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Dual phosphodiesterase 3 and 4 inhibition in chronic obstructive pulmonary disease: mechanistic rationale and clinical translation of Ensifentrine

Abstract

Chronic obstructive pulmonary disease (COPD) remains a leading cause of morbidity, mortality, and healthcare utilization globally, despite the widespread adoption of dual bronchodilator and triple inhaled corticosteroid–containing regimens. A substantial proportion of patients continue to experience persistent dyspnea, impaired health status, and recurrent exacerbations, underscoring significant therapeutic gaps in current management paradigms. Targeting both bronchomotor tone and airway inflammation through complementary mechanisms represents a rational strategy to improve clinical outcomes. Phosphodiesterase (PDE) enzymes regulate intracellular cyclic adenosine monophosphate (cAMP), a central mediator of airway smooth muscle relaxation and inflammatory signaling. While selective PDE4 inhibition, exemplified by roflumilast, reduces exacerbation risk in selected COPD phenotypes, its systemic adverse effects have limited its routine clinical utility. Dual inhibition of PDE3 and PDE4 via inhaled delivery offers the potential to combine bronchodilation and anti-inflammatory activity while minimizing systemic exposure. Ensifentrine, a first-in-class inhaled dual PDE3/4 inhibitor, has demonstrated clinically meaningful improvements in lung function, respiratory symptoms, and exacerbation outcomes with a favorable safety profile in the pivotal Phase 3 ENHANCE trials. This mini-review synthesizes the mechanistic rationale for dual PDE inhibition, evaluates available clinical evidence, and discusses its potential positioning within contemporary COPD management. We also highlight limitations of current data and future research priorities. Dual PDE inhibition represents a biologically coherent and clinically promising strategy that may expand therapeutic options for patients with persistent symptom burden and exacerbation risk despite optimized inhaled therapy.

Keywords: chronic obstructive pulmonary disease, ensifentrine, phosphodiesterase 3/4 inhibition, exacerbations, bronchodilation, airway inflammation

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Abbreviations: AECOPD, Acute exacerbation of chronic obstructive pulmonary disease; AUC, Area under the curve; BEC, Blood eosinophil count; CBF, Ciliary beat frequency; COPD, Chronic obstructive pulmonary disease; cAMP, Cyclic adenosine monophosphate; ED, Emergency department; FEV1, Forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HCRU, Healthcare resource utilization; ICS, Inhaled corticosteroid; LABA, Long-acting β2-agonist; LAMA, Long-acting muscarinic antagonist; MACE, Major adverse cardiovascular events; PDE, Phosphodiesterase; SGRQ, St. George's Respiratory Questionnaire; TNF-α, Tumor necrosis factor-alpha; IL, Interleukin; ERS, Evaluating Respiratory Symptoms

Introduction

Chronic obstructive pulmonary disease (COPD) affects more than 300 million individuals worldwide and remains a leading cause of death and disability.[1,2] In the United States, COPD is a major contributor to hospital admissions and healthcare expenditure, particularly among older adults with multiple comorbidities.[3] Although long-acting bronchodilators (LABA and LAMA) and inhaled corticosteroids (ICS) have transformed disease management, many patients continue to experience debilitating dyspnea and frequent exacerbations. Large contemporary trials, including IMPACT and ETHOS, demonstrated that triple therapy (LABA-LAMA-ICS) reduces exacerbation rates compared with dual bronchodilation.[4,5] However, residual exacerbation risk remains substantial, particularly among patients with chronic bronchitis, high symptom burden, or frequent prior exacerbations. Moreover, ICS use carries inherent risks, including an increased incidence of pneumonia, especially in patients with low blood eosinophil counts or severe airflow limitation.[6]

Oral PDE4 inhibition with roflumilast provided proof-of-concept that modulation of cyclic nucleotide signaling can reduce exacerbations in chronic bronchitis phenotypes.[7] However, gastrointestinal intolerance, weight loss, and neuropsychiatric adverse effects have limited its widespread adoption in clinical practice.[8] These limitations underscore the need for inhaled therapies that deliver potent anti-inflammatory effects with an improved tolerability profile. Dual inhibition of phosphodiesterase (PDE) 3 and 4 represent a mechanistically integrated strategy designed to augment bronchodilation and suppress airway inflammation through modulation of cyclic adenosine monophosphate (cAMP) signaling.

Ensifentrine, a novel, low-molecular-weight, selective dual inhibitor of PDE3 and PDE4 was designed specifically for inhaled delivery to combine bronchodilatory and anti-inflammatory effects in a single molecular entity. Receiving FDA-approval for COPD maintenance in 2024, Ensifentrine provides an opportunity to reassess therapeutic escalation paradigms in COPD.

Methods

This mini-review was conducted by systematically searching PubMed and EMBASE using the terms ensifentrine, COPD, exacerbation, and inflammatory. We included English-language randomized controlled trials, systematic reviews, meta-analyses,

and well-designed prospective or controlled observational studies in adults with COPD, reporting on symptom improvement or exacerbation outcomes. Studies were excluded if they involved non-human subjects, pediatric populations, non-English publications, case reports, small case series, conference abstracts, or opinion/editorial pieces. Relevant qualitative and quantitative data were extracted and critically appraised to evaluate the clinical utility of ensifentrine.

Discussion

Biological basis for dual PDE3/4 inhibition

Cyclic nucleotide signaling in COPD: Intracellular cAMP is a critical regulator of airway smooth muscle relaxation, mucociliary function, and inflammatory cell activation.[9] PDE enzymes degrade cAMP, thereby attenuating its downstream effects. Increased PDE expression has been observed in inflammatory cells and airway tissues of patients with COPD, providing a strong biologic rationale for PDE inhibition as a therapeutic target.[10]

PDE3 and bronchomotor tone: PDE3 is expressed in airway smooth muscle and vascular endothelium. Inhibition of PDE3 increases intracellular cAMP, leading to relaxation of airway smooth muscle independent of β2-receptor stimulation. This mechanism complements LABA therapy by preventing cAMP degradation rather than solely increasing its synthesis via adenylate cyclase activation.[11] Preclinical data demonstrate additive bronchodilator effects when PDE3 inhibition is combined with β2-agonists, suggesting a synergistic potential in overcoming airflow limitation. Additionally, ensifentrine has been shown to increase ciliary beat frequency (CBF) in human bronchial epithelial cells, suggesting potential enhancement of mucociliary clearance, an important consideration in chronic bronchitis phenotypes characterized by mucus hypersecretion and impaired clearance.[12]

PDE4 and airway inflammation: PDE4 is the predominant PDE isoform expressed in neutrophils, macrophages, T cells, and airway epithelial cells. Its inhibition suppresses the release of pro-inflammatory cytokines, including TNF-α and IL-8, and reduces neutrophil activation and chemotaxis.[13] The clinical utility of PDE4 inhibition is well-established by the reduction in exacerbation rates observed with roflumilast in patients with chronic bronchitis and severe airflow limitation.[7] However, the systemic nature of oral PDE4 inhibition leads to off-target emetic effects in the central nervous system and gastrointestinal tract, such as nausea and vomiting.

Integrated rationale for dual inhibition: Dual PDE3/4 inhibition combines bronchodilatory and anti-inflammatory effects in a single inhaled agent. Preclinical models demonstrate that dual inhibition produces significantly greater airway relaxation and inflammatory suppression than selective inhibition of either enzyme alone.[14] Importantly, PDE3 and PDE4 regulate distinct yet complementary compartments of cAMP signaling within the airway microenvironment. While LABA therapy increases cAMP synthesis via adenylate cyclase activation, PDE inhibition preserves intracellular cAMP by preventing its degradation. Dual PDE3/4 inhibition therefore amplifies both bronchodilatory and anti-inflammatory signaling through stabilization of cAMP-dependent pathways. This mechanistic convergence may explain the additive effects observed in preclinical and clinical studies and provides a biologically coherent rationale for combining these targets within a single inhaled therapy.

Dual inhibition therefore provides simultaneous bronchodilatory and anti-inflammatory effects. Importantly, cAMP signaling within airway cells is spatially compartmentalized, with discrete microdomains regulated by distinct phosphodiesterase isoforms.[15] Selective inhibition of a single PDE subtype may incompletely modulate these localized signaling pools.[16] Dual inhibition may therefore broaden cAMP stabilization across structural and inflammatory compartments of the airway microenvironment. This compartmental amplification of cAMP signaling provides a biologically coherent explanation for the additive bronchodilatory and anti-inflammatory effects observed in preclinical and clinical studies.

Inhaled delivery localizes drug exposure to pulmonary tissues, achieving high local concentrations while maintaining low systemic levels, thereby mitigating the adverse effects associated with oral PDE4 inhibition.[17,18] This dual mechanism provides a non-steroidal anti-inflammatory strategy, which may be particularly relevant for patients at risk of ICS-related adverse events or those with non-eosinophilic inflammation.

Ensifentrine: pharmacologic and clinical profile

Ensifentrine is administered via nebulization, achieving direct and efficient airway deposition. Pharmacokinetic studies indicate low systemic concentrations relative to oral PDE4 inhibitors, which is likely a contributor to its favorable tolerability profile.[19] Unlike ICS, ensifentrine does not rely on glucocorticoid receptor activation, thus avoiding steroid-associated risks such as pneumonia, hyperglycemia, or osteoporosis. Its dual mechanism differentiates it from existing bronchodilator monotherapies and positions it as a novel adjunctive therapy that addresses both the mechanical and inflammatory components of COPD.

Clinical evidence in stable COPD

The Phase 3 evaluation of ensifentrine was conducted in the comprehensive ENHANCE clinical program, comprising two replicate trials: ENHANCE-1 and ENHANCE-2.[12] These randomized, double-blind, placebo-controlled trials evaluated nebulized ensifentrine 3 mg twice daily for the maintenance treatment of moderate to severe COPD. These trials were conducted between September 2020 and December 2022 at 250 research centers across 17 countries.

Lung function: Both trials met their primary endpoint of demonstrating a change in baseline of FEV1 area under the curve at week 12 (AUC0–12h). ENHANCE-1 showed a mean difference of 87 mL (95% CI 55–119; $p<0.001$) and ENHANCE-2 demonstrated 94mL (95% CI 65–124; $p<0.001$) compared with placebo.[12] These improvements were sustained over the 24-week treatment period and were observed regardless of background bronchodilator therapy, confirming the additive effects of ensifentrine. Improvements in morning trough FEV1 (35-40mL) further support the durability of its bronchodilatory effect over the dosing interval.

Symptom burden and health status: In ENHANCE-1, significant improvements were observed in St. George's Respiratory Questionnaire (SGRQ) total scores (-2.4 units vs placebo; $p = 0.01$) and Evaluating Respiratory Symptoms (E-RS) scores at week 24.[12] While ENHANCE-2 did not reach statistical significance for these endpoints at the same time point, pooled analyses demonstrated statistically significant improvements in SGRQ and dyspnea measures across the entire study population.[13] Reductions in daily rescue medication use further corroborate the symptomatic benefit perceived by patients. These findings are clinically meaningful, as SGRQ improvements are strongly associated with better patient-perceived health status and reduced disease impact. A pooled post-hoc analysis further demonstrated that ensifentrine treatment resulted in a significantly higher proportion of SGRQ responders (defined by a

≥4-unit improvement) compared to placebo, with benefits observed as early as week 6 and sustained through week 24.[20]

Exacerbation outcomes: One of the most striking findings from the ENHANCE program was the impact on exacerbations. In a pre-specified pooled analysis, ensifentrine reduced the annualized rate of moderate or severe exacerbations by 41% (rate ratio 0.59; 95% CI 0.44–0.81; p=0.001).[13] Furthermore, the risk of experiencing a first exacerbation was reduced by 42% (hazard ratio 0.58; 95% CI 0.42–0.81; p=0.001). These results were consistent across individual trials, with ENHANCE-1 showing a 36% reduction (p=0.050) and ENHANCE-2 showing a 43% reduction (p=0.009).[12] The magnitude of reduction is within the range observed with established anti-inflammatory strategies in selected COPD populations, highlighting the potency of dual PDE3/4 inhibition in preventing acute clinical worsening.

Although the relative reductions in exacerbation rates were substantial, absolute event rates were modest and the individual trials were not primarily powered for exacerbation endpoints. Nonetheless, the consistency of effect across replicate studies and pooled analyses supports the biological plausibility of a true anti-inflammatory signal. Ensifentrine significantly reduced moderate and severe COPD exacerbations, which are a primary contributor to hospitalizations and emergency department visits, thereby suggesting a potential reduction in COPD-related healthcare resource utilization.[21]

Safety and Tolerability: Across the Phase 3 trials, the overall incidence of adverse events was similar between the ensifentrine and placebo groups.[12] Gastrointestinal events, such as diarrhea and nausea, were infrequent and generally mild, representing a major safety advantage over roflumilast.[8] Specifically, pooled safety data confirmed that the incidence of diarrhea was 1.4% for ensifentrine versus 0.9% for placebo, with no evidence of the temporal relationship or weight loss typically associated with oral PDE4 inhibition.[22] Importantly, no meaningful signals for weight loss or neuropsychiatric effects (e.g., depression or anxiety) emerged during the studies. Cardiovascular safety, a historical concern for PDE inhibitors, was also favorable, with no increase in major adverse cardiovascular events (MACE) reported.[12,19]

Positioning within contemporary COPD management

The introduction of dual PDE3/4 inhibition invites comparison with existing anti-inflammatory strategies in COPD. Inhaled corticosteroids provide exacerbation reduction primarily in patients with elevated blood eosinophil counts, suggesting a phenotype-dependent response.[23] Systemic PDE4 inhibition with roflumilast reduces exacerbations in patients with chronic bronchitis and frequent exacerbations but is limited by gastrointestinal and neuropsychiatric adverse effects.[18] Long-term macrolide therapy offers immunomodulatory benefits but raises concerns regarding antimicrobial resistance and cardiac toxicity.[24] In contrast, inhaled dual PDE inhibition delivers localized anti-inflammatory activity without systemic steroid exposure or antibiotic-related risks, potentially broadening the therapeutic landscape for patients with persistent symptoms or exacerbations despite optimized bronchodilator therapy.[11]

The 2026 GOLD Report emphasizes individualized therapy based on symptom burden and exacerbation risk.[1] While dual PDE inhibition is not yet fully integrated into existing algorithms, its mechanistic profile aligns with GOLD's emphasis on individualized therapy. Ensifentrine occupies a unique therapeutic niche and may be positioned as follows:

i. Add-on therapy for persistent symptoms: For patients who remain symptomatic (dyspnea, cough) despite optimized LABA/LAMA therapy, ensifentrine provides an additional bronchodilatory and anti-inflammatory boost.

ii. Alternative for ICS-intolerant patients: In patients with a high exacerbation risk who are intolerant to ICS or have contraindications (e.g., recurrent pneumonia), ensifentrine offers a non-steroidal pathway to reduce exacerbation frequency.

iii. Inhaled alternative to roflumilast: For patients with chronic bronchitis who would benefit from PDE4 inhibition but cannot tolerate the systemic side effects of oral roflumilast.

iv. Nebulized option for specific populations: The nebulized formulation is particularly suitable for patients with poor hand-breath coordination or those who prefer the ease of nebulized therapy, common in advanced age or during post-exacerbation recovery.

Whether ensifentrine should be positioned before or after ICS escalation in specific phenotypes remains uncertain and will likely depend on exacerbation history, blood eosinophil count, and tolerability considerations. Prospective comparative effectiveness studies will be necessary to clarify optimal sequencing within existing treatment algorithms. Furthermore, health economic evaluations suggest that the cost-effectiveness of ensifentrine will depend on patient selection and its impact on exacerbation-related healthcare utilization.[14]

Limitations and future directions

Despite the robust Phase 3 data, several limitations warrant consideration. The ENHANCE trials were 24 weeks in duration; thus, longer-term data on disease progression and mortality are still needed. Direct head-to-head comparisons with triple therapy or oral PDE4 inhibitors are currently lacking, which would further clarify its relative efficacy. Additionally, real-world evidence will be essential to assess long-term adherence and the impact of the nebulized delivery system on patient outcomes in non-trial settings.

Given the clinical and molecular heterogeneity of COPD, response to dual PDE3/4 inhibition is unlikely to be uniform. Patients with chronic bronchitis, frequent exacerbations, or evidence of neutrophil-predominant inflammation may derive disproportionate benefit. The integration of clinical phenotyping with emerging biomarkers, including blood eosinophil count, sputum inflammatory profiles, and exacerbation history, may enable more individualized therapeutic selection. Future studies should aim to identify predictive markers of response and clarify optimal sequencing within phenotype-directed treatment algorithms. As with other novel inhaled therapies, payer coverage and real-world adherence will influence its ultimate clinical uptake.

The identification of clinical or molecular phenotypes most likely to respond to dual PDE inhibition represents an important next step. Biomarker-driven approaches incorporating sputum inflammatory profiles, exacerbation history, or measures of mucus hypersecretion may refine patient selection and move dual PDE3/4 inhibition toward a precision-medicine framework. Preclinical and early clinical data indicate that ensifentrine significantly reduces key sputum inflammatory markers, including total neutrophil counts, IL-8, TNF-α, and interleukin-6 (IL-6).[25,26] These findings suggest a direct anti-inflammatory effect that could be particularly beneficial in patients with elevated levels of these mediators. Furthermore, pooled

subgroup analyses from the ENHANCE trials demonstrated consistent exacerbation reduction regardless of baseline blood eosinophil counts (BEC), with significant benefits observed even in patients with BEC < 100 cells/μL and BEC < 150 cells/μL, populations that typically derive limited benefit from ICS.[13] This highlights ensifentrine's potential as a potent non-steroidal anti-inflammatory option for the 'low-eosinophil' phenotype, often associated with chronic bronchitis and bacterial colonization. For patients with the chronic bronchitis phenotype, ensifentrine's ability to increase CBF in human bronchial epithelial cells suggests enhanced mucociliary clearance, which could translate to improved clinical outcomes.[27] Future research utilizing high-throughput sputum proteomics may further identify 'treatable traits,' such as specific mucin profiles or proteolytic signatures, that could predict enhanced responsiveness to the dual bronchodilatory and anti-inflammatory effects of ensifentrine.

Conclusion

Dual inhibition of PDE3 and PDE4 with ensifentrine represents a novel approach in COPD pharmacotherapy. By concurrently addressing airflow limitation and airway inflammation through localized inhaled delivery, ensifentrine has demonstrated consistent improvements in lung function and possible reductions in exacerbation risk while maintaining a favorable safety profile. As one of the first new inhaled mechanistic classes introduced in COPD management in over two decades, dual PDE inhibition expands the therapeutic landscape and warrants continued investigation to define its optimal role within individualized treatment algorithms.

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Conflicts of interest

There is no conflict of interest in the manuscript including financial, consultant, institutional, and other relationships that might lead to bias or a conflict of interest.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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