

COPD Foundation Comments for ICER on Ensifentrine for Maintenance Therapy of Chronic Obstructive Pulmonary Disease

Comments

1. Ensifentrine should be referred to as “maintenance therapy” for chronic obstructive pulmonary disease (COPD). [ref. to ICER 11/21/23 Draft Background and Scope – title]
2. Symptoms of COPD are often persistent for patients. [ref. to ICER 11/21/23 Draft Background and Scope – page 1, paragraph 2, line 4]
3. While the leading causes of COPD in the United States are cigarette smoking and exposure to airborne irritants and pollutants, 25% of COPD patients have never smoked. This proportion of non-smoker patients is larger in low- and middle-income countries. [ref. to ICER 11/21/23 Draft Background and Scope – page 1, paragraph 2, line 7]
4. Pulmonary rehabilitation is significantly associated with a lower risk of mortality.¹ [ref. to ICER 11/21/23 Draft Background and Scope – page 2, line 1]
5. Combination therapy with long- acting beta-2-agonists (LABA) and antimuscarinics (LAMA) therapy is more effective than monotherapy, where appropriate. [ref. to ICER 11/21/23 Draft Background and Scope – page 2, paragraph 2, line 7]
6. For patients with moderate to severe COPD, inhaled corticosteroids (ICS) are more effective than bronchodilators alone in improving lung function and reducing exacerbations. [ref. to ICER 11/21/23 Draft Background and Scope – page 2, paragraph 2, line 11]
7. Potential negative effects of long-term ICS use include pneumonia. Other potential adverse effects are systemic and include osteoporosis, cataracts, glaucoma, and poor glycemic control though these have not been consistently observed in all studies. [ref. to ICER 11/21/23 Draft Background and Scope – page 2, paragraph 2, line 11]
8. COPD patients on maximal therapy with continued exacerbations may benefit from roflumilast; patients with hypoxemia may benefit from supplemental oxygen therapy; some patients with emphysema may benefit from bronchoscopically-placed valves or lung volume reduction surgery. [ref. to ICER 11/21/23 Draft Background and Scope – page 2, paragraph 2, lines 11 through 14]
9. Inhibition of PDE3 and PDE4 enzymes can relax airway smooth muscle, decrease inflammatory cells, improve ciliary function, and potentiate CFTR. [ref. to ICER 11/21/23 Draft Background and Scope – page 2, paragraph 3, line 3]
10. Masking is not an option to mitigate risk of respiratory infection for all patients as face masks can increase the work of breathing. [ref. to ICER 11/21/23 Draft Background and Scope – page 3, paragraph 2, line 3]
11. COPD Action Plans should be updated by patients at least every six months.² [ref. to ICER 11/21/23 Draft Background and Scope – page 3, paragraph 2, line 7]
12. Patient challenges with medication adherence include proper inhaler technique.^{3,4} [ref. to ICER 11/21/23 Draft Background and Scope – page 3, paragraph 3, line 3]

13. “Ensifentrine” is misspelled in the Report Aim section. [ref. to ICER 11/21/23 Draft Background and Scope – page 3, paragraph 4, line 1]
14. Published randomized trial information will be limited until information from P3 trials is made available. [ref. to ICER 11/21/23 Draft Background and Scope – page 3, paragraph 5, line 3]
15. Head-to-head studies of the interventions and comparators of interest may not exist in this space. [ref. to ICER 11/21/23 Draft Background and Scope – page 4, paragraph 2, line 2]
16. Medical comorbidities of note include cardiovascular disease, diabetes mellitus, and frailty. [ref. to ICER 11/21/23 Draft Background and Scope – page 4, paragraph 5, line 2]
17. The means by which emphysema versus chronic bronchitis are ascertained and defined must be explained. [ref. to ICER 11/21/23 Draft Background and Scope – page 4, paragraph 5, line 6]
18. Moderate versus severe cases of COPD are defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifications 1 and 2 versus 3 and 4. [ref. to ICER 11/21/23 Draft Background and Scope – page 4, paragraph 5, line 8]
19. Additional COPD maintenance drug therapies include Roflumilast, Azithromycin (off label) and systemic steroids in some. [ref. to ICER 11/21/23 Draft Background and Scope – page 5, paragraph 2, line 7]
20. A patient’s change in dyspnea is not an outcome used in clinical trials. [ref. to ICER 11/21/23 Draft Background and Scope – page 5, paragraph 4, line 2]
21. A patient’s requirement for long-term continuous or intermittent oxygen use does not change in response to therapy. [ref. to ICER 11/21/23 Draft Background and Scope – page 5, paragraph 4, line 5]
22. The patient-reported outcome of “quality of life” should be narrowed to “health-related quality of life.” [ref. to ICER 11/21/23 Draft Background and Scope – page 5, paragraph 4, line 6]
23. Patient-reported exacerbations as outcomes should be divided between hospitalized exacerbations versus non-hospitalized exacerbations. [ref. to ICER 11/21/23 Draft Background and Scope – page 5, paragraph 4, line 7]
24. A patient’s GOLD category does not change along with the patient’s relative or absolute change in lung function. [ref. to ICER 11/21/23 Draft Background and Scope – page 5, paragraph 5, line 2]
25. Urinary tract risks include urinary retention. [ref. to ICER 11/21/23 Draft Background and Scope – page 5, paragraph 6, line 9]
26. Because ensifentrine is not yet approved, there is no data available outside of clinical trials. [ref. to ICER 11/21/23 Draft Background and Scope – page 6, paragraph 1, line 1]
27. Clinical trials for ensifentrine included adults with COPD of all levels of severity, including people on no maintenance therapy. [ref. to ICER 11/21/23 Draft Background and Scope – page 7, paragraph 2, line 1]
28. The statement “A cohort of patients will transition between the health states during predetermined cycles of three months over a lifetime time horizon, modeling patients from treatment initiation until death.” requires further explanation. Additionally, this may

- not be a lifetime therapy. [ref. to ICER 11/21/23 Draft Background and Scope – page 7, paragraph 2, lines 4 through 6]
29. The effect of a therapy that matters most to patients is relief for daily symptoms of breathlessness, cough and sputum, and fatigue.⁵ [ref. to ICER 11/21/23 Draft Background and Scope – page 7, paragraph 3, line 4]
 30. The statement “Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs.” requires further explanation. [ref. to ICER 11/21/23 Draft Background and Scope – page 7, paragraph 4, lines 1 through 2]
 31. Ensifentrine could potentially impact emergency department visits and hospitalizations, along with unscheduled outpatient visits. [ref. to ICER 11/21/23 Draft Background and Scope – page 8, paragraph 1, lines 4 through 5]

References

1. Lindenauer, Peter K. MD, MSc, et al. "Association Between Initiation of Pulmonary Rehabilitation After Hospitalization for COPD and 1-Year Survival Among Medicare Beneficiaries." JAMA, 2020, <https://doi.org/10.1001/jama.2020.4437>.
2. "My COPD Action Plan." The COPD Foundation, www.copdfoundation.org/Learn-More/Educational-Materials-Resources/Downloads.aspx#MyCOPDActionPlan.
3. "COPD Educational Video Series." The COPD Foundation, www.copdfoundation.org/Learn-More/Educational-Materials-Resources/Educational-Video-Series.aspx.
4. "The COPD Pocket Consultant Guide Mobile App" The COPD Foundation, www.copdfoundation.org/Learn-More/The-COPD-Pocket-Consultant-Guide/Healthcare-Provider-Track.aspx.
5. "Guides for Better Living" The COPD Foundation, www.copdfoundation.org/Learn-More/Educational-Materials-Resources/Downloads.aspx#guides



Sulabha Ramachandran, PhD
Vice President, US and Regions
Value, Evidence and Outcomes
GSK

December 8, 2023

Steven D. Pearson, MD, MSc
Institute for Clinical and Economic Review (ICER)
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Email: publiccomments@icer.org

RE: Draft scoping document for assessment of ensifentrine for the treatment of chronic obstructive pulmonary disease (COPD)

Dear Dr. Pearson,

GSK appreciates the opportunity to provide comments in response to the draft scoping document for ICER's assessment of ensifentrine for COPD. With over 50 years of experience in respiratory care, GSK is committed to helping patients breathe better by continuously redefining treatment for COPD. While no GSK therapies are interventions of interest in this assessment, given our experience in COPD and the likelihood of GSK therapies serving as comparators, we offer the following suggestions on the draft scoping document for ICER's consideration.

Grouping of comparators

As outlined in the draft scoping document, there are multiple classes of pharmacologic therapies for COPD, including both short-acting and long-acting beta2-agonists (SABA and LABA) and anticholinergics (SAMA and LAMA). The long-acting therapies are recommended for ongoing maintenance, and may be used together in combination as dual therapy and with inhaled corticosteroids (ICS) as triple therapy.¹

The choice of appropriate therapy is dependent on the patient's individual needs and preferences. The GOLD guidelines recommend a "tailored approach to initiate treatment based on the level of symptoms and risk for exacerbations," with some therapies recommended over others based on evidence of clinical efficacy.¹ For instance, for initial treatment of symptomatic patients with exacerbation history, guidelines recommend double therapy over single and the addition of ICS in patients with high eosinophil count (≥ 300 cells/ μ L).

Given the differences across maintenance classes in efficacy and clinical appropriateness based on patient need, we encourage ICER to compare ensifentrine to individual classes of therapies rather than pooling all therapies across these classes into a single comparator.

¹ Global Initiative for Chronic Obstructive Lung Disease. Pocket Guide to COPD Diagnosis, Management, And Prevention, 2023 Edition. Available at https://goldcopd.org/wp-content/uploads/2023/03/POCKET-GUIDE-GOLD-2023-ver-1.2-17Feb2023_WMV.pdf.

Addressing differences in disease severity

Relatedly, as ICER makes comparisons between ensifentrine and various classes of maintenance therapies, it is critical to consider and account for the fact that the patient populations are different – even if they fall under the classification of “moderate to severe COPD.”

The differences in patient populations are clear from a review of clinical trials of ensifentrine compared to those of other therapies. While the ENHANCE trials of ensifentrine focused on patients with moderate to severe COPD, based on a review of the demographic and baseline characteristics, patients in these trials did not have the level of severity seen in other COPD trials. For example, in the IMPACT study comparing once-daily single inhaler triple therapy to dual therapy, 64% of patients had a GOLD grade of 3 or 4.² In the ENHANCE trials, pooled data from the two trials shows that 44% of patients were GRADE 3 or 4.³ This difference is not unexpected given that the ENHANCE trials excluded patients with an exacerbation requiring oral and parenteral steroids within 3 months prior to screening, as well as patients currently on LAMA-LABA or triple therapy, which are generally recommended for patients with higher disease severity.^{3,4}

Notably, there also appear to be differences in patient severity *within* the ENHANCE trials. Across the two trials, in the ensifentrine arms, 42% of patients had GOLD grade 3 or 4 compared to 47% in the placebo arms. Also, ENHANCE-2 had a higher portion of patients with grade 3 or 4 compared to ENHANCE-1 (47% vs. 38%).³

The lack of direct comparisons with LAMA-LABA dual therapy and triple therapy and differences in patient populations across trials calls into question whether it is clinically and scientifically appropriate for ICER to compare ensifentrine to these classes. If LAMA-LABA and triple therapy classes are included as comparators, ICER must take clear and transparent steps to account for differences in patient severity. Additionally, we suggest that ICER critically assess potential differences in disease severity within the ENHANCE trials and their impact on the trials’ results. We suggest that these issues be addressed in detail in ICER’s forthcoming Research Protocol.

Exacerbation as an outcome

We applaud ICER for including a broad set of outcomes in the draft scoping document, including patient-important outcomes such as quality of life, use of rescue medications, and exacerbations.

However, we encourage ICER to take into account the quality of evidence for these outcomes, and especially for exacerbation rates for ensifentrine. While the ENHANCE studies include exacerbations

² Lipson DA, Barnhart F, Brealey N, Brooks J, Criner CJ, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *N Engl J Med* 2018; 378:1671-1680.

³ Anzueto A, Barjaktarevic IZ, Siler TM, Rheault T, Bengtsson T, et al. Ensisentrine, 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 Aug 15;208(4):406-416. Some information derived from online supplement.

⁴ Clinicaltrials.gov. A Phase 3 Clinical Trial to Evaluate the Safety and Efficacy of Ensisentrine in Patients With COPD. Available at <https://clinicaltrials.gov/study/NCT04535986> (ENHANCE-1) and <https://clinicaltrials.gov/study/NCT04535986> (ENHANCE-2).

as an outcome, it was not a pre-specified endpoint and there was no comparison to patients' baseline exacerbation rates.⁴

Given this fact and the points made above about differences in disease severity, we strongly encourage ICER to consider the quality and comparability of evidence of exacerbation reductions across interventions and make adjustments accordingly. This should also be addressed in the Research Protocol as well as the Model Analysis Plan.

* * *

Thank you again for the opportunity to comment on the draft scoping document, and we look forward to engaging with ICER further on this assessment. If you have any questions about our comments or would like to discuss any other aspects of the assessment with GSK, please contact Russ Montgomery, Sr. Director of US Value Assessment, at russ.w.montgomery@gsk.com.

Sincerely,

Sulabha Ramachandran

Sulabha Ramachandran, PhD
Vice President, US and Regions
Value Evidence and Outcomes
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December 13, 2023

Institute for Clinical and Economic Review (ICER)
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Boston, MA 02108

RE: Verona response to the proposed scope for ICER's value assessment of ensifentrine for COPD

Dear ICER Review Team:

Verona Pharma appreciates the opportunity to participate in ICER's evaluation of ensifentrine for the treatment of chronic obstructive pulmonary disease (COPD). Verona aims to improve health and quality of life for the millions of people affected by the burden of chronic respiratory diseases. We are a clinical-stage biopharmaceutical company focused on developing and commercializing innovative therapies for the treatment of respiratory diseases with significant unmet medical needs. Most notably, ensifentrine is our first-in-class treatment for respiratory disease that combines bronchodilator and nonsteroidal anti-inflammatory activities in one compound.

ICER's description of the severity of COPD and its associated complications, impact on quality of life, and burden to the healthcare system was well characterized. Verona offers the following comments on the burden of COPD and therapeutic advancements as additional context to support ICER's evaluation of ensifentrine.

Burden of COPD

COPD is a heterogeneous, inflammatory lung condition characterized by chronic respiratory symptoms due to airway and/or alveoli abnormalities that cause persistent, progressive airflow obstruction and poses significant burden due to its chronic nature, necessitating ongoing management and care.¹ Verona acknowledges and appreciates ICER's assessment of the overall burden of COPD as a major contributor to mortality and morbidity in the United States, representing the 6th leading cause of death and costing nearly \$50 billion per year, with \$29.5 billion attributable to direct medical costs.

The symptom burden of COPD is significant. In a 2021 survey of patients with COPD (N=1,994), 78% of patients reported experiencing COPD symptoms for at least 3 years, and 49% of patients said that symptoms affect them 24 to 30 days out of each month. In this same survey, 47% of patients said symptoms have a moderate-to-great impact on their emotional well-being, and 65% said that their COPD has a moderate-to-great impact on everyday life.² Symptoms, including dyspnea, are associated with an increased risk of exacerbations.¹ Exacerbations contribute to COPD disease progression, as a greater number of exacerbations is associated with a greater decline in forced expiratory volume in the first second (FEV₁).³ Symptoms of an exacerbation typically last from 7-10 days, but up to 20% of patients report that their symptoms are still present

after 8 weeks.⁴ A longer symptomatic duration has been associated with a shorter interval to the next exacerbation.⁵ Many exacerbations are not reported by patients; although milder and often shorter in duration compared with reported events, these unreported exacerbations also have a significant impact on health status.⁶ Patients with COPD often require hospitalizations or other medical interventions, resulting in a high burden on the US medical system due to high direct and indirect costs. In addition to ongoing monitoring and maintenance medication costs, exacerbations are a primary contributor to COPD costs.⁷

Current Treatment and Therapeutic Advancements

The goals of COPD maintenance treatment are to better control symptoms, improve patient quality of life, and to reduce the frequency and severity of exacerbations. Current inhaled treatment options for the maintenance of COPD include: long-acting muscarinic antagonists (LAMAs), long-acting beta-adrenoceptor agonists (LABAs), and inhaled corticosteroids (ICS). Treatment for COPD may involve single, dual, or triple combinations of therapy depending on symptom severity and patient history of frequent exacerbations.¹

Despite the multitude of therapies available, there remain patients who are poorly controlled and continue to experience symptoms, including exacerbations. Cross-sectional data from surveys conducted in the US, Europe, Japan, and China demonstrated that 64.4% of patients (N=690) maximally treated with stable dual therapy or triple therapy still had symptom burden that affected their everyday lives and impaired their health status.⁸

Ensifentrine is currently under FDA review and if approved would be the first maintenance treatment with a novel mechanism of action in over a decade for symptomatic patients with moderate to severe COPD. Ensifentrine is a novel, selective, dual inhibitor of phosphodiesterase-3 (PDE3) and PDE4, which provides bronchodilation and nonsteroidal anti-inflammatory action in one molecule and is complementary to mechanisms of action of other therapies. Ensifentrine is delivered via a standard jet nebulizer, which is easy to use and consistently provides effective drug delivery to the lungs without the need for high inspiratory flow rates (as required for dry powder inhaler [DPI] devices) or complex hand-breath coordination (as required with the use of pressurized metered dose inhalers [pMDIs]). Studies indicate that up to 78% of COPD outpatients using a DPI have suboptimal peak inspiratory flow rates, and most patients with COPD demonstrate errors in pMDI technique.^{9,10} Therefore, administration of treatment via a standard jet nebulizer may help to optimize medication delivery. In addition, delivery of ensifentrine via the nebulized route directly to the lungs can optimize the benefit-risk profile of pharmacological inhibition of PDE3 and PDE4 by minimizing systemic exposure and any associated potential undesired systemic effects.

Across a broad range of patients with COPD, ensifentrine treatment demonstrates early, sustained, and clinically meaningful improvements in lung function, symptoms, and quality of life while also reducing the rate and risk of exacerbations. The phase 3 ENHANCE-1 and ENHANCE-2 trials enrolled symptomatic patients with moderate-to-severe COPD, utilizing broad inclusion criteria to ensure the study population closely represents the overall COPD population. In both ENHANCE-



1 and ENHANCE-2, ensifentrine 3 mg twice daily provided significant and clinically meaningful improvements across key primary and secondary endpoints. Additionally, in both studies, ensifentrine substantially reduced the rate of moderate/severe COPD exacerbations and delayed the time to first exacerbation over 24 weeks compared with placebo. Furthermore, long-term follow-up in ENHANCE-1 demonstrated a significant reduction in exacerbation risk and delayed the time to exacerbation over 48 weeks.¹¹ Ensifentrine was well tolerated, and rate of adverse events (AEs) and discontinuations due to AEs were similar between ensifentrine and placebo in both trials.¹¹

Ensifentrine represents a novel COPD maintenance treatment that will help address the ongoing burden that patients experience in managing their COPD. Verona appreciates the consideration of our comments and appreciates the opportunity to participate in ICER's clinical and economic review of ensifentrine.

Kind regards,

Kavita Aggarwal, PharmD
Senior Vice President, Medical Affairs
Verona Pharma

¹ Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2024 Report. Available at: [https:// goldcopd.org/2024-gold-report/](https://goldcopd.org/2024-gold-report/)

² Phreesia Life Sciences. Patients in focus: COPD treatment and perceptions. Accessed February 28, 2023. Available at: <https://lifesciences.phreesia.com/reports/patients-in-focus-copd-treatment-and-perceptions/>.

³ Kerkhof M, Voorham J, Dorinsky P, et al. The long-term burden of COPD exacerbations during maintenance therapy and lung function decline. *Int J Chron Obstruct Pulmon Dis*. 2020;15:1909-1918.

⁴ Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161(5):1608-1613.

⁵ Donaldson GC, Law M, Kowlessar B, et al. Impact of prolonged exacerbation recovery in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2015;192(8):943-950.

⁶ Vijayasaritha K, Stockley RA. Reported and unreported exacerbations of COPD: analysis by diary cards. *CHEST*. 2008;133(1):34-41.

⁷ Sethi S, Make BJ, Robinson SB, et al. Relationship of COPD exacerbation severity and frequency on risks for future events and economic burden in the Medicare fee-for-service population. *Int J Chron Obstruct Pulmon Dis*. 2022;17:593-608.

⁸ 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.

⁹ Barjaktarevic IZ, Milstone AP. Nebulized Therapies in COPD: Past, Present, and the Future. *Int J Chron Obstruct Pulmon Dis*. 2020;15:1665-1677.

¹⁰ Chrystyn H, van der Palen J, Sharma R, et al. Device errors in asthma and COPD: systematic literature review and meta-analysis. *NPJ Prim Care Respir Med*. 2017;27(1):22.

¹¹ Anzueto A, Barjaktarevic IZ, Siler TM, et al. Ensfentrine, 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.