Chronic Obstructive Pulmonary Diseases:
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Review

# Phosphodiesterase Inhibition as a Therapeutic Strategy for Chronic Obstructive Pulmonary Disease: Where We Have Been and What Lies Ahead

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## Abstract

Chronic obstructive pulmonary disease (COPD) is a highly prevalent inflammatory lung condition characterized by chronic respiratory symptoms and airflow obstruction that often leads to diminished quality of life. Nonpharmacologic management for patients with COPD involves smoking cessation and healthy lifestyle changes. Pharmacologic treatments include inhaled bronchodilators with or without the use of inhaled corticosteroids, which can be administered through inhalation or nebulization. In addition, oral medications including macrolide antibiotics and phosphodiesterase (PDE) 4 inhibitors can help reduce exacerbation risk. However, many of these medications provide suboptimal disease control, owing to limited efficacy, increased risk of adverse events with long-term use, or difficulty in administration technique. PDE3 plays an important role in maintaining smooth muscle function, and PDE4 plays a crucial role in the inflammatory response in airway smooth muscle. Direct molecular inhibition of PDE3 or PDE4 has been shown to provide benefit in COPD. Dual PDE3 and PDE4 inhibition may, therefore, have synergistic anti-inflammatory and bronchodilator effects. These results have been observed in clinical trials of nebulized ensifentrine, a novel, dual-action PDE3 and PDE4 inhibitor that is the first in its class to be approved by the U.S. Food and Drug Administration for maintenance treatment of COPD in adult patients. In this review, we explore the pathophysiologic mechanisms of COPD, describe current paradigms and methods of drug delivery for the treatment of the disease, and illustrate how dual inhibition of PDE3 and PDE4 may provide additional benefit to current standard-of-care regimens.

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### Abbreviations:

**$AUC_{0\text{-}12h}$**=area under the concentration time curve from 0 to 12 hours; **BID**=twice daily; **cAMP**=cyclic adenosine monophosphate; **CFTR**=cystic fibrosis transmembrane conductance regulator; **cGMP**=cyclic guanosine monophosphate; **COPD**=chronic obstructive pulmonary disease; **C-X-C**=chemokine; **DPI**=dry powder inhaler; **ENHANCE**=Ensifentrine as a Novel Inhaled Nebulized COPD Therapy; **E-RS**=Evaluating Respiratory Symptoms in COPD; **FDA**=U.S. Food and Drug Administration; **$FEV_1$**=forced expiratory volume in 1 second; **GM-CSF**=granulocyte-macrophage colony-stimulating factor; **GOLD**=Global initiative for chronic Obstructive Lung Disease; **ICS**=inhaled corticosteroid; **IL-1 β**=interleukin 1β; **IL-8**=ligand 8; **LABA**=long-acting beta2-agonist; **LAMA**=long-acting muscarinic antagonist; **NCT**=National Clinical Trial; **PDE**=phosphodiesterase; **pMDI**=pressurized metered-dose inhaler; **SMI**=soft mist inhaler; **SGRQ-C**=St George's Respiratory Questionnaire – COPD Specific; **TDI**=Transition Dyspnea Index; **TNF**=tumor necrosis factor; **TGF-β**=transforming growth factor β

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by respiratory symptoms that cause persistent, progressive airflow obstruction.[1] As a leading cause of morbidity and mortality both in the United States and globally,[1,2] COPD affects approximately 10.6% (480 million) of people worldwide, and its prevalence is projected[3] to increase to a total of 592 million by 2050. In addition to a substantial symptom burden such as chronic coughing, dyspnea, and fatigue, many patients experience frequent exacerbations that affect their quality of life and lead to accelerated lung function decline and risk of death.[1,4] Furthermore, patients with COPD have a high prevalence of multimorbidities including cardiovascular, cerebrovascular, metabolic, renal, and musculoskeletal disorders, some of which independently contribute to an increased overall risk of death in these patients.[5-7] Despite the use of current therapies, many patients with COPD continue to experience exacerbations and a substantial symptom burden that impacts daily living and quality of life.[8] This underlines the need for new COPD treatment approaches.

In this narrative review, we describe the general pathophysiology, inflammatory processes, and current treatment paradigms for COPD and introduce dual inhibition of phosphodiesterase (PDE) 3 and PDE4 as a novel, broadly applicable treatment strategy for patients with COPD.

## Pathophysiology and Inflammatory Processes in COPD

The manifestations of COPD are chronic in nature and include pulmonary inflammation, airway remodeling, excessive mucus production, and destruction of lung parenchyma.[1,9] For most patients, COPD inflammatory disease involves the interplay of systemic and lung-specific inflammatory processes that contribute to its pathogenesis.[10-12] The inflammation in COPD is driven by exposure to cigarette smoke and other inhaled toxic pollutants and results in the production of cytokines and chemokines that activate both structural and inflammatory cells[10,11,13] involved in both the innate and adaptive immune responses, including tumor necrosis factor (TNF), interleukin 1β (IL-1β), granulocyte-macrophage colony-stimulating factor (GM-CSF), chemokine (C-X-C motif) ligand 8 (IL-8), and transforming growth factor β (TGF-β).[10-12] Macrophages are also activated to release inflammatory mediators by cigarette smoke, and their density is markedly increased in the airways and lung parenchyma of patients with COPD.[10-12] Cigarette smoke has a direct stimulatory effect on granulocyte production and release from the bone marrow.[12] Accordingly, increased numbers of activated neutrophils can be found in the sputum and bronchoalveolar lavage fluid of patients with COPD. In addition, lymphocytes, including CD8+ T cells, CD4+ T cells, and B cells, have been identified in the lungs of patients with COPD, suggesting a potential role of altered immunity in the pathogenesis of this disease.[10-12,14]

Cigarette smoke or bacterial or viral antigens activate these adaptive immune cells to release proteolytic enzymes and cytokines causing neutrophilic inflammation and inducing structural cell death.[10-12] Together, these pathologic responses cause the physiologic abnormalities commonly seen in patients with COPD, including ciliary dysfunction and airflow obstruction, which ultimately results in gas exchange abnormalities, functional disability, and, in extreme cases, pulmonary hypertension and respiratory insufficiency.[9]

## Current Therapies for COPD

According to the Global initiative for chronic Obstructive Lung Disease (GOLD), the goals of the management and treatment of COPD are symptom reduction, improvement in lung function and quality of life, and mitigation of future risk of disease progression and exacerbations.[1] Based on current evidence, GOLD recommends a tailored treatment approach for COPD based on symptom burden and exacerbation risk.[1] Nonpharmacologic management includes identification and reduction of risk factor exposure (e.g., cigarette smoking and mitigation of environmental exposures), healthy lifestyle habits, and appropriate vaccinations. As COPD progresses, the patient may benefit from pulmonary rehabilitation, in some cases oxygen therapy, and, in a small number of patients, ventilatory support.[1,4]

Currently, the central core of pharmacologic maintenance therapies for COPD consists of long-acting inhaled bronchodilators, which include 2 major classes: long-acting beta2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs). In some patients, the addition of inhaled corticosteroids (ICSs) decreases the risk of exacerbations and their sequelae.[15-17] Bronchodilators, as a single therapy or part of a dual regimen, are recommended as maintenance therapy across all patient groups.[1] For patients who are at increased risk of exacerbations (≥2/year or ≥1/year leading to hospitalization) and who have elevated blood eosinophil levels (≥100cells or ≥300cells/μL), GOLD recommends the addition of an ICS in combination with dual long-acting bronchodilator therapy.[1] While dual bronchodilator therapy and to a greater extent triple therapy (dual bronchodilator+ICS) have been shown to improve lung function, relieve symptoms, and reduce exacerbations and possibly mortality risk in patients with COPD, around half of the patients using triple therapy continue to experience both exacerbations and symptoms

that impact their quality of life.[1,8,18] Real-world studies show that patients with COPD receiving either dual or triple maintenance therapy still have a substantial symptom burden and around 40% still experience ≥1 moderate or severe exacerbation per year.[19-22] In particular, patients are bothered by dyspnea, which was noted as the most impactful symptom on patients' daily activities and quality of life.[21-23] In addition, ICS therapy can be associated with adverse events, including increased risk of pneumonia, and, with long-term therapy, osteopenia, osteoporosis, hyperglycemia, and cataracts.[24,25]

Recent studies have explored the potential role of biologics in select populations of patients with COPD. Initial large trials of mepolizumab[26] and benralizumab[27] demonstrated that these treatments failed to have an impact on the incidence of exacerbations, which was the primary outcome of those studies. However, subgroup analyses of the collected data suggested a beneficial effect in patients with a high eosinophil count (>300cells/dL). Subsequent trials with dupilumab have shown positive results in reducing exacerbation frequency compared to placebo in patients with repeated or severe exacerbations and elevated eosinophil counts.[28] Based on these results, the U.S. Food and Drug Administration (FDA) has approved dupilumab as a medication with potential use in those patients on maximal conventional therapy who remain very symptomatic and continue to experience moderate or severe exacerbations. In addition, some preliminary data with the use of itepekimab, a monoclonal antibody with anti–IL-33 activity, has demonstrated decreased exacerbation rates in former smokers with COPD independent of blood eosinophil count, suggesting a potential benefit in those patients.[29] Several studies are underway with different biologics targeting type 2 inflammatory pathways, the readout of which will provide information about their specific use in COPD patients with severe disease who continue to exacerbate despite optimal medical therapy.

## Methods of Drug Delivery in COPD

Delivery of medications through the inhalation route has become the preferred method of drug delivery for COPD therapy, as it achieves a high drug concentration locally within the lungs to maximize the therapeutic effect.[30,31] Current inhalation delivery systems include handheld inhalers such as pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and soft mist inhalers (SMIs); these devices have the widest acceptance and are used by most patients with COPD.[31] However, the use of such delivery systems has been hampered by the fact that many patients commit critical errors during use, especially given that many patients with COPD have dexterity and cognitive problems. Nebulizers are a preferred mode of administration for medications in such groups of patients with COPD with cognitive, neuromuscular, or ventilatory impairments.[31] Furthermore, nebulizers have other advantages in elderly patients because they do not require patient coordination between inhalation or a generally optimal inspiratory flow rate, making them ideal for such patient populations.[31] Indeed, in patient and caregiver surveys, up to 80% of both patients and caregivers reported that using a nebulizer was better than using an inhaler (pMDI/DPI).[32,33]

Oral medications have also been widely used for the treatment of COPD. Macrolide antibiotics, which potentially have immunomodulatory and anti-inflammatory properties, have shown varying efficacies across several clinical studies that enrolled patients who continued to have acute exacerbations despite treatment with standard-of-care therapy.[34] Among the most studied macrolide antibiotics is azithromycin, which has been shown to decrease exacerbations, particularly in former smokers.[34,35] An alternative oral medication that has been shown to reduce risk of exacerbations in patients with COPD on optimal inhaled therapy is roflumilast, a PDE4 inhibitor that is somewhat limited in its use and tolerance, owing to its frequent gastrointestinal adverse events.[36,37] In some regions of the world, the use of oral antioxidants is favored, as several randomized clinical trials of patients with COPD have shown a significant reduction of exacerbation risk with the use of carbocysteine and N-acetylcysteine.[38]

## Phosphodiesterases in COPD

PDEs are a superfamily of enzymes that are grouped into 11 subfamilies with different structures, substrate specificity, and regulatory mechanisms.[39-41] PDE enzymes catalyze the hydrolysis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).[41,42] cAMP and cGMP themselves are regulators of intracellular signal transductions that play an important role in regulating cell proliferation and differentiation, as well as inflammation and the immune response.[41] Given that COPD is an inflammatory disease, both cAMP and cGMP play critical roles in its pathogenesis.[43]

### *Role of Phosphodiesterase-4 in COPD*

PDE4 is highly expressed in leukocytes and other inflammatory cells as well as in airway smooth muscle and pulmonary nerves.[44,45] As a cAMP-specific inhibitor, PDE4 plays a critical role in the regulation of the inflammatory response.[39,43,45] In patients with COPD, increased levels of PDE4 have been observed in inflammatory cells from the lungs, particularly in patients who are current smokers.[46,47] Therefore, PDE4

is a rational target to modulate aberrant inflammatory processes in COPD.[44,48,49] In vitro experiments have shown that inhibition of PDE4 suppresses airway inflammation by decreasing the release of inflammatory mediators and by inhibiting inflammatory and immune cell infiltration, thereby controlling their accumulation in the lungs.[50-52] It has further been demonstrated that PDE4 inhibitors can suppress the release of inflammatory mediators neutrophil elastase and matrix metalloproteinase-9 from primed neutrophils and TGF-β and TNF-α from primed macrophages.[51,53] These preclinical studies have also demonstrated that inhibition of PDE4 stimulates cystic fibrosis transmembrane conductance regulator (CFTR), increases ciliary function in bronchial epithelial cells,[54] and decreases mucus hypersecretion through the suppression of key mucin genes.[55] In a guinea pig model of cigarette smoke–induced lung injury, PDE4 inhibition mitigated the infiltration of macrophages and neutrophils into alveolar areas and small airways in the lungs.[56]

### *Phosphodiesterase-4 Inhibition in COPD*

Roflumilast, an oral PDE4 inhibitor, was approved in the United States in 2010 as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations, and in Europe in 2011 for the treatment of severe COPD associated with chronic bronchitis in adult patients with a history of frequent exacerbations.[48,57,58] GOLD recommends roflumilast as an add-on treatment for patients on LABA+LAMA+ICS who continue to experience exacerbations,[1] with recommended dosing of 250mg once daily for 4 weeks followed by a maintenance dose of 500mg per day.[58] Clinical studies (Table 1) have demonstrated that roflumilast significantly improved pulmonary function tests, reduced inflammatory cell load, and reduced the risk of exacerbations in patients with COPD.[59,60] Adverse events with roflumilast treatment were mild to moderate, the most common being gastrointestinal disorders (diarrhea and nausea) and weight loss.[61] A pooled safety analysis of 14 clinical trials showed that adverse events with intermediate- and long-term treatment were generally similar compared to placebo.[61] However, real-world studies showed a much higher incidence of adverse events, mainly related to the gastrointestinal system, leading to frequent treatment discontinuation.[62-64]

Inhaled drug delivery methods represent a potential approach to reduce the gastrointestinal side effects associated with oral PDE4 inhibitors. A number of inhaled PDE4 inhibitors for the treatment of COPD have been evaluated in clinical trials, but their development was ultimately discontinued owing to limited efficacy.[30] These compounds include AWD-12-281, tofimilast, UK-500.001, and GSK256066, which showed promising preclinical results but demonstrated poor efficacy in clinical studies in patients with COPD.[30] Other inhaled PDE4 inhibitors, including SCH900182P, 12b, GS-5759, naphthyridinone, and pyridazinone, did not advance past preclinical development.[30] Currently, the only inhaled PDE4 inhibitor under clinical investigation for the treatment of COPD is tanimilast, a DPI-administered twice daily treatment.[65] Tanimilast is 10 times more potent in inhibiting PDE4 enzymatic activity compared with roflumilast,[65] and it has been shown to significantly reduce inflammatory mediators in sputum compared with placebo yet with little effect on inflammatory cell numbers in the sputum or on blood inflammatory markers.[66] Results from the 24-week, dose-ranging, phase 2b PIONEER study of tanimilast as add-on maintenance therapy to the LABA formoterol showed that tanimilast had similar effects as a placebo on lung function (forced expiratory volume in 1 second [$FEV_1$]), symptom-related endpoints, and rescue medication usage; however, post hoc analyses demonstrated a numerically larger exacerbation rate reduction in patients with a chronic bronchitis phenotype compared to the overall population (24%–37% reduction).[67] Tanimilast was well tolerated in all treatment groups, and the rate of gastrointestinal adverse events was low and comparable to placebo.[67] Two phase 3 studies evaluating the efficacy and safety of tanimilast as an add-on to triple maintenance therapy (LAMA+LABA+ICS) in patients with COPD and chronic bronchitis are currently ongoing (Table 1) and slated to have final readouts in the near future.

### *Role of Phosphodiesterase-3 in COPD*

PDE3 is expressed in the lung epithelium, endothelium, smooth muscle cells, and inflammatory cells.[45,68] It is the major PDE present in vascular smooth muscle cells and plays a significant role in maintaining smooth muscle tone.[45,69,70] Accordingly, preclinical studies have shown that inhibition of PDE3 relaxes smooth muscle cells and inhibits allergic airway inflammation.[68,71] In a guinea pig model of histamine- and acetylcholine-induced tracheal tension, PDE3 inhibition antagonized the contractional ability of histamine.[71] Moreover, in a house dust mite–driven asthma mouse model, the PDE3 inhibitor enoximone had significant reductions in lung inflammatory cell numbers including eosinophils, macrophages, and T cells compared with mice treated with phosphate-buffered saline.[68] Clinical studies in patients with asthma demonstrate the efficacy of the PDE3 inhibitor olprinone in inducing bronchodilation as measured by mean increases in $FEV_1$.[72,73] However, despite these promising preclinical and limited clinical

**Table 1. Late-Phase Clinical Trial Designs of Phosphodiesterase-4 and Phosphodiesterase-3/4 Inhibitors in COPD**

| Compound | Inhibitor Type and Mode of Delivery | Study | NCT Number | Trial Design | Patients | Primary Endpoint |
|---|---|---|---|---|---|---|
| **Roflumilast** | PDE4<br><br>Oral Tablets | RELIANCE<br>Roflumilast or azithromycin to prevent COPD exacerbations | 04069312 | • Phase 3<br>• Randomized, parallel-group, non-inferiority<br>• 250µg/day×4 weeks, then 500µg/day (or alternate regimen) for 6–72 months | • N=1200<br>• Age ≥40 y<br>• Severe COPD with chronic bronchitis<br>• On LABA, LABA/LAMA, or ICS/LABA maintenance therapy | • All-cause hospitalization<br>• All-cause deaths |
| | | ARGO<br>Effectiveness of roflumilast treatment in Greek patients with COPD | 05426915 | • Prospective, observational | • N=750<br>• Severe COPD with chronic bronchitis<br>• History exacerbations on maintenance therapy | • Changes in Clinical COPD Questionnaire at 3, 6, 9, and 12 months |
| **Tanimilast** | PDE4<br><br>Inhaled With Dry Powder Inhaler | PILASTER<br>Tanimilast add-on to triple therapy in patients with COPD and chronic bronchitis | 04636801 | • Phase 3<br>• Randomized, double-blind, placebo-controlled<br>• 1600µg or 3200µg total/day | • N=3435<br>• COPD with chronic bronchitis<br>• History of exacerbations on maintenance therapy | • Moderate and severe exacerbations |
| | | PILLAR<br>Tanimilast add-on to triple therapy in patients with COPD and chronic bronchitis | 04636814 | • Phase 3<br>• Randomized, double-blind, placebo- and active-controlled (roflumilast)<br>• 1600µg or 3200µg total/day | • N=3980<br>• COPD with chronic bronchitis<br>• History of exacerbations on maintenance therapy | • Moderate and severe exacerbations |
| **Ensifentrine** | Dual PDE3/PDE4<br><br>Inhaled With Standard Jet Nebulizer | ENHANCE-1<br>Ensifentrine in patients with moderate to severe COPD | 04535986 | • Phase 3<br>• Randomized, double-blind, placebo-controlled<br>• 3mg BID | • N=763<br>• Age ≥40–80 y<br>• Moderate to severe COPD<br>• On no or stable maintenance therapy | • Least squares mean change from baseline in $FEV_1$ $AUC_{0\text{-}12h}$ at week 12 |
| | | ENHANCE-2<br>Ensifentrine in patients with moderate to severe COPD | 04542057 | • Phase 3<br>• Randomized, double-blind, placebo-controlled<br>• 3mg BID | • N=790<br>• Age ≥40–80 y<br>• Moderate to severe COPD<br>• On no or stable maintenance therapy | • Least squares mean change from baseline in $FEV_1$ $AUC_{0\text{-}12h}$ at week 12 |

COPD=chronic obstructive pulmonary disease; NCT=National Clinical Trial; PDE=phosphodiesterase; LABA=long-acting beta2-agonist; LAMA=long-acting muscarinic antagonist; ICS=inhaled corticosteroid; $FEV_1$=forced expiratory volume in 1 second; BID=twice daily; $AUC_{0\text{-}12h}$, area under the concentration time curve from 0 to 12 hours

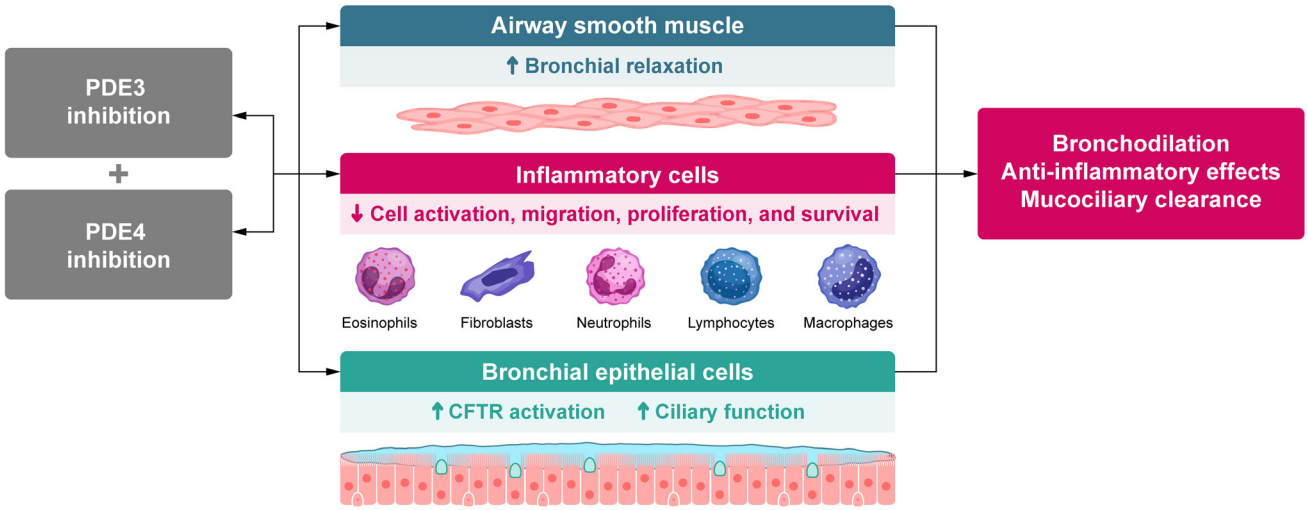
data in asthma, there is currently no single-action PDE3 inhibitor in development for COPD. Therefore, there remains limited clinical evidence of the efficacy of this drug class in COPD.

### *Dual Phosphodiesterase-3/4 Inhibition in COPD*

Together, inhibition of both PDE3 and PDE4 may have additive or synergistic anti-inflammatory and bronchodilator effects, as both are expressed in inflammatory cells and lung structural cells.[39] Indeed, dual inhibition of PDE3 and PDE4 has shown enhanced or synergistic effects on the anti-inflammatory response and airway smooth muscle relaxation compared with either PDE3 or PDE4 alone (Figure 1).[74-76]

Ensifentrine is a novel, selective, dual-action, inhaled inhibitor of PDE3 and PDE4 that was approved by the FDA in June 2024 for the maintenance treatment of COPD in adult patients. Preclinical studies have demonstrated the anti-inflammatory activity and bronchodilator effects of ensifentrine.[77,78] Guinea pig models of allergic bronchoconstriction have demonstrated that inhaled ensifentrine significantly reduced inflammatory cell recruitment into the bronchoalveolar lavage fluid and nasal passages.[77,78] Furthermore, pretreatment with inhaled ensifentrine[77] inhibited antigen-induced eosinophil migration by >80%. A phase 2b randomized, double-blind, placebo-controlled, dose-ranging study in patients with COPD demonstrated that, compared with placebo, treatment with nebulized ensifentrine monotherapy significantly increased bronchodilation as evidenced by increased $FEV_1$ at 1 day and at 4 weeks after dosing and progressively improved patient symptoms

**Figure 1. Mechanisms of Action of Phosphodiesterase-3/4 Inhibitors**




CFTR= cystic fibrosis transmembrane conductance regulator; PDE=phosphodiesterase

and health-related quality of life as measured by the Evaluating Respiratory Symptoms in COPD (E-RS) and St George's Respiratory Questionnaire–COPD Specific (SGRQ-C) total scores, respectively.[79] Importantly, there were also substantial improvements in dyspnea after 4 weeks, as measured by the Transition Dyspnea Index (TDI).[66,79] Overall, the frequency of adverse events with ensifentrine was similar to placebo, and treatment-related adverse events were limited, with no gastrointestinal or cardiovascular treatment-related adverse events observed.[79] Randomized, double-blind, placebo-controlled phase 2 studies have evaluated ensifentrine in conjunction with other bronchodilators in patients with COPD.[80,81] A significantly greater increase in $FEV_1$ was observed in patients treated with ensifentrine in conjunction with salbutamol (mean 295mL; $p<0.0001$) or ipratropium (mean 292mL; $p<0.0001$) compared to treatment with either bronchodilator alone (mean 108mL and mean 94mL with salbutamol or ipratropium alone, respectively).[81] In a 3-day study, ensifentrine also produced a significant improvement in peak $FEV_1$ when combined with the LAMA tiotropium (mean 477 [$p=0.002$] and 500mL [$p<0.0001$] with ensifentrine 1.5 and 6mg, respectively) compared with tiotropium alone (mean 373mL); similar results were recapitulated in a 4-week, dose-ranging study of ensifentrine on top of tiotropium maintenance therapy.[80,81] Patients treated with the combination of ensifentrine and tiotropium also had statistically significant improvements in SGRQ-C scores at 4 weeks compared with patients treated with tiotropium alone.[80] In all studies, ensifentrine was well tolerated and the addition of ensifentrine to bronchodilators did not change the adverse event profile.[79-81] These promising results in early-phase clinical studies led to 2 large, randomized, double-blind, placebo-controlled, phase 3 studies[82]: ENHANCE (Ensifentrine as a Novel Inhaled Nebulized COPD Therapy)-1 and ENHANCE-2. In these studies, the efficacy and safety of ensifentrine (3mg) versus placebo was measured on twice-daily administration for 24 weeks via a standard jet nebulizer in patients with symptomatic, moderate to severe COPD (Table 1).[82] The ENHANCE program enrolled a broad population of patients, mostly those with moderate to severe COPD who were receiving maintenance therapy. Patients aged 40 to 80 years were randomized and treated in ENHANCE-1 (N=763) and ENHANCE-2 (N=790) across 17 countries and from 250 research centers and pulmonary practices.[82] More than half of the patients in both trials were also receiving a LABA or LAMA with or without an ICS (69% and 55% in ENHANCE-1 and ENHANCE-2 respectively).[82] The primary endpoint was met in both ENHANCE-1 and ENHANCE-2, as treatment with ensifentrine significantly improved $FEV_1$ area under the concentration time curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) at week 12, with placebo-corrected increases from baseline of 87mL in ENHANCE-1 ($p<0.001$) and 94mL in ENHANCE-2 ($p<0.001$).[82] Mean E-RS and SGRQ total scores were also improved versus placebo in patients treated with ensifentrine and exceeded the minimally clinically important differences in both trials, and ensifentrine treatment also resulted in significant improvements in dyspnea as measured by TDI scores.[82] Both studies showed reductions in daily rescue medication usages and COPD exacerbations with ensifentrine.[82] The rate of moderate or severe exacerbations over 24 weeks was reduced by 36% in ENHANCE-1 (nominal $p=0.05$) and by 43% in ENHANCE-2 (nominal $p<0.01$) with ensifentrine treatment compared with placebo.[82] Efficacy results were similar to the overall population in patients receiving a concomitant LAMA or LABA, with or without an ICS. These efficacy results were further demonstrated over

48 weeks[82] in a subset of patients in ENHANCE-1. In both trials, ensifentrine was well tolerated and a similar proportion of treatment-emergent adverse events were reported[82] in patients receiving ensifentrine (38.4% in ENHANCE-1 and 35.3% in ENHANCE-2) and placebo (36.4% in ENHANCE-1 and 35.4% in ENHANCE-2). Gastrointestinal adverse events were similar in both treatment groups and no differences were observed in safety laboratory tests, electrocardiogram parameters, or vital signs.[82] Given the significant improvements in lung function in patients with moderate to severe COPD and the favorable adverse events profile, ensifentrine has been approved by the FDA as a maintenance treatment in this patient population.[83] The approval of ensifentrine for the treatment of patients with symptomatic moderate to severe COPD is important as it represents the first inhaled product with a novel mechanism of action that has been approved for the treatment of COPD in >20 years.[83] Its introduction into the armamentarium for COPD has given patients and health care practitioners an alternative treatment option, taken alone or in combination with other inhaled maintenance therapies, that effectively reduces exacerbation rate and risk[84] and achieves clinically meaningful improvements in dyspnea[85] in a broad population of patients with COPD.

## Conclusions

Despite numerous currently available maintenance therapies for COPD, the continued presence of symptoms and risk for exacerbation in patients with COPD underscores the need for new treatment approaches. In the lungs, PDE3 and PDE4 play important roles in inflammation and airway smooth muscle contraction that is evident in conditions such as COPD. Dual inhibition of PDE3 and PDE4, particularly with a nebulized mode of delivery, may provide clinical benefit to a broad range of patients with COPD and represents a promising new treatment strategy. Future clinical trials assessing the efficacy of dual PDE3 and PDE4 inhibition in combination with ICS and its positioning in the pharmacologic armamentarium to treat patients with COPD are warranted.

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