

Revefenacin: A Once-Daily, Long-Acting Bronchodilator For Nebulized Treatment Of COPD

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Abstract: Bronchodilation with muscarinic antagonists, β_2 -agonists, and inhaled corticosteroids remains the foundation of pharmaceutical treatment for patients with stable COPD. These drugs are delivered from a variety of devices, including dry powder inhalers, pressurized metered-dose inhalers, soft-mist inhalers, or nebulizers. Nebulized delivery is often preferable in patients who are elderly, are cognitively impaired, are unable to generate sufficient inspiratory force to use their inhaler, have difficulty coordinating hand-breath activity, are too dyspneic to hold their breath for a sufficient time, and/or may be acutely ill. Revefenacin, a once-daily long-acting muscarinic antagonist for nebulization recently approved by the US FDA for the treatment of patients with COPD, was discovered and developed using “duration and lung selectivity-by-design.” This strategy selected a molecule with a high lung-selective index to maximize bronchodilation and limit systemic antimuscarinic side effects. In early-phase clinical studies, revefenacin for nebulization led to a rapid onset of bronchodilation that was sustained for 24 hrs in patients with moderate to severe COPD. Revefenacin also demonstrated minimal systemic exposure and good tolerability in these studies. Statistically and clinically significant improvements in lung function (ie, peak and/or trough FEV₁) relative to placebo were observed with revefenacin in Phase III clinical trials of up to 3 months in patients with moderate to very severe COPD. Revefenacin was well tolerated in Phase III clinical trials with a low incidence of systemic antimuscarinic adverse events, which is consistent with its lung-selective design. There was no evidence of an increased risk of major cardiovascular events. Patient-reported outcome data from clinical trials indicated statistically significant improvements in several disease-specific measures. Revefenacin 175 μ g for nebulization provides an effective once-daily treatment option for patients with moderate to very severe COPD who require or prefer nebulized therapy.

Keywords: long-acting muscarinic antagonist, LAMA, bronchodilator, inhaled, once daily, nebulizer

Introduction

Bronchodilation remains the mainstay of treatment for patients with COPD to relieve symptoms of dyspnea. Short- and long-acting muscarinic antagonists (LAMAs) and short- and long-acting β_2 -agonists (LABAs) administered alone or in combination, with or without inhaled corticosteroids (ICSs), are the foundation of pharmaceutical treatment in patients with stable COPD (Table 1^{1–3}). These agents are commonly delivered through a variety of devices, including dry powder inhalers (DPIs), pressurized metered-dose inhalers, soft-mist inhalers, or nebulizers. When used appropriately, these delivery devices offer similar efficacy.^{4–6} However, adherence to inhaled therapy in patients with COPD is poor, and nonadherence rates

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Table 1 Commonly Used Long-Acting Anticholinergics For Maintenance Treatment Of COPD¹

LAMA	Inhaler Type ^a	Mode Of Delivery/Frequency	Duration Of Action
Acclidinium bromide	DPI, MDI	Oral inhalation/twice daily	12 hrs
Glycopyrrolate	DPI, nebulizer	Oral inhalation/twice daily ^b Nebulizer/twice daily	12–24 hrs
Tiotropium bromide	DPI, SMI	Oral inhalation/once daily	24 hrs
Umeclidinium bromide	DPI	Oral inhalation/once daily	24 hrs

Notes: ^aNot all formulations are available in all countries. ^bGlycopyrrolate is approved for once-daily dosing in some countries.^{2,3}

Abbreviations: DPI, dry powder inhaler; LAMA, long-acting muscarinic antagonist; MDI, metered-dose inhaler; SMI, soft-mist inhaler.

range from 50% to 80%.^{7–9} One of the main reasons for nonadherence is the misuse of inhalers.¹⁰ Certain groups of patients – such as patients who are elderly, are cognitively impaired, are unable to generate sufficient inspiratory force against the resistance of their inhaler, have difficulty coordinating hand-breath activity, are too dyspneic to hold their breath for a sufficient time, and/or may be acutely ill – may have difficulty using the handheld inhalers effectively. Recent evidence suggests that certain individuals with severe COPD have difficulty generating optimal peak inspiratory flow rate (PIFR), which is required for effective handheld inhaler use. The 2019 GOLD strategy emphasizes a personalized approach to the treatment of patients with COPD, and therefore, nebulized delivery may be preferable in these groups of patients.^{1,11} Where appropriate, using nebulizers can improve patient confidence and treatment adherence,¹² achieving comparable symptom relief with greater ease of use compared with DPIs, pressurized metered-dose inhalers, and soft-mist inhalers.^{13–15} According to a survey by Sharafkhaneh et al, 80% of patients with COPD and caregivers reported that using a nebulizer was better than using only an inhaler.¹⁴

Standard jet and vibrating mesh nebulizers are the two most commonly used nebulizing devices. Depending on the model, limitations reported include longer administration time, variability in residual volume and particle size, daily cleaning requirements, limited portability, and need for device assembly.^{11,16} Older, cheaper models have also shown inefficiencies in drug delivery.¹⁶ Additionally, the same dose of bronchodilator administered using the newer models of vibrating mesh nebulizers may vary substantially from the dose administered with jet nebulizers, increasing the potential for overdosing. However, the benefits of nebulizers may outweigh their limitations,

specifically for patients who require or prefer the use of nebulizers.¹¹

LAMAs relieve the symptoms of COPD by preventing bronchoconstriction caused by the binding of acetylcholine to M₃ muscarinic receptors expressed in airway smooth muscle.¹⁷ Revefenacin is a once-daily, lung-selective LAMA, delivered via a standard jet nebulizer that was approved by the FDA in November 2018 for maintenance treatment of patients with COPD who require or prefer nebulized drug delivery.¹⁸ This review summarizes the clinical data on once-daily revefenacin for nebulization and examines the role of this new LAMA in the management of patients with COPD.

Duration And Lung Selectivity By Design: The Discovery Of Revefenacin

From a chemical standpoint, revefenacin is structurally distinct from existing once-daily LAMAs (Figure 1^{19–21}). First, it has a distinct M₃ binding orthostere, a biphenyl carbamate moiety. Second, unlike tiotropium, it lacks an ester substituent. Third, unlike tiotropium and umeclidinium, revefenacin possesses two tertiary amines instead of a quaternary amine. These characteristics make revefenacin the only nonester, nonquaternary ammonium LAMA discovered to date.

Revefenacin's lung selectivity, prolonged duration of action, limited antimuscarinic side effects, and formulation for nebulized delivery are characteristics that were sought specifically during the “duration and lung selectivity-by-design” strategy used to identify a LAMA with the ideal structural and pharmacological characteristics to support once-daily nebulized delivery.²² Based on the expectation that a nonester, nonquaternary ammonium-based molecule would enhance tissue residency and maximize chemical stability for aqueous formulation and aerosol delivery, a new

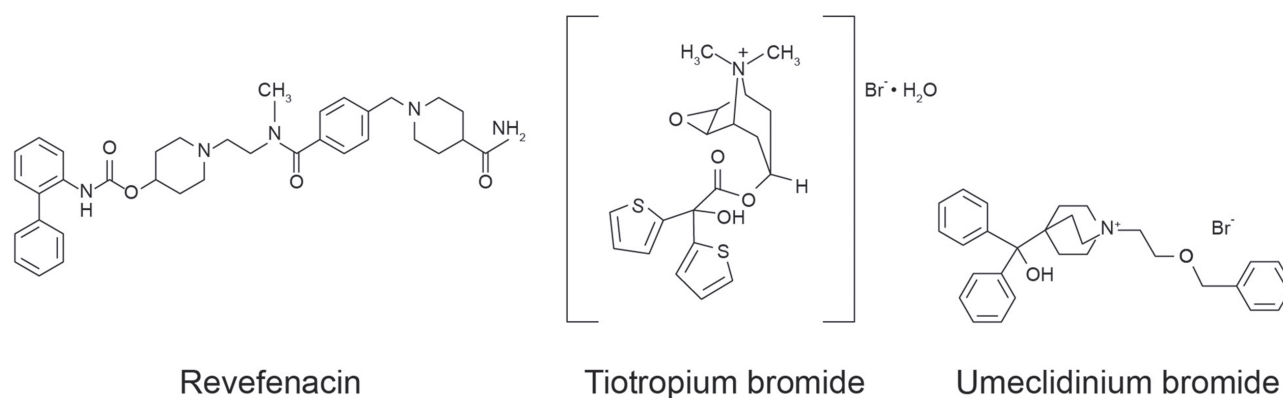


Figure 1 Structural formulas of once-daily LAMAs.^{19–21}
Abbreviation: LAMA, long-acting muscarinic antagonist.

orthostere was linked with secondary binding elements to generate novel, chemically stable inhaled antagonists with high-affinity binding and a slow off-rate from the M_3 receptor. Drug candidates with high muscarinic receptor affinity, slow off-rate at M_3 receptors, slowly reversible antagonism in airway tissues, high functional lung selectivity, ≥ 24 -hr inhibition of agonist-induced bronchoconstriction, metabolic lability (to ensure stability in the lung, with hydrolysis to a less active metabolite in the systemic circulation), and limited gastrointestinal absorption were progressed through the screening funnel. Long-acting bronchodilator efficacy (confirmed in a canine model of bronchoconstriction), rapid plasma clearance via primarily nonrenal mechanisms (also confirmed in animal models), and favorable non-clinical safety were requirements for the final selection of the development candidate.

After identifying a 4-piperidyl biphenyl-2-ylcarbamate (BPC) tertiary amine head group as a chemically stable orthostere starting point, a linker was installed on the BPC head group to preserve M_3 potency and extend antagonist binding to distal receptor sites through a secondary allosteric site, on which an amide was installed to create a metabolic “soft site.” The final candidate was TD-4208 (revefenacin), a competitive antagonist of human muscarinic receptors. It displayed kinetic selectivity at M_3 receptors, produced potent and slowly reversible antagonism in animal and human airway tissues with a 24-hr inhibition of bronchoconstriction in rats and dogs after nebulized inhalation,^{23,24} had low oral bioavailability, and had a favorable lung-selectivity index compared with tiotropium. Revefenacin was chemically stable in the lung but quickly degraded to a metabolite with minimal antimuscarinic activity in the systemic circulation, reducing the potential for side effects.

Exposure–Response Characteristics

The pharmacokinetic and pharmacodynamic properties of revefenacin were evaluated in several clinical trials (Table 2^{25–30}). The initial assessment of efficacy and safety of revefenacin in patients with moderate to severe COPD was done in two Phase II trials: Study 0059 (N=32), a single-dose, double-blind, crossover study of revefenacin (350 or 700 μ g) versus active-control ipratropium (500 μ g) or placebo solution, all administered via standard jet nebulizer,²⁵ and Study 0091 (N=59), a multidose, double-blind, 7-day, 5-way crossover study that evaluated revefenacin (22, 44, 88, 175, 350, or 700 μ g once daily) versus placebo.²⁵ In both studies, revefenacin was rapidly absorbed and demonstrated rapid onset (within 1 hr), peak effect 2–3 hrs postdose, and >24 hrs of bronchodilator activity. In the single-dose study, the primary endpoint – mean change in peak FEV_1 (0–6 hrs) from baseline – was significantly greater with revefenacin than placebo (least squares [LS] mean treatment difference vs placebo: 177 and 162 mL for 350- and 700- μ g doses, respectively, vs 191 mL with ipratropium; all $p < 0.001$; Figure 2A^{25,31}). In the multidose study, the primary endpoint of change from baseline in trough FEV_1 24 hrs after the seventh dose showed significant benefit over placebo for all revefenacin doses, with a dose–response effect observed up to 175 μ g. Beyond that point, there was no further benefit increasing the dose (LS mean treatment difference vs placebo: 54, 55, 75, 114, 94, and 82 mL for revefenacin doses of 22, 44, 88, 175, 350, and 700 μ g, respectively; all $p \leq 0.006$). Peak FEV_1 difference from placebo also showed dose-dependency (Figure 2B^{25,31}). The minimally clinically important difference for bronchodilation is commonly accepted as a trough $FEV_1 \geq 100$ mL.³¹ This threshold was reached for peak and

Table 2 Summary Of Trials Evaluating Efficacy And Safety Of Revefenacin

Trial Identifier/ Publication	Phase	Trial Design	Population	Dosing	Efficacy/Safety
U1111-1120-8290; NCT03064113 ²⁵	Phase II	Randomized, double-blind, placebo- and ipratropium-controlled, crossover, single-dose study	Moderate to severe COPD	Single dose of 350 or 700 µg	Significant change in peak FEV ₁ (0–6 hrs) vs placebo Significant improvement in trough FEV ₁ vs placebo AEs generally mild; few antimuscarinic AEs
NCT01704404 ²⁵	Phase II	Randomized, double-blind, placebo- controlled, 5-way crossover, multidose study	Moderate to severe COPD	22, 44, 88, 175, 350, or 700 µg once daily for 7 days	Significant improvement in mean trough FEV ₁ on Day 7 vs placebo Rapid onset and sustained bronchodilator effect for 24 hrs AEs generally mild; few antimuscarinic AEs
NCT02109172 ²⁶	Phase II	7-day, randomized, double-blind, placebo-controlled, crossover study	Moderate to severe COPD	44 µg twice-daily or 175 µg once daily	Improvement in weighted mean (0–24 hrs) change from baseline FEV ₁ with both doses vs placebo Well tolerated with no major safety concerns
NCT02040792 ²⁷	Phase II	28-day, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study	Moderate to severe COPD	44, 88, 175, or 350 µg once daily	Significant improvement in mean trough FEV ₁ vs placebo ≥100 mL increase in FEV ₁ in >80% of patients within 4 hrs postdose Effective dose: ≥88 µg Bronchodilation sustained for 24 hrs Well tolerated, with few antimuscarinic AEs
NCT02459080, NCT02512510 ²⁸	Phase III	12-week, replicate, randomized, double-blind, placebo-controlled, multiple-dose, parallel-group studies	Moderate to very severe COPD	88 or 175 µg once daily	Significant improvement in day 85 mean trough FEV ₁ vs placebo Significant improvement in OTE trough FEV ₁ and peak FEV ₁ vs placebo 175-µg dose more effective than 88 µg Well tolerated, with no major safety concerns
NCT02518139 ²⁹	Phase III	52-week, randomized, partially double-blind, tiotropium-controlled, parallel-group safety study	Moderate to very severe COPD	REV 88 or 175 µg or TIO 18 µg once daily	AEs comparable across treatments Fewer exacerbations with REV 175 µg vs REV 88 µg and TIO Fewer serious AEs with REV 175 µg vs REV 88 µg and TIO
NCT03095456 ³⁰	Phase III	28-day, randomized, double-blind, double-dummy, tiotropium-controlled study	Moderate to very severe COPD; PIFR <60 L/min	REV 175 µg or TIO 18 µg once daily	Significant improvements in trough FEV ₁ and forced vital capacity in patients with FEV ₁ <50% predicted vs TIO Subgroups with lower PIFR cut points (33–56 L/min) had a more pronounced effect

Abbreviations: AE, adverse event; OTE, overall treatment effect; PIFR, peak inspiratory flow rate; REV, revefenacin; TIO, tiotropium.

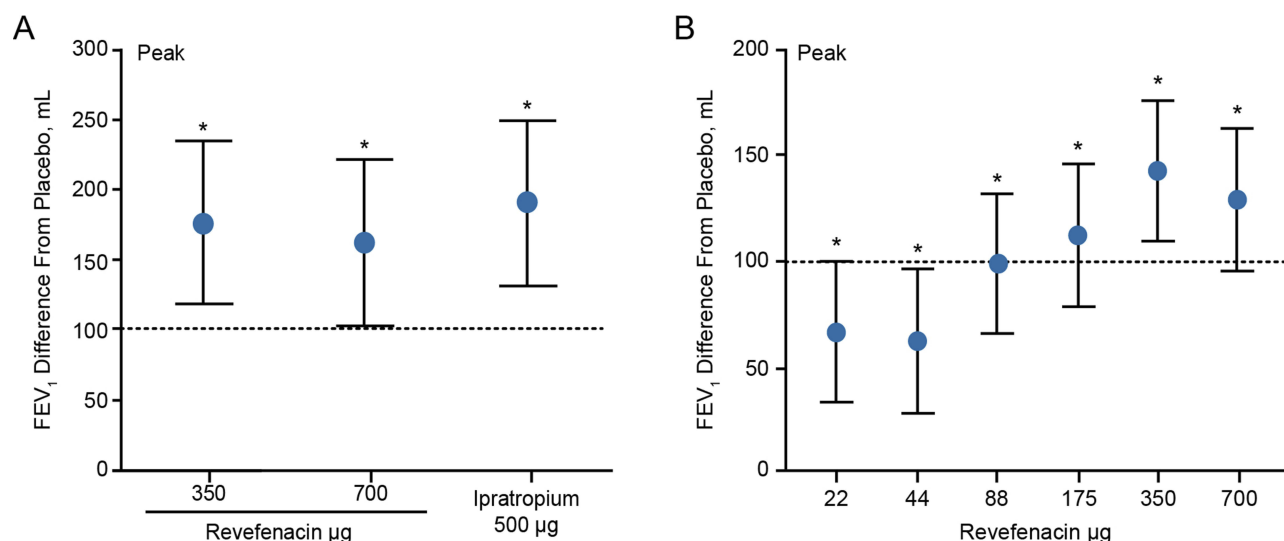


Figure 2 Peak FEV₁ treatment difference from placebo in single-dose (A) and multi-dose 7-day (B) trials. Peak FEV₁ is the highest value obtained between 0 and 6 hrs after the first dose. * $p < 0.001$. Data are least squares mean \pm 95% confidence interval treatment difference from placebo. Dotted line indicates minimal clinically important difference.³¹
Notes: Reproduced from Quinn D, Barnes CN, Yates W, et al Pharmacodynamics, pharmacokinetics and safety of revefenacin (TD-4208), a long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD): results of two randomized, double-blind, phase 2 studies. *Pulm Pharmacol Ther.* 2018;48:71–79. Creative Commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>.²⁵

trough FEV₁ after single doses of 350 and 700 µg in the single-dose study, and peak FEV₁ exceeded this threshold at doses > 88 µg in the multidose study (Figure 2A and B^{25,31}). Other spirometry endpoints were consistent with the primary endpoint in both studies.

The effect of revefenacin on bronchodilation was further confirmed in two multiple-dose Phase II studies in patients with moderate to severe COPD.^{26,27} In a 7-day randomized, double-blind, placebo-controlled, crossover, Phase II study of 64 patients, twice-daily administration of 44-µg revefenacin and once-daily administration of 175-µg revefenacin produced substantial improvements from baseline in day 7 weighted mean (0–24 hr) FEV₁ over placebo (LS mean difference, 105 mL and 113 mL for 44-µg and 175-µg revefenacin, respectively).²⁶ In a longer 28-day, double-blind, dose-ranging study, 355 adults with moderate to severe COPD were randomized to once-daily revefenacin (44, 88, 175, or 350 µg) or matching placebo, administered by standard jet nebulizer for 28 days.²⁷ Revefenacin improved Day 28 trough FEV₁ significantly more than placebo at daily doses of 88, 175, and 350 µg (187, 167, and 171 mL, respectively; all $p < 0.001$); the 44-µg once-daily dose was subtherapeutic. At 88 µg and higher doses, $> 80\%$ of patients randomized to revefenacin (vs 33% of those who received placebo) achieved a ≥ 100 mL increase from baseline FEV₁ in the first 4 hrs postdose, with sustained bronchodilation for 24 hrs, allowing an average decrease in rescue medication of > 1 albuterol puff per day.

Improvements over placebo in mean FEV₁ increase from baseline exceeded 114 mL and were apparent within 1 hr postdose on Day 1 and throughout the 28-day trial. The 350-µg daily dose offered no additional benefit over 175 µg.

Revefenacin was extensively metabolized to its hydrolytic metabolite (THR-195518) with metabolite-to-parent ratios for the area under the plasma concentration-time curve from time 0 to last detectable time point (AUC_{0-t}) of 4- to 6-fold at doses of 350 and 700 µg in the single-dose study, and 3- to 6-fold on Day 7 at doses ≥ 175 µg in the multidose study. Elimination was slow, and there was minimal accumulation of either revefenacin or its metabolite on repeat dosing. Across all three studies reported above, revefenacin was well tolerated, with no evidence of sustained systemic exposure.

Exposure–Response Conclusions

In early-phase clinical studies, revefenacin for nebulization led to rapid onset and sustained the duration of bronchodilator effect for 24 hrs in patients with moderate to severe COPD, with minimal systemic exposure and good tolerability. Doses of 88 and 175 µg once daily offered the optimal efficacy-to-exposure ratio for further investigation in Phase III trials.

Efficacy And Safety Of Revefenacin In Moderate To Very Severe COPD

The efficacy and safety of revefenacin in patients with moderate to very severe COPD were evaluated in three

randomized, controlled Phase III trials. In this review, we focus mainly on data for the 175- μ g dose of revefenacin, which is the FDA-approved daily dose for the maintenance treatment of COPD.¹⁸

Efficacy Of Revefenacin

The efficacy of revefenacin administered using a standard jet nebulizer for 12 weeks was examined in patients with moderate to very severe COPD with high risk for exacerbation, in 2 replicate multicenter, randomized, double-blind, placebo-controlled Phase III trials (Study 0126, NCT02459080, and Study 0127, NCT02512510).²⁸ Up to 40% of patients received concomitant LABA or ICS/LABA therapy. FEV₁ increased significantly within 2 hrs of revefenacin treatment in both studies, as well as in pooled data analysis (placebo-adjusted LS mean increase in peak FEV₁ [0–2 hrs] after the first dose of revefenacin 175 μ g was 130 mL in the pooled analysis; $p < 0.0001$). Revefenacin demonstrated statistically significant improvements over placebo in trough FEV₁ throughout the treatment period (Figure 3^{28,31}) and at 12 weeks (placebo-adjusted LS mean increase in trough FEV₁ at Day 85 was ~147 mL in both individual studies, as well as in pooled data analysis [Figure 4^{28,31}]). The 175- μ g dose also increased overall treatment effect on trough FEV₁ by ≥ 100 mL relative to placebo in both individual studies, and by 142 mL in the

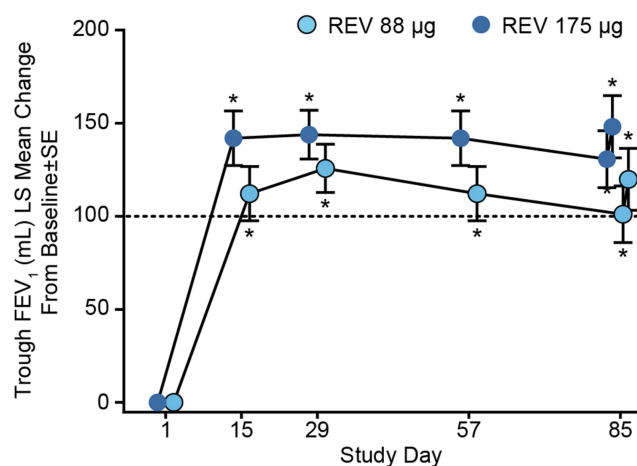


Figure 3 Sustained increase in trough FEV₁ for 85 days in two randomized, double-blind, placebo-controlled Phase III trials in patients with moderate to severe COPD (pooled data from NCT02459080 and NCT02512510; N=1,255). Dotted line indicates minimal clinically important difference.³¹

Notes: Reproduced with permission from Ferguson GT, Feldman G, Pudi KK, et al. Improvements in lung function with nebulized revefenacin in the treatment of patients with moderate to very severe COPD: results from two replicate phase III clinical trials. *Chronic Obstr Pulm Dis.* 2019;6(2):154–165. doi:10.15326/jcopdf.6.2.2018.0152. ²⁸ * $p < 0.0001$ vs placebo.

Abbreviations: LS, least squares; REV, revefenacin; SE, standard error.

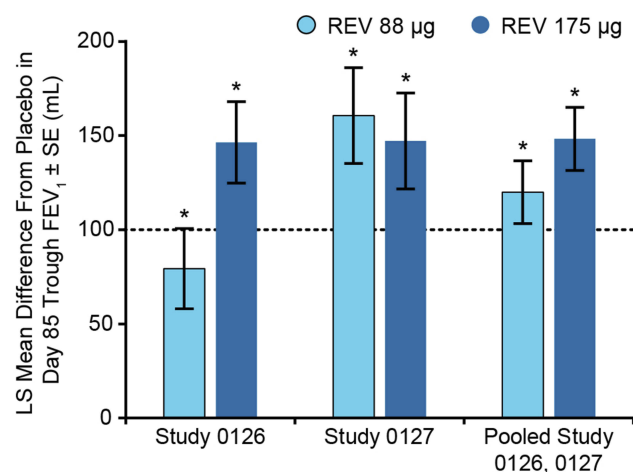


Figure 4 Placebo-adjusted changes from baseline at day 85 trough FEV₁ in patients with COPD who received once-daily revefenacin (88 and 175 μ g) for nebulization.²⁸

* $p < 0.001$ vs placebo. Day 85 trough FEV₁ was the average of values obtained at 23.25 and 23.75 hrs following the 84th dose. Dotted line indicates minimal clinically important difference.³¹

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Abbreviations: LS, least squares; OTE, overall treatment effect; REV, revefenacin; SE, standard error.

pooled analysis. Subgroup analysis of pooled data showed that revefenacin produced greater improvements in Day 85 trough FEV₁ than placebo in patients taking concomitant LABA or ICS, in those aged > 65 years, in those with very severe airflow limitation, in those with a modified Medical Research Council dyspnea scale ≥ 2 (severe dyspnea), and in former smokers. Importantly, patient-reported measures of respiratory health (St George's Respiratory Questionnaire [SGRQ], a secondary endpoint, and COPD Assessment Test, an exploratory endpoint) showed significant improvements in one of the studies.³² In Study 0126, revefenacin produced significant improvements in the SGRQ responders (patients with a score decrease ≥ 4 ; the odds ratio for revefenacin 175 μ g vs placebo, 2.11; $p = 0.02$) and change from baseline in total score (LS mean placebo-adjusted change from baseline, -4.16 ; $p = 0.001$). Because of a greater-than-expected placebo response in Study 0127, only change from baseline reached statistical significance versus placebo (LS mean placebo-adjusted change with revefenacin 175 μ g, -2.58 ; $p = 0.02$). The COPD Assessment Test results were consistent with SGRQ.

Efficacy In Patients With Markers Of Severe Disease And Suboptimal PIFR

In the 12-week studies described above (Study 0126 and Study 0127), subgroup analyses were conducted among

COPD patients with markers of severe disease (age ≥ 65 years, classified as GOLD class D,³³ or concurrent ICS or LABA use).³⁴ Revefenacin 175 μg produced significant improvement in trough FEV₁ in the intention-to-treat population and the key subgroups of patients with markers of more severe disease.

Patients with COPD and suboptimal PIFR (<60 L/min) against the resistance of a DPI may have difficulty generating sufficient force during inhalation to overcome the internal resistance of DPI devices, deaggregate the powdered medication, and receive the correct dose.³⁵ In observational studies, up to 78% of stable outpatients with COPD and 32%–52% of inpatients after treatment for COPD exacerbation had suboptimal PIFR.^{36–40} These patients, in particular, may benefit from nebulized therapy.

In a 28-day, double-blind, parallel-group Phase IIb trial (NCT03095456), 207 patients with moderate to very severe COPD and PIFR <60 L/min measured using the In-CheckTM DIAL device against simulated resistance of the Diskus[®] DPI (GlaxoSmithKline, Brentford, UK) were randomized to receive revefenacin 175 μg once daily or tiotropium 18 μg once daily.³⁰ In the intention-to-treat population, revefenacin produced numerically greater improvements in the trough FEV₁ and trough forced vital capacity than tiotropium, but the difference was not significant (LS mean difference \pm standard error [SE], 17 \pm 22 mL; $p=0.45$). Patients with severe airflow obstruction (ie, FEV₁ $<50\%$ predicted; $\sim 80\%$ of the population) experienced significantly greater improvements with revefenacin than tiotropium in trough FEV₁ (between-treatment difference in LS mean change from baseline \pm SE: 49 \pm 22 mL; $p=0.03$) and trough forced vital capacity (104 \pm 49 mL; $p=0.03$). Revefenacin also led to greater improvement than tiotropium in trough FEV₁ among patients with lower PIFR cut points (33–56 L/min).

Safety Of Revefenacin Up To 1 Year General Safety And Tolerability

A summary of adverse events (AEs) associated with revefenacin 175 μg once daily in Phase II and Phase III trials is presented in Table 3.^{25,27–29} In the two 12-week randomized controlled trials (Study 0126 and Study 0127), the incidence of treatment-emergent AEs and serious adverse events (SAEs) was similar in all treatment groups in both studies.²⁸ Of the 15 patients (7.6%) taking revefenacin 175 μg who reported SAEs, only two were considered treatment-related (COPD exacerbation and pneumonia).

Antimuscarinic AEs (≤ 1 per patient, most commonly constipation and dry mouth) were evenly distributed across treatment and placebo groups.

In the 52-week tiotropium-controlled safety trial (Study 0128, NCT02518139), the incidence of treatment-emergent AEs was similar in all groups and numerically higher in the tiotropium group (72% for revefenacin 175 μg vs 77% for tiotropium).²⁹ The incidence of AEs was not affected by concomitant ICS/LABA use for patients taking revefenacin 175 μg but was higher for patients taking tiotropium and ICS/LABA than those taking tiotropium alone. The most frequently reported AE was COPD exacerbation, which occurred less frequently with revefenacin 175 μg (97 events in 73 patients [22%]; moderate/severe in 17% of patients) than tiotropium (137 events in 100 patients [28%]; moderate/severe in 26% of patients). The incidence of SAEs was lower for revefenacin 175 μg than tiotropium (12.8% vs 16.3%, respectively); the most frequently reported SAEs were COPD exacerbation and pneumonia. Two treatment-related SAEs were reported during the trial (1 each with revefenacin 175 μg and tiotropium). Antimuscarinic events were less frequent with revefenacin than tiotropium. More patients in the revefenacin 175 μg than the tiotropium group discontinued treatment because of AEs (12% vs 9%, respectively).

Cardiovascular Safety

Cardiovascular disease, including potentially life-threatening arrhythmias, is a well-recognized comorbidity in patients with COPD.⁴¹ Revefenacin shows limited inhibition of human ether-à-go-go (hERG) gene-encoded ion channels and is therefore predicted to have a low potential for major adverse cardiovascular events (MACEs) (Theravance Biopharma US, Inc., data on file). This was demonstrated in clinical trials of up to 52 weeks, which showed no increase in the risk of MACE with revefenacin treatment.⁴²

The clinical events committee adjudicated only 1 MACE in the revefenacin 175- μg group in the replicate 12-week studies, and this was considered unrelated to treatment.⁴² In the 52-week study, only 1 of the 10 MACEs reported in the revefenacin 175- μg group (atrial fibrillation) was appraised as possibly or probably related to treatment.⁴²

Efficacy And Safety Conclusions

Once-daily revefenacin, delivered via standard jet nebulizer at a dose of 175 μg to patients with moderate to very severe COPD, led to statistically and clinically significant improvements in bronchodilation (trough FEV₁) from baseline. The

Table 3 Incidence (n, %) Of Treatment-Emergent AEs Reported In $\geq 2\%$ Patients^a Receiving Revefenacin 175 μg Once Daily In Phase II And III Clinical Trials

	Quinn et al 2018 ²⁵ (N=37)	Pudi et al 2017 ²⁷ (N=71)	Ferguson et al 2019 ²⁸		Donohue et al 2019 ²⁹ (N=335)
			Study 0126 (N=198)	Study 0127 (N=197)	
Study design	7-day, 5-way crossover, multidose Phase II study	28-day, dose-ranging Phase II study	12-week, replicate Phase III studies		52-week, randomized Phase III safety study
Any AE	17 (45.9)	22 (31.0)	101 (51.0)	102 (51.8)	242 (72.2)
SAEs	0	2 (2.8)	10 (5.1)	5 (2.5)	43 (12.8)
AEs leading to drug interruption or discontinuation	1 (2.7)	5 (7.0)	-	-	41 (12.2)
Antimuscarinic effects	0	0	4 (2.0)	-	7 (2.1)
Headache	4 (10.8)	-	8 (4.0)	8 (4.1)	13 (3.9)
Dyspnea	2 (5.4)	3 (4.2)	4 (2.0)	8 (4.1)	13 (3.9)
Cough	2 (5.4)	3 (4.2)	7 (3.5)	10 (5.1)	25 (7.5)
COPD exacerbation [as SAE]	-	-	21 (10.6) [4 (2.0)]	21 (10.7) -	73 (21.8) [8 (2.4)]
Pneumonia [as SAE]	-	-	-	-	[1 (0.3)]
Back pain	1 (2.7)	2 (2.8)	-	7 (3.6)	-
Oropharyngeal pain	2 (5.4)	-	4 (2.0)	-	-
Hypertension	-	-	-	4 (2.0)	-
Dizziness	-	-	-	4 (2.0)	-
Upper respiratory tract infection	-	-	-	10 (5.1)	20 (6.0)
Urinary tract infection	-	-	-	-	11 (3.3)
Nasopharyngitis	0	-	6 (3.0)	9 (4.6)	26 (7.8)
Bronchitis	-	-	-	-	17 (5.1)
Sinusitis	-	-	5 (2.5)	4 (2.0)	-
Rash	2 (5.4)	-	-	-	-
Nausea	1 (2.7)	-	-	-	-
Death	-	-	0	0	1 (0.3)

Note: ^a $\geq 5\%$ in Donohue et al 2019.²⁹

Abbreviations: -, not reported or incidence $< 2\%$; AE, adverse event; SAE, serious adverse event.

benefit was also observed in patients with suboptimal PIFR against the resistance of Diskus DPI and those who had markers of more severe disease. Revefenacin was well tolerated and, consistent with its lung-selective design, led to a low (placebo-level) incidence of systemic antimuscarinic

AEs. Revefenacin treatment was not associated with an increased risk for MACEs. Additionally, patient-reported outcome data suggest that revefenacin may improve patients' subjective respiratory health, but further studies are needed to clarify whether these improvements are clinically significant.

Discussion

Nebulized bronchodilator treatment offers patients with COPD and cognitive or physical limitations, and those experiencing COPD exacerbations, a simpler medication delivery that avoids the need for manual dexterity, strength, or complex hand-breath coordination. As technology advances, quieter, more portable, and increasingly efficient nebulizer models are becoming available. The advent of adaptive aerosol delivery, which works in concert with the patient's breathing pattern, continues to improve the reliability and precision of dosing, improving dyspnea and fatigue.^{16,43}

The structural and pharmacological design of revefenacin supports once-daily dosing and is associated with limited systemic exposure, thereby reducing the potential for AEs associated with systemic drug distribution.^{22,25,27} Data generated in 2 replicate 12-week Phase III studies indicate that revefenacin 175 µg once daily, the dose approved by the FDA in 2018 for maintenance COPD treatment,¹⁸ has a rapid onset of action and sustained efficacy, measured using peak and/or trough FEV₁ versus placebo.²⁸ The data presented provide evidence that the bronchodilator effects associated with this dose meet the minimally clinically important difference threshold of FEV₁ ≥100 mL, including in patients with markers of more severe disease, and may reduce the need for rescue medication in some patients.^{28,34} These data are consistent with studies that evaluated the efficacy and rescue medication use in patients with COPD who received tiotropium via HandiHaler. The results demonstrated significant improvements in FEV₁⁴⁴ and a significant decrease in rescue medication usage in those who received tiotropium versus placebo.^{44,45}

The once-daily LAMA tiotropium and twice-daily LABAs salmeterol and formoterol are the most commonly prescribed single bronchodilators for maintenance therapy in patients with COPD and are delivered using handheld inhalers.^{46–48} Until recently, two LABAs (arformoterol and formoterol) and the anticholinergic agent glycopyrrolate were the only long-acting bronchodilators available for nebulized delivery, and all require twice-daily administration.^{49–51} Furthermore, a number of clinical trials have been completed to assess a new nebulized bronchodilator, RPL554, for the maintenance treatment of patients with COPD (NCT02307162, NCT03673670, NCT04027439, NCT03443414, NCT02542254, NCT03028142). RPL554 works by inhibiting the phosphodiesterase 3 and phosphodiesterase 4

enzymes. A nebulized ICS (budesonide) is available for the treatment of patients with asthma.⁵² Other nebulized ICSs (beclomethasone dipropionate, flunisolide) have been used for the treatment of patients with COPD exacerbations.^{53,54} The FDA approved the first commercially available nebulized LAMA, a glycopyrrolate (SUN-101/eFlow[®]; Sunovion, Marlborough, MA, USA), in 2017 for twice-daily maintenance treatment of patients with COPD, based on the Glycopyrrolate for Obstructive Lung Disease via Electronic Nebulizer (GOLDEN) Phase III trial program.^{55,56} Glycopyrrolate can only be administered by the eFlow[®] closed system vibrating membrane nebulizer, whereas revefenacin can be used with a standard jet nebulizer with a mouthpiece connected to an air compressor.^{18,49} As the only LAMA approved for once-daily nebulized delivery, revefenacin may have benefits in patients who need or prefer nebulized treatment, and in those for whom reduced dosing frequency is important. The ability to administer revefenacin using a standard jet nebulizer instead of a proprietary mesh nebulizer may be an additional benefit.

Revefenacin for nebulization may play an important role during recovery after COPD exacerbations when patients commonly have reduced PIFR and/or limited ability to use a handheld device, although further studies are needed to test this hypothesis. Evidence from studies in patients with moderate to very severe COPD and/or suboptimal PIFR suggests that revefenacin may be as effective as tiotropium in patients with suboptimal PIFR and significantly more effective than tiotropium in patients with suboptimal PIFR and severe airflow limitation.³⁰ The design of revefenacin also results in fewer antimuscarinic AEs than with tiotropium.²² Furthermore, nebulized drug delivery is generally preferred by patients discharged after a hospitalization, who have shown consistent difficulty using handheld inhalers and who have impaired manual dexterity, impaired cognition, or chronic muscle weakness.⁵ A higher percentage of patients have previously reported that they generally prefer nebulizers versus inhalers.¹⁴

The safety and efficacy of revefenacin are also being tested sequentially and in combination with formoterol via a standard jet nebulizer in patients with moderate to very severe COPD (NCT0353817). This is of importance to patients who continue to have exacerbations on bronchodilator monotherapy. Additional patient-reported outcomes data will also be important in establishing the value of this once-daily nebulized treatment in patients with moderate to very severe COPD.

Conclusion

Once-daily revefenacin 175 µg for nebulization was well tolerated and improved bronchodilation in patients with moderate to very severe COPD, including those with the markers of more severe disease, without evidence of cardiovascular toxicity. This novel bronchoselective LAMA offers patients with COPD who require or prefer nebulized therapy an effective, convenient once-daily treatment option with low risk of adverse effects.

Abbreviations

AE, adverse event; BPC, 4-piperidyl biphenyl-2-ylcarbamate; DPI, dry powder inhaler; GOLDEN, Glycopyrrolate for Obstructive Lung Disease via Electronic Nebulizer; ICS, inhaled corticosteroid; hERG, human ether-à-go-go; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LS, least squares; MACE, major adverse cardiovascular event; MDI, metered-dose inhaler; OTE, overall treatment effect; PIFR, peak inspiratory flow rate; REV, revefenacin; SAE, serious adverse event; SGRQ, St George's Respiratory Questionnaire; SMI, soft-mist inhaler; TIO, tiotropium.

Data Sharing Statement

Theravance Biopharma (and its affiliates) will not be sharing individual deidentified participant data or other relevant study documents.

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Disclosure

JFD is a consultant and advisory committee member for Theravance Biopharma US, Inc., AstraZeneca, GSK, Novartis Pharmaceuticals, Mylan Inc., and Sunovion Pharmaceuticals.

DAM has served on advisory boards for AstraZeneca, Boehringer Ingelheim, GSK, Grifols, Sunovion Pharmaceuticals, Theravance Biopharma US, Inc., and Trevi, and is on the

speaker's bureau for AstraZeneca, Boehringer Ingelheim, and Sunovion Pharmaceuticals.

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