹⁷ Among patients who previously tried maintenance therapies, the majority (77%) indicated that they would be willing to try other therapies.¹⁶ The ongoing symptom burden in COPD patients despite dual or triple therapy highlights the need for additional treatment options that can provide benefit beyond commonly used therapies.

Ensifentrine is a novel, first-in-class, selective, dual inhibitor of phosphodiesterase (PDE)3 and PDE4 with demonstrated bronchodilatory and nonsteroidal anti-inflammatory effects that is approved for the maintenance treatment for COPD in adult patients.^{18–23} In two phase 3 clinical trials, ENHANCE-1 and ENHANCE-2, ensifentrine 3 mg demonstrated statistically significant improvements across all key forced expiratory volume in 1 second (FEV₁) endpoints in patients with or without additional bronchodilator background therapy.²⁰ In a pooled analysis of the ENHANCE trials, ensifentrine resulted in clinically meaningful improvements in dyspnea (assessed with the Transition Dyspnea Index [TDI]) and showed statistically significant improvements in COPD symptoms (assessed by E-RS daily diary) and quality of life (SGRQ) as early as 6 weeks, including when added on to LAMA or LABA + ICS treatment.^{4,20,24} Additionally, ensifentrine statistically significantly reduced the rate and risk of exacerbations in patients with moderate to severe COPD and in patients treated with LAMA (48% and 50%, respectively) and LABA + ICS (51% and 56%, respectively).^{4,20,24,25} Although the ENHANCE program demonstrated a statistically significant impact of ensifentrine on COPD symptoms and quality of life, the trials did not include patients on background dual (LAMA/LABA) or triple therapy (LAMA/LABA/ICS) regimens. Therefore, the objective of this study was to evaluate the effect of ensifentrine on health status when added on to routinely prescribed dual (LAMA/LABA) or triple (LAMA/LABA/ICS) therapy in patients with moderate to severe, symptomatic (baseline CAT score ≥ 10) COPD using the CAT questionnaire. This is

a real-world, single-center, non-randomized and uncontrolled study to assess the effectiveness of ensifentrine in routine clinical practice.

Materials and Methods

Study Design

This study was a phase 3b, single-center, open-label study in 20 patients with symptomatic (baseline modified Medical Research Council [mMRC] Dyspnea Scale ≥ 2 and CAT ≥ 10), moderate-to-severe COPD receiving standard dual (LAMA/LABA) or triple (LAMA/LABA/ICS) therapy, intended to model the real-world experience of ensifentrine add-on therapy in a clinical practice ([Figure S1](#)). The CAT questionnaire was self-administered on paper at baseline, week 6, and week 12. Baseline CAT and mMRC Dyspnea Scale questionnaire scores were evaluated at visit 1. Enrolled patients received twice-daily ensifentrine 3 mg over 12 weeks via standard jet nebulizer. Medications permitted during study participation included continued use of prescribed inhaled short-acting muscarinic antagonists, short-acting β_2 -agonists (SABAs), or any form (except nebulized) of approved COPD doses of LABA/LAMA or LABA/LAMA/ICS and non-COPD medication not on the prohibited medications list ([Table S1](#)).

Patients

Eligible patients were aged 40 to 80 years with a confirmed diagnosis of moderate to severe COPD, defined as postbronchodilator FEV₁/forced vital capacity (FVC) ratio of <0.7 and FEV₁ of 30% to 75% of predicted normal. Patients were required to be symptomatic, with an mMRC Dyspnea Scale score ≥ 2 , CAT score of ≥ 10 , and smoking history of ≥ 10 pack-years. Stable use of background dual (LAMA/LABA) or triple (LABA/LAMA/ICS) maintenance therapy for ≥ 8 weeks prior to screening was also required. Prior to screening spirometry, patients were required to withhold twice-daily maintenance therapy for 24 hours, once-daily maintenance therapy for 48 hours, and SABA rescue medication for ≥ 4 hours. Patients with concomitant pulmonary diseases including asthma, lower respiratory tract infection, or major surgery within 6 weeks of screening; lung resection or reduction surgery within 1 year of screening; history of life-threatening COPD; recent hospitalizations due to COPD; pneumonia; or treatment requiring oral, intravenous, or intramuscular steroids within 3 months of screening were excluded. Full inclusion and exclusion criteria are described in [Table S2](#).

Efficacy and Safety Evaluations

This study investigated the effect of nebulized ensifentrine over 12 weeks on symptoms and health status as assessed via CAT scores in patients with COPD. The primary endpoint evaluated proportion of CAT score responders, defined as an improvement from baseline of ≥ 2 units, at week 12. Secondary endpoints included the proportion of CAT score responders at week 6 and change from baseline in total and individual item CAT scores ([Table S3](#)). Safety assessments included the incidence of adverse events and change from baseline in vital signs (ie, blood pressure and pulse rate).

Statistical Analysis

Efficacy analyses were conducted using the full analysis set (FAS) population, which included all patients who received the study medication on day 1, had a baseline CAT, and had ≥ 1 post-treatment CAT assessment. Safety analyses were based on the safety analysis set (SAS) population, which included all patients who received the study medication on day 1. The proportion, standard error, and 95% CI for the percentage of CAT responders was estimated using Poisson regression, with a separate model fit to each assessment, and a term for background medication (linear contrast scaled to the proportion of subjects on dual therapy), and baseline CAT score as a covariate. A 2-sided unadjusted 95% CI for estimated proportions was used to determine study success, with the lower bound of the CI >0 indicating success. Change from baseline CAT scores (total and item-level) were analyzed using a mixed model for repeated measures model with terms for time, background medication (linear contrast scaled to the proportion of subjects on dual therapy), and baseline included as a covariate. Least-squares mean estimates, standard errors, and corresponding 95% CIs were generated for week 6 and week 12. Safety outcomes were analyzed descriptively as frequencies and percentages. Assuming 30%

response rate in the study population, a sample size of 20 subjects provided the ability to demonstrate the responder proportion estimate and estimates of mean change from baseline did not extend to the clinically meaningful change limit of ≥ 2 units.

Oversight

The study was conducted in accordance with the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation, and Good Clinical Practice guidelines. All patients provided written informed consent prior to study participation.

Results

Patients

The study was conducted at a single center in the United States. In total, 23 patients provided consent and were screened for eligibility in the study; 20 eligible patients were administered nebulized ensifentrine and included in the SAS population. Of these, 18 (90.0%) patients had both a baseline CAT and ≥ 1 postbaseline CAT assessment and were included in the FAS population (Figure 1). All 18 patients in the FAS also completed 12 weeks of treatment. Treatment withdrawal occurred in 2 (10.0%) patients due to withdrawal of consent and not due to an adverse event.

Baseline demographics and characteristics in the FAS population are shown in Table 1. Briefly, the mean (SD) age of patients was 71.3 (7.1) years; 44.0% of patients were female and 100.0% of patients were White, with mean post-bronchodilator FEV₁ percent predicted of 56.0%. The most common COPD diagnoses in patients were emphysema (94.0%) and chronic bronchitis (83.0%). At baseline, 56.0% and 44.0% of patients were receiving background dual LABA/LAMA or triple LABA/LAMA/ICS therapy, respectively. The mean (SD) time since COPD diagnosis was 13.7 (7.8) years. Patients were symptomatic despite receiving dual or triple maintenance therapies. The majority of patients (56.0%) had a baseline CAT score range of 10 to 20, 39.0% had a CAT score range of 21 to 20, and 6.0% had a CAT score of >30 . Among these patients, 33.0%, 61.0%, and 6.0% of patients had a baseline mMRC Dyspnea Scale score of 2, 3, and 4, respectively. The most frequently reported concomitant illnesses were hypertension (72.0%), gastroesophageal reflux disease (33.0%), depression (28.0%), anxiety (22.0%), hypercholesterolemia (22.0%), osteoarthritis (22.0%), and seasonal allergies (22.0%).

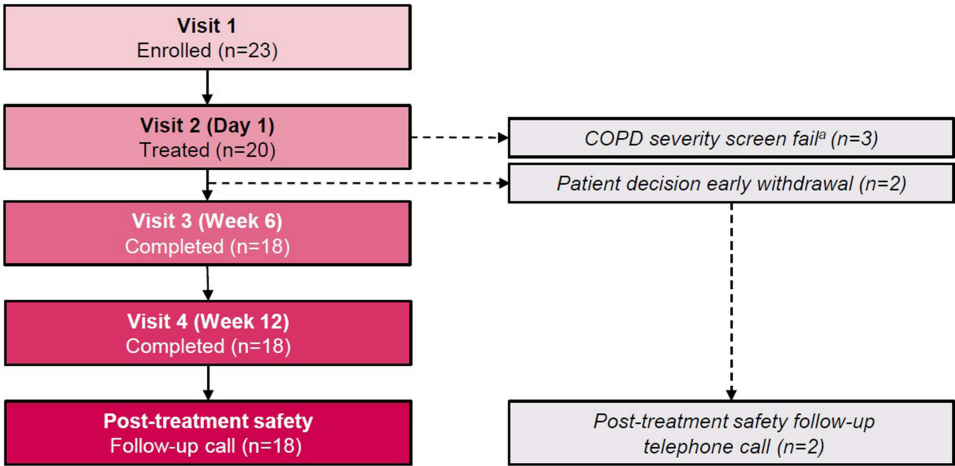


Figure 1 Patient enrollment and disposition. *COPD severity screen failure due to pre- and postbronchodilator $>75\%$; FEV₁/FVC ratio ≥ 0.70 .
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 1 Baseline Demographics and Clinical Characteristics, Full Analysis Set

Demographics	Ensifentrine 3 mg (N=18)
Age, y, mean (SD)	71.3 (7.1)
Sex, female, n (%)	8.0 (44.0)
Race, White, n (%)	18.0 (100.0)
Baseline disease characteristics, n (%)	
History of chronic bronchitis ^a	15.0 (83.0)
Diagnosis of emphysema	17.0 (94.0)
Mean postbronchodilator FEV ₁ , L (SD) ^b	1.6 (0.5)
% predicted	56.0%
Mean time since diagnosis, y (SD)	13.7 (7.8)
Exacerbation within 1 y before screening	2.0 (11.0)
Current smoker	11.0 (61.0)
Baseline ^c CAT score distribution, n (%)	
10-20	10.0 (56.0)
21-30	7.0 (39.0)
>30	1.0 (6.0)
Baseline ^c mMRC Dyspnea Scale score distribution, n (%)	
2	6.0 (33.0)
3	11.0 (61.0)
4	1.0 (6.0)
Background medications, n (%)	
LABA/LAMA	10.0 (56.0)
LABA/LAMA/ICS	8.0 (44.0)
Duration of background medications, y (SD)	
LABA/LAMA	4.6 (2.7)
LABA/LAMA/ICS	4.3 (4.0)
Most frequently reported (≥20%) concomitant illnesses, n (%) ^d	
Hypertension	13.0 (72.0)
Gastroesophageal reflux disease	6.0 (33.0)
Depression	5.0 (28.0)
Anxiety	4.0 (22.0)
Hypercholesterolemia	4.0 (22.0)
Osteoarthritis	4.0 (22.0)
Seasonal allergy	4.0 (22.0)

Notes: Full analysis set (N=18). ^aChronic bronchitis was defined as regular production of sputum for ≥3 months in 2 consecutive years in the absence of other conditions that may explain it. ^bScreening spirometry was evaluated at visit 2 (day 1). ^cBaseline CAT and mMRC Dyspnea Scale scores were evaluated at visit 1. CAT score ranges are defined as medium impact on daily life (10–20); high impact on daily life (21–30); very high impact on daily life (>30). ^dConcomitant illness refers to events ongoing or beginning after screening test.

Abbreviations: CAT, COPD Assessment Test™; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; mMRC, Modified Medical Research Council.

Primary Endpoint

Ensifentrine added on to dual (LABA/LAMA) or triple (LABA/LAMA/ICS) therapy resulted in a ≥2-unit CAT score improvement in 67.0% (95% CI, 38.0%, 100.0%) of patients at week 12 (Table 2). Higher responder rates were observed in patients using dual therapy (80.0%) and triple therapy (50.0%) at week 12 (Figure 2). The 95% CI for the responder rate at week 12 excluded 0.

Table 2 Mean CAT Score and Percent Responders Over 12 Weeks, Full Analysis Set

Timepoint	CAT Score, Mean (SD)	LSM Change from Baseline, Units (95% CI)	% CAT Responders ^a (95% CI)
Baseline	18.3 (6.4)	–	–
Week 6	16.7 (7.6)	–1.5 (–4.0, 1.1)	44.4% (22.0%, 89.5%)
Week 12	15.9 (7.3)	–2.3 (–4.0, –0.6)	67.0% (38.0%, 100.0%)

Notes: Full analysis set (N=18). ^aResponders were defined as patients with improvement of ≥ 2 units in CAT score compared with baseline.

Abbreviations: CAT, COPD Assessment Test™; COPD, chronic obstructive pulmonary disease; LSM, least squares mean.

Secondary Endpoints

At week 6, the mean (SD) CAT score was 16.7 (7.6) with an estimated change from baseline of –1.5 (1.0, 95% CI [–4.0, 1.1]) units. At week 12, the mean (SD) CAT score was 15.9 (7.3) with an estimated change from baseline of –2.3 (0.8, 95% CI [–4.0, –0.6]) units, exceeding the MCID of –2 units, with the null result within the CI (Table 2). Ensifentrine treatment resulted in a ≥ 2 -unit CAT score improvement in 44.4% (95% CI, 22.0%, 89.5%) of patients at week 6. The responder rates were 50.0% and 38.0% in patients using dual and triple therapies, respectively. The 95% CI for responder rate at week 6 excluded 0. Treatment with ensifentrine demonstrated progressive improvement in CAT scores from week 6 to week 12 (Table 2 and Figure 3). Among the individual CAT items, the largest magnitudes of improvement were observed at week 12 in the LS mean estimates for Mucus, Chest Tightness, and Breathlessness scores (Table S4).

Safety

Ensifentrine was well tolerated over 12 weeks, with no reports of adverse events, deaths, or other serious adverse events. Overall, no trends or clinically significant changes or abnormal values in systolic blood pressure, diastolic pressure, or pulse rate were observed during the study (Table S5).

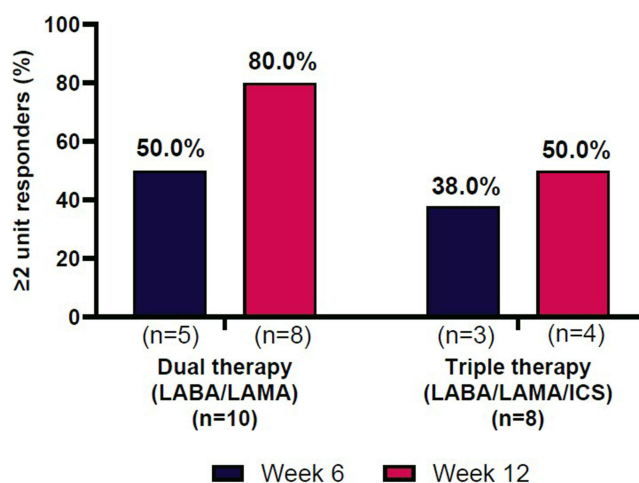


Figure 2 Percentage of CAT score responders by background medication over 12 weeks, FAS.

Abbreviations: CAT, COPD Assessment Test™; COPD, chronic obstructive pulmonary disease; FAS, full analysis set (N=18); LABA, long-acting β -agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid.

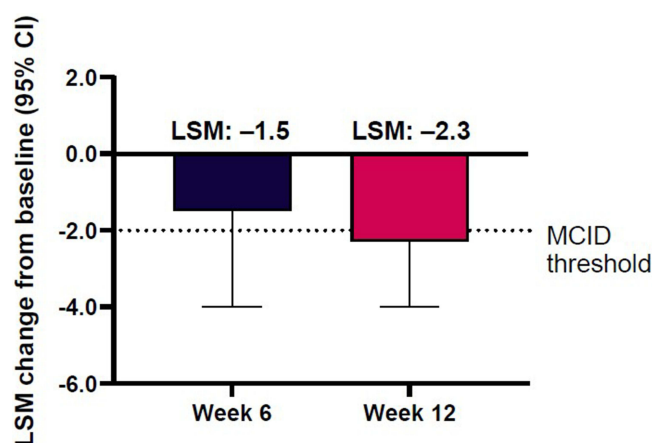


Figure 3 LSM change from baseline in CAT scores over 12 weeks, FAS.

Abbreviations: CAT, COPD Assessment Test™; COPD, chronic obstructive pulmonary disease; FAS, full analysis set (N=18); LSM, least squares mean; MCID, minimum clinically important difference.

Discussion

The intent of this study was to characterize symptomatic response in patients already receiving maximal dual or triple maintenance therapy. The strict inclusion and exclusion criteria of traditional randomized controlled trials inherently limit generalizability to all patient populations, or may not fully capture real-world treatment patterns and adherence. Therefore, this study was designed as an uncontrolled, single-center, real-world evaluation to reflect the use of ensifentrine in routine clinical practice. In this study, twice-daily nebulized ensifentrine added to dual and triple maintenance therapy demonstrated a clinically meaningful improvement in COPD symptoms assessed by the CAT. These findings reflect a real-world example of a single center's experience of treating patients with moderate to severe COPD with ensifentrine among patients who remain symptomatic with what was considered maximal bronchodilator therapy. Importantly, this is the first study to evaluate the effect of ensifentrine on health status and COPD symptoms, assessed by the CAT, in patients receiving background dual (LABA/LAMA) and triple (LABA/LAMA/ICS) therapy. In this study population, enrolled patients were highly symptomatic, with a mean (SD) baseline CAT score of 18.3 (6.4) units and mean (SD) time since COPD diagnosis was 13.7 (7.8) years, despite stable treatment with maintenance therapies. These findings align with previous reports highlighting that patients with COPD continue to experience substantial symptom burden even with good adherence to dual and triple therapy, with CAT scores exceeding 20 units in >60% of patients.¹⁴

Treatment with ensifentrine demonstrated clinically meaningful improvements in CAT scores at week 12 in 67.0% of symptomatic patients. Among patients receiving dual (LABA/LAMA) and triple (LABA/LAMA/ICS) therapy, the week 12 CAT responder rate was 80.0% and 50.0%, respectively, and demonstrated a clinically meaningful improvement from baseline with ensifentrine added on to their existing therapy. Analysis of these data excluded 0 at both time points in the 95% CI, suggesting a statistical nonzero effect. The larger percentage improvement in the dual therapy group may be due to the anti-inflammatory effect of ensifentrine.^{19,26,27} Ensifentrine also produced progressive improvement in total CAT score reduction over the 12-week treatment period, suggesting incremental increases over time due to anti-inflammatory or other pharmacology beyond bronchodilation alone.^{19,26–31} These data support the use of ensifentrine as a complementary treatment to add on to LAMA and LABA combination therapies, providing a clinically meaningful improvement in two-thirds of patients who remain symptomatic on dual and triple maintenance therapy. By providing a clinically meaningful response in these patients who previously had limited options for additional therapy, ensifentrine helps meet an unmet need in moderate to severe COPD management. Treatment with ensifentrine also demonstrated the largest magnitude of improvement in Mucus, Chest Tightness, and Breathlessness scores, which are profound symptoms in COPD and have debilitating effects on patients' daily lives. Furthermore, these improvements are consistent with mechanisms associated with ensifentrine, including additional bronchodilation, reduced airway inflammation, and

enhanced mucociliary clearance.^{19,26–32} As a new treatment for COPD, its dual mechanism of action allows ensifentrine to be used as a monotherapy or added to current inhaled routinely prescribed bronchodilator and anti-inflammatory therapies, producing complementary effects in patients needing additional therapeutic options.

Ensifentrine was well tolerated, with no adverse events reported after the addition of ensifentrine to dual and triple therapy. Overall, these findings confirm and extend the results of the ENHANCE program which demonstrated important improvements in symptoms and quality of life in patients,^{4,20,24} but did not include patients on dual and triple therapy. These results demonstrate that ensifentrine provides additional improvement in symptoms despite patients receiving maximal bronchodilator therapy.

As a small, single-center study with limited sample size and patient diversity, these findings may not be generalizable to broader or more diverse patient populations, including frequent exacerbators or those treated in different clinical settings.

Conclusions

COPD is a debilitating chronic disease due to profound daily breathlessness, cough and impaired mucus clearance. Ensifentrine provided clinically meaningful improvement in symptom burden, measured by the CAT, in symptomatic patients with COPD taking dual (LAMA/LABA) or triple (LAMA/LABA/ICS) maintenance therapy over 12 weeks, with the greatest magnitude of improvement in Mucus, Chest Tightness, and Breathlessness scores. Thus, nebulized ensifentrine provided additional clinically important benefits to patients with COPD who remain symptomatic despite receiving maximum treatment with current routinely prescribed COPD maintenance therapies.

Abbreviations

COPD, chronic obstructive pulmonary disease; LAMA, long-acting muscarinic antagonist; LABA, long-acting β -agonist; ICS, inhaled corticosteroid; SGRQ, St. George's Respiratory Questionnaire; E-RS, Evaluating-Respiratory Symptoms; CAT, COPD Assessment Test™; MCID, minimum clinically important difference; UMEC, umeclidinium; VI, vilanterol; PDE, phosphodiesterase; FEV₁, forced expiratory volume in 1 second; TDI, Transition Dyspnea Index; mMRC, modified Medical Research Council; SABA, short-acting β 2-agonist; FVC, forced vital capacity; SAMA, short-acting muscarinic antagonist; FAS, full analysis set; SAS, safety analysis set.

Data Sharing Statement

Aggregate data that support the findings of this study are available from the corresponding author (TS) upon reasonable request.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation, and Good Clinical Practice guidelines. The study protocol, all study protocol amendments, written study informed consent form, Verona Pharma ensifentrine Clinical Investigators Brochure, and any other relevant documents were reviewed and approved by WCG Institutional Review Board (IRB: 20241980). All patients provided written informed consent prior to study participation.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

TS received grants or contracts from Verona Pharma, GSK, Chiesi, Sanofi, Genentech, DevPro, Amgen, Compleware, Amphastar, AstraZeneca, and Areteia. TR, DR, MM-B, and KR are employees of Verona Pharma. JD is an employee of Stat One, which provides consultant statistical services to Verona Pharma. The authors report no other conflicts of interest in this work.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2025 report. Available from: <https://goldcopd.org/2025-gold-report/>. Accessed June 19, 2025.
2. World Health Organization. Global health estimates: leading causes of DALYs: disease burden, 2000–2021. Available from: <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/global-health-estimates-leading-causes-of-dalys>. Accessed April 7, 2025.
3. World Health Organization. Global health estimates: life expectancy and leading causes of death and disability. Available from: <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates>. Accessed November 9, 2023.
4. Dransfield M, Marchetti N, Kalhan R, et al. Ensifentrine in COPD patients taking long-acting bronchodilators: a pooled post-hoc analysis of the ENHANCE-1/2 studies. *Chron Respir Dis*. 2025;22:14799731251314874. doi:10.1177/14799731251314874
5. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J*. 2009;34(3):648–654. doi:10.1183/09031936.00102509
6. Jones PW, Tabberer M, Chen WH. Creating scenarios of the impact of COPD and their relationship to COPD Assessment Test (CAT) scores. *BMC Pulm Med*. 2011;11:42. doi:10.1186/1471-2466-11-42
7. Dodd JW, Hogg L, Nolan J, et al. The COPD assessment test (CAT): response to pulmonary rehabilitation. A multicentre, prospective study. *Thorax*. 2011;66(5):425–429. doi:10.1136/thx.2010.156372
8. Kon SS, Canavan JL, Jones SE, et al. Minimum clinically important difference for the COPD assessment test: a prospective analysis. *Lancet Respir Med*. 2014;2(3):195–203. doi:10.1016/S2213-2600(14)70001-3
9. COPD Assessment Test Governance Board. COPD assessment test (CAT™): healthcare professional user Guide. 2022. Available from: <https://www.catestonline.org>. Accessed February 3, 2026.
10. Kerwin EM, Kalberg CJ, Galkin DV, et al. Umeclidinium/vilanterol as step-up therapy from tiotropium in patients with moderate COPD: a randomized, parallel-group, 12-week study. *Int J Chron Obstruct Pulmon Dis*. 2017;12:745–755. doi:10.2147/COPD.S119032
11. Tabberer M, Lomas DA, Birk R, et al. Once-daily triple therapy in patients with COPD: patient-reported symptoms and quality of life. *Adv Ther*. 2018;35(1):56–71. doi:10.1007/s12325-017-0650-4
12. Tabberer M, Jones CE, Kilbride S, et al. Single-inhaler triple therapy and health-related quality of life in COPD: the IMPACT study. *Adv Ther*. 2020;37(9):3775–3790. doi:10.1007/s12325-020-01409-8
13. Feldman GJ, Sousa AR, Lipson DA, et al. Comparative efficacy of once-daily umeclidinium/vilanterol and tiotropium/olodaterol therapy in symptomatic chronic obstructive pulmonary disease: a randomized study. *Adv Ther*. 2017;34(11):2518–2533. doi:10.1007/s12325-017-0626-4
14. Chen S, Small M, Lindner L, Xu X. Symptomatic burden of COPD for patients receiving dual or triple therapy. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1365–1376. doi:10.2147/COPD.S163717
15. Phreesia Life Sciences. Patients in focus: COPD treatment and perceptions. Available from: <https://lifesciences.phreesia.com/reports/patients-in-focus-copd-treatment-and-perceptions/>. Accessed November 9, 2023.
16. Mannino DM, Trac S, Seth J, Dixon A, Aggarwal K, Kuhn B. Patient burden and insights in COPD: a survey analysis. *Chronic Obstr Pulm Dis*. 2025. doi:10.15326/jcopdf.2025.0616
17. Phreesia Life Sciences. Patients in focus: COPD treatment and perceptions. Available from: <https://lifesciences.phreesia.com/reports/patients-in-focus-copd-treatment-and-perceptions/>. Accessed September 3, 2024.
18. Watz H, Rickard K, Rheault T, Bengtsson T, Singh D. Symptom improvement following treatment with the inhaled dual phosphodiesterase 3 and 4 inhibitor ensifentrine in patients with moderate to severe COPD - a detailed analysis. *Int J Chron Obstruct Pulmon Dis*. 2020;15:2199–2206. doi:10.2147/copd.S263025
19. Franciosi LG, Diamant Z, Banner KH, et al. Efficacy and safety of RPL554, a dual PDE3 and PDE4 inhibitor, in healthy volunteers and in patients with asthma or chronic obstructive pulmonary disease: findings from four clinical trials. *Lancet Respir Med*. 2013;1(9):714–727. doi:10.1016/S2213-2600(13)70187-5
20. Anzueto A, Barjaktarevic IZ, Siler TM, et al. Ensifentrine, a novel phosphodiesterase 3 and 4 inhibitor for the treatment of chronic obstructive pulmonary disease: randomized, double-blind, placebo-controlled, multicenter Phase III trials (the ENHANCE trials). *Am J Respir Crit Care Med*. 2023;208(4):406–416. doi:10.1164/rccm.202306-0944OC
21. Ohtuvayre (ensifentrine). Full Prescribing Information. Raleigh, NC: Verona Pharma, Inc.; 2024.
22. Verona Pharma, plc. Data on file. Raleigh, NC: 2025.
23. Ferguson GT, Kerwin EM, Rheault T, Bengtsson T, Rickard K. A dose-ranging study of the novel inhaled dual PDE 3 and 4 inhibitor ensifentrine in patients with COPD receiving maintenance tiotropium therapy. *Int J Chron Obstruct Pulmon Dis*. 2021;16:1137–1148. doi:10.2147/copd.S307160
24. Mahler DA, Bhatt SP, Rheault T, et al. Effect of ensifentrine on dyspnea in patients with moderate-to-severe chronic obstructive pulmonary disease: pooled analysis of the ENHANCE trials. *Expert Rev Respir Med*. 2024;18(8):645–654. doi:10.1080/17476348.2024.2389960

25. Sciurba FC, Christenson SA, Rheault T, Bengtsson T, Rickard K, Barjaktarevic IZ. Effect of dual phosphodiesterase 3 and 4 inhibitor ensifentrine on exacerbation rate and risk in patients with moderate to severe COPD. *Chest*. **2025**;167(2):425–435. doi:10.1016/j.chest.2024.07.168
26. Boswell-Smith V, Spina D, Oxford AW, Comer MB, Seeds EA, Page CP. The pharmacology of two novel long-acting phosphodiesterase 3/4 inhibitors, RPL554 [9,10-dimethoxy-2-(2,4,6-trimethylphenylimino)-3-(n-carbamoyl-2-aminoethyl)-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one] and RPL565 [6,7-dihydro-2-(2,6-diisopropylphenoxy)-9,10-dimethoxy-4H-pyrimido[6,1-a]isoquinolin-4-one]. *J Pharmacol Exp Ther*. **2006**;318(2):840–848. doi:10.1124/jpet.105.099192
27. Spina D, Franciosi L, Venkatasamy R, Saint DA, MacDonald-Berko M, Rheault T. Anti-inflammatory activity of ensifentrine: a novel, selective dual inhibitor of phosphodiesterase 3 and phosphodiesterase 4. *Respiration*. **2025**;1–10. doi:10.1159/000545645
28. Singh D, Abbott-Banner K, Bengtsson T, Newman K. The short-term bronchodilator effects of the dual phosphodiesterase 3 and 4 inhibitor RPL554 in COPD. *Eur Respir J*. **2018**;52(5):1801074. doi:10.1183/13993003.01074-2018
29. Keir S, Page C. RPL554, a dual phosphodiesterase (PDE) 3/4 inhibitor acts synergistically with muscarinic receptor antagonists and beta-adrenoceptor agonists to produce bronchodilation in vivo [A4218]. Presented at: American Thoracic Society; May 16–21; **2014**; San Diego, CA.
30. Calzetta L, Page CP, Spina D, et al. Effect of the mixed phosphodiesterase 3/4 inhibitor RPL554 on human isolated bronchial smooth muscle tone. *J Pharmacol Exp Ther*. **2013**;346(3):414–423. doi:10.1124/jpet.113.204644
31. Calzetta L, Cazzola M, Page CP, Rogliani P, Facciolo F, Matera MG. Pharmacological characterization of the interaction between the dual phosphodiesterase (PDE) 3/4 inhibitor RPL554 and glycopyrronium on human isolated bronchi and small airways. *Pulm Pharmacol Ther*. **2015**;32:15–23. doi:10.1016/j.pupt.2015.03.007
32. Donohue JF, Rheault T, MacDonald-Berko M, Bengtsson T, Rickard K. Ensifentrine as a novel, inhaled treatment for patients with COPD. *Int J Chron Obstruct Pulmon Dis*. **2023**;18:1611–1622. doi:10.2147/COPD.S413436

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