frequency of exacerbations and extended the time to first exacerbation among patients with moderate to severe exacerbations. It is worth mentioning that the rates of adverse events associated with ensifentrine were similar to those observed with placebo.

Previous research has shown that PDE inhibitors have synergistic effects when used in combination with LAMA or LABA treatment (4). This study also revealed that the combination of ensifentrine and a LAMA or LABA resulted in more significant bronchodilation effects, leading to improved COPD symptom management (3). With these findings, ensifentrine can be considered an additional medication to enhance the overall management of COPD symptoms and provide greater relief for patients with COPD.

However, there are still some issues that require further discussion. First, the safety and position of ICSs in the treatment of COPD are much debated because of their associated side effects, such as pneumonia, an increased risk of bone fractures, diabetes, oropharyngeal candidiasis, and *Mycobacterium tuberculosis* infection (5). Consequently, there is ongoing discussion concerning the long-term use of ICSs in patients with COPD. Ensifentrine exhibits antiinflammatory effects by inhibiting the activation and chemotaxis of inflammatory cells, as well as the release of inflammatory mediators (2). Previous studies have demonstrated that the combination of PDE3 and PDE4 inhibitors can enhance the transcription of glucocorticoid receptor genes, thereby amplifying the antiinflammatory effects of ICSs (6). Anzueto and colleagues found that ensifentrine has been shown to reduce the occurrence of acute exacerbations in patients with COPD, irrespective of whether they are using ICSs (3). Given its antiinflammatory properties, it is worth exploring whether ensifentrine can serve as an alternative to ICSs or reduce the reliance on ICSs to mitigate the risk of acute exacerbations. Therefore, it is necessary to conduct studies to compare the effects of ensifentrine and ICSs in patients with COPD when initiating antiinflammatory therapy, which will identify the potential role of ensifentrine in optimizing treatment strategies for COPD. Second, COPD, a heterogeneous disorder, has been categorized into different phenotypes in many ways, such as a chronic bronchitis phenotype, an emphysema phenotype, an eosinophilic phenotype, and others (7, 8). Therefore, it is highly recommended that the authors perform subgroup analysis on the basis of different phenotypes. This analysis will help identify the most suitable phenotype for ensifentrine, which is an essential step in developing more precise and individualized treatments tailored to meet the specific needs of patients. This endeavor holds significant importance in optimizing COPD management and enhancing patient outcomes.

Although there are still some issues that need to be discussed, ensifentrine, as a novel PDE3 and PDE4 inhibitor, shows promising potential as a therapeutic option for patients with COPD, as it demonstrates good safety and has the potential to improve lung function and reduce the risk of acute exacerbations. ■

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## Pharmacological Interpretation of the Efficacy of Ensifentrine in Chronic Obstructive Pulmonary Disease: Insights from ENHANCE Trials

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*To the Editor*:

We have read with interest, in a previous issue of the *Journal*, the paper by Anzueto and colleagues (1) regarding the results of the ENHANCE-1 and ENHANCE-2 trials investigating the novel phosphodiesterase (PDE) 3 and PDE4 inhibitor ensifentrine administered by means of nebulization in patients with chronic obstructive pulmonary disease (COPD). This paper marks a significant development as, more than a decade since the approval of the PDE4 inhibitor roflumilast (2), a new class of drug is concluding



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Phase III development with a high likelihood of gaining approval in the treatment of COPD.

Because of their promising and intriguing nature, and according to the peculiar bifunctional characteristics of ensifentrine, the reported results are worthy of a comprehensive clinical pharmacological interpretation.

The pharmacological characteristics of ensifentrine indicate that the affinity for PDE3 is ≃3,700-fold higher than that for PDE4 (3). PDE3 is prevalently expressed in airway smooth muscle (4). Consequently, the combination of ensifentrine with other bronchodilators in the ENHANCE-1 and ENHANCE-2 trials has demonstrated efficacy in trough $FEV_1$, although it did not reach the minimal clinically important difference for drugs administered in combination with other active treatments (minimal clinically important difference: >60 ml; ensifentrine: 49 ml in the ENHANCE-2 trial) (1, 3). Moreover, although trough $FEV_1$ is currently used in registration trials because of its association with patients' reported outcomes (3), $FEV_1$ area under the curve from 0 to 12 hours—but not trough $FEV_1$—was the primary outcome of the ENHANCE-1 and ENANCE-2 trials (1). According to its pharmacodynamic characteristics against airway smooth muscle contractility, the clinical use of ensifentrine should be in combination with other bronchodilator agents—probably a LAMA such as glycopyrronium—in a twice-daily regimen to optimize the synergistic interaction demonstrated when ensifentrine is combined with an antimuscarinic agent and not with a $\beta_2$-adrenoceptor agonist (3).

PDE4 is prevalently expressed in most inflammatory cells involved in the pathogenesis of COPD (4). Therefore, despite the low affinity for PDE4, ensifentrine may have also a certain antiinflammatory activity. Effectively, in the study by Anzueto and colleagues (1), ensifentrine showed an impressive impact in reducing the rate of moderate to severe exacerbation and increasing the time to first exacerbation. Such a protective effect against exacerbation could be related to the primary antiinflammatory action of ensifentrine through PDE4 inhibition. However, the majority of patients participating in the ENHANCE-1 and ENHANCE-2 trials were concurrently treated with a long-acting beta-2 agonist (LABA) or a long-acting muscarinic antagonist (LAMA). Therefore, considering the predominant bronchorelaxant effect of ensifentrine resulting from PDE3 inhibition, it is possible that the prevention of exacerbation was due to the protective interaction achieved by combining two bronchodilator agents—namely, LABA plus ensifentrine or LAMA plus ensifentrine—as previously demonstrated in the FLAME study (5). Moreover, combining a PDE3 and PDE4 inhibitor with either a LABA or a LAMA represents a therapeutic strategy acting on three different targets in the airways, a condition leading to synergistic bronchorelaxant and antiinflammatory effects in the bronchial tissue (6). In any case, because the assessment of exacerbation was not prespecified in the study protocol (ClinicalTrials.gov IDs NCT04535986 and NCT04542057) or in the methods of Anzueto and colleagues's paper (1), the rate of moderate to severe exacerbation was included neither in the primary nor in the secondary endpoints, and the impact of ensifentrine on exacerbation resulting from the ENHANCE-1 and ENHANCE-2 trials should be interpreted with caution.

Ensifentrine is the only novel drug that may be approved for the treatment of COPD in the near future (3). For this reason, it is very important to optimize the strategic development of this PDE3 and PDE4 inhibitor in combination with the right bronchodilator agent to confirm its real impact on COPD exacerbation and to definitely assess its antiinflammatory profile at the level of the airways. Moreover, further Phase III studies on ensifentrine administered by means of dry powder and metered dose inhalers, and not nebulization, are needed to definitely consider this drug as a suitable option in the treatment of COPD. ■

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## Still Thirsty in COPD!

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*To the Editor*:

New therapies for chronic obstructive pulmonary disease (COPD) are desperately needed (1). We read with great interest the work by



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