Ohtuvayre™
(ensifentrine) Inhalation Suspension
3 mg/2.5 mL

Ohtuvayre: ENHANCE (Phase III) Clinical Trials

A clinical summary of *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).* Anzueto A, Barjaktarevic IZ, Siler TM, et al. American Journal of Respiratory and Critical Care Medicine. Volume 208, Issue 4, published August 2023.

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Addressing an unmet need in patients with COPD

Persistent symptoms reveal patients' need for innovation in chronic obstructive pulmonary disease (COPD) treatment.[1]

- Despite the use of dual bronchodilator and triple therapies, patients report a significant burden of persistent COPD symptoms.[2]
- These symptoms impose a considerable burden, impair health-related quality of life (HRQoL), and increase morbidity.[2,3]

Introducing Ohtuvayre: A novel, inhaled, non-steroidal maintenance treatment.[1,4]

- Ohtuvayre is a selective, dual inhibitor of phosphodiesterase 3 (PDE3) and PDE4 indicated for the maintenance treatment of COPD in adult patients.[4]
- Dual inhibition of PDE3 and PDE4 has shown effects on airway smooth muscle and suppression of the inflammatory response, which may make it a promising strategy for the treatment of COPD. [5-10]

Indication and Important Safety Information

INDICATION

Ohtuvayre is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients.

IMPORTANT SAFETY INFORMATION

Contraindication: Ohtuvayre is contraindicated in patients with hypersensitivity to ensifentrine or any component of this product.

Please see Full Important Safety Information throughout and Full Prescribing Information for Ohtuvayre, also available at OhtuvayreHCP.com.

To read the full study, please scan the QR code or click here.

ENHANCE Study Program Design

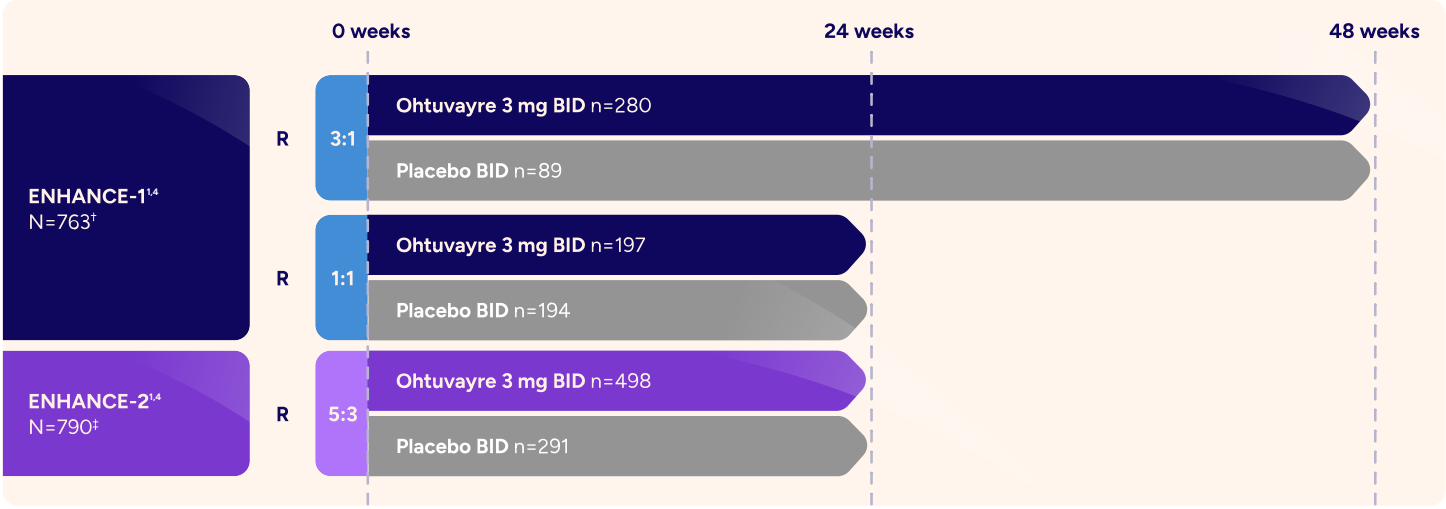
Endpoints:

Primary endpoint[1,4]: Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ post dose at Week 12.*

Patients:

Selected Eligibility Criteria[1]:

- COPD diagnosis: FEV_1/FVC <0.7
- Post-bronchodilator FEV_1 30–70% predicted normal
- mMRC dyspnea scale score ≥2
- Current or former smoker (≥10 pack-years)
- No asthma diagnosis
- No exacerbation history requirement (other than no steroid-treated exacerbation in past 12 weeks)



- **62%** of patients were on a long-acting bronchodilator treatment[1]
  - **18%** were also on an inhaled corticosteroid[1]
- **38%** had no concomitant maintenance COPD therapy[1]
- **23%** of patients had an exacerbation in the 15 months prior to screening[1]

*Average FEV_1 $AUC_{0\text{-}12h}$ is defined as the AUC over 12 hours of the FEV_1, divided by 12 hours.[1]
†Randomized set: N=763; mITT population: N=760[1,4]
‡Randomized set: N=790; mITT population: N=789[1,4]
AUC = area under the curve; BID = twice daily; ENHANCE = **E**nsifentrine as a **N**ovel in**HA**led **N**ebulized **C**OPD th**E**rapy; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; mITT = modified intention to treat; mMRC = modified Medical Research Council; R = randomization.

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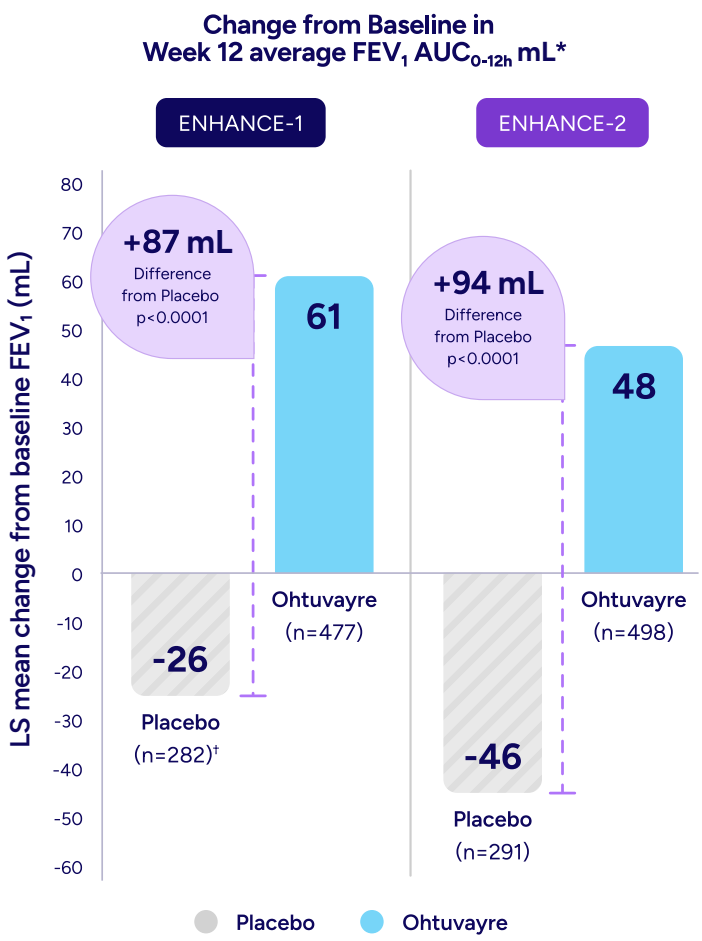
Significant Improvement in Lung Function[1,4]

As shown by change from baseline in average FEV_1 $AUC_{0\text{-}12h}$ at Week 12.



*Average FEV_1 $AUC_{0\text{-}12h}$ is defined as the AUC over 12 hours of the FEV_1, divided by 12 hours.[1]
†One patient was randomized to placebo and treated but was not included in the endpoint analysis due to missing baseline FEV_1.[11]
LS = least squares.

Warnings and Precautions:

Acute Episodes of Bronchospasm Ohtuvayre should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting bronchodilator.

Please see Full Important Safety Information throughout and Full Prescribing Information for Ohtuvayre, also available at OhtuvayreHCP.com.

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Common adverse reaction incidence rates were low and similar to placebo[1]

The adverse reactions reported in the 48-week subset were consistent with those observed in the 24-week placebo-controlled trials.[4]

Discontinuation of Ohtuvayre due to adverse reactions was low and similar to placebo (7.6% in the Ohtuvayre group vs 8.2% on placebo).[4]

Pooled Ohtuvayre Safety Profile Over 24 Weeks (Adverse reactions ≥1% and greater than placebo)[4]

Adverse Reaction	Ohtuvayre N=975	Placebo N=574
Back Pain	1.8%	1.0%
Hypertension	1.7%	0.9%
Urinary Tract Infection	1.3%	1.0%
Diarrhea	1.0%	0.7%

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IMPORTANT SAFETY INFORMATION (continued)

Paradoxical Bronchospasm As with other inhaled medicines, Ohtuvayre may produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with Ohtuvayre, it should be treated immediately with an inhaled, short-acting bronchodilator. Ohtuvayre should be discontinued immediately and alternative therapy should be instituted.

Psychiatric Events Including Suicidality Before initiating treatment with Ohtuvayre, healthcare providers should carefully weigh the risk and benefits of treatment with Ohtuvayre in patients with a history of depression and/or suicidal thoughts or behavior. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts, or other mood changes, and if such changes occur to contact their healthcare provider. Healthcare providers should carefully evaluate the risks and benefits of continuing treatment with Ohtuvayre if such events occur.

Treatment with Ohtuvayre is associated with an increase in psychiatric adverse reactions. Psychiatric events including suicide-related adverse reactions were reported in clinical studies in patients who received Ohtuvayre (1 suicide attempt and 1 suicide). Additionally, the most commonly reported psychiatric adverse reactions in the pooled 24-week safety population were insomnia (6 patients [0.6%] Ohtuvayre 3 mg; 2 patients [0.3%] placebo), and anxiety (2 patients [0.2%] Ohtuvayre 3 mg; 1 patient [0.2%] placebo). Depression-related reactions including depression, major depression, and adjustment disorder with depressed mood occurred in 4 patients [0.4%] receiving Ohtuvayre and no patients receiving placebo.

Adverse Reactions: The most common adverse reactions ≥1% in Ohtuvayre and greater than placebo in the pooled population were back pain 1.8%, hypertension 1.7%, urinary tract infection 1.3%, and diarrhea 1.0%.

These are not all of the possible risks associated with Ohtuvayre. **Please see the Full Prescribing Information for Ohtuvayre.**

To report suspected adverse reactions, contact Verona Pharma, Inc. at 1-888-672-0371 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

References:

1. 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. **2.** 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. **3.** Phreesia Life Sciences. Patients in focus: COPD treatment and perceptions. Accessed July 5, 2024. https://lifesciences.phreesia.com/reports/patients-in-focus-copd-treatment-and-perceptions/. **4.** Ohtuvayre™ (ensifentrine). Prescribing Information. Raleigh, NC: Verona Pharma plc; 2024. **5.** 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. **6.** Singh D, Martinez FJ, Watz H, Bengtsson T, Maurer BT. A dose-ranging study of the inhaled dual phosphodiesterase 3 and 4 inhibitor ensifentrine in COPD. *Respir Res.* 2020;21(1):47. **7.** 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. **8.** 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. **9.** 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. **10.** Rheault T, MacDonald-Berko M. Anti-inflammatory pharmacology of ensifentrine. Poster presented virtually at: CHEST Annual Meeting, October 18-21, 2020. **11.** Data on File. Raleigh, NC: Verona Pharma plc.

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