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ORIGINAL RESEARCH

Revefenacin Area Under the Curve Spirometry in Patients with Moderate to Very Severe COPD

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Purpose: Several lung function endpoints are utilized in clinical trials of inhaled bronchodilators for chronic obstructive pulmonary disease (COPD). Trough forced expiratory volume in 1 second (FEV_1) is a commonly reported endpoint in COPD trials and can be complemented by area under the FEV_1 vs time curve (FEV_1 AUC), which provides information on duration and consistency of bronchodilation over a dosing interval. Revefenacin, a once-daily bronchodilator, significantly improved lung function in patients with COPD when measured by trough FEV_1 in two replicate Phase 3 trials. Here, we report an FEV_1 AUC substudy using data from these trials.

Patients and Methods: This post hoc analysis examined substudy data from 12-week replicate Phase 3 trials (NCT02459080/NCT02512510); patients with moderate to very severe COPD were randomized 1:1 to revefenacin 175 µg or placebo once daily. The substudy patients had FEV_1 $AUC_{0–2h}$ assessed on Day 1, and those who continued to Day 84 also underwent 24-hour serial spirometry postdose where FEV_1 $AUC_{0–2h}$, $AUC_{0–12h}$, AUC_{12-24h}, and $AUC_{0–24h}$ were evaluated.

Results: Fifty and 47 patients who received revefenacin and placebo underwent 24-hour serial spirometry; most baseline characteristics were aligned between groups. At Day 84 postdose, revefenacin demonstrated sustained improvements in bronchodilation over 24 hours; differences in least squares mean vs placebo were 282, 220, 205, and 212 mL for FEV_1 $AUC_{0–2h}$, $AUC_{0–12h}$, $AUC_{12–24h}$, and $AUC_{0–24h}$ (all P <0.001), respectively.

Conclusion: This substudy analysis supplements previous findings that revefenacin provides sustained bronchodilation over 24 hours. Assessing additional complementary COPD clinical trial endpoints can help clinicians make treatment decisions.

Keywords: Bronchodilators, long-acting muscarinic antagonist, outcome measures, spirometry, forced expiratory volume in 1 second

Introduction

Patients with chronic obstructive pulmonary disease (COPD) rely on bronchodilation to relieve their symptoms of dyspnea, cough, and mucus hypersecretion and to improve lung function.[1–4] In addition to smoking cessation, long-acting muscarinic antagonist (LAMA) and/or long-acting beta-agonist (LABA) bronchodilators administered alone or in combination, with or without inhaled corticosteroids (ICS), are important treatment options for patients with COPD.[3,5,6]

Historically, a majority of clinical trials in COPD examining long-acting bronchodilator therapies have used trough forced expiratory volume in 1 second (FEV_1) as the primary efficacy endpoint when assessing lung function.[7–10] Other endpoints, such as area under the FEV_1 vs time curve (FEV_1 AUC) and peak FEV_1, are typically included as secondary or exploratory endpoints. For example, all Phase 3 trials assessing once-daily LAMAs for the treatment of COPD have reported trough FEV_1 as a lung function primary endpoint,[11–13] while FEV_1 AUC has been reported as a secondary or exploratory endpoint in a limited number of other Phase 3 trials.[14–20] While no minimal clinically important difference (MCID) has been established for FEV_1 AUC over any particular interval postdose, the MCID for trough FEV_1 is defined as 100 mL by the American Thoracic Society (ATS)/European Respiratory Society guidelines.[8,21,22] The effect of treatment on trough FEV_1 is assumed to be at its nadir immediately before the next dose. When the trough FEV_1 exceeds the MCID, it is

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inferred that the effect is greater than that threshold throughout the entire dosing period. FEV_1 AUC can provide supplemental information on the magnitude of a response over a wider dosing interval vs trough FEV_1 (and therefore may be less sensitive to outliers compared with other measures of lung function).[23] Therefore, the combination of lung function endpoints is valuable to comprehensively assess the extent of bronchodilation over the interval between doses.

Revefenacin is a novel, once-daily LAMA approved by the US Food and Drug Administration (FDA) in 2018 for the maintenance treatment of patients with COPD.[1,24] In two replicate Phase 3 trials, revefenacin significantly improved trough FEV_1 at Day 85 (Trial 0126: 146 mL and Trial 0127: 147 mL) and peak FEV_1 (pooled across both trials: 130 mL) vs placebo (all P <0.001) in patients with moderate to very severe COPD.[11] Furthermore, revefenacin improved health-related quality of life parameters in these patients.[25] The safety profile of revefenacin may be attributed to its lung selectivity, as well as minimal systemic drug exposure.[1,26] Revefenacin Phase 3 FEV_1 AUC data have not been reported previously given the strong trough FEV_1 values observed in the Phase 3 trial program.[11,27] The purpose of this post hoc analysis is to report FEV_1 AUC revefenacin data from the two replicate Phase 3 trials to more fully define its 24-hour bronchodilatory profile.

Material and Methods

Analysis Design and Patient Population

This post hoc analysis examined data from two 12-week, randomized, double-blind, placebo-controlled replicate Phase 3 trials (Trials 0126 [NCT02459080] and 0127 [NCT02512510]).[11] Detailed methods of these trials have been published previously.[11] Briefly, these trials included adults ≥40 years old with documented moderate to very severe COPD, who had a current or past smoking history of ≥10 pack-years, and were randomized 1:1:1 to receive revefenacin 88 µg, revefenacin 175 µg, or placebo administered once daily in the morning by a standard jet nebulizer (PARI LC Sprint) for 12 weeks.[11] The prespecified primary efficacy endpoint was change from baseline in trough FEV_1 on Day 85.[11] Peak FEV_1 on Day 1 was a secondary endpoint[11] and FEV_1 AUC from 0 to 2 hours (FEV_1 $AUC_{0–2h}$) on Days 1, 15, 29, 57, and 84 was a prespecified exploratory endpoint. While both revefenacin 88 µg and 175 µg doses were investigated in these trials, the post hoc analysis reported herein focused only on the 175 µg dose as this is the dose approved by the FDA.[24]

On Day 84, a subgroup of patients at preselected sites underwent 24-hour serial spirometry following the last dose of trial medication on Day 84 in addition to their standard assessments. Patients included in this substudy provided sufficient spirometry serial assessments for FEV_1 AUC from 0 to 12 hours (FEV_1 $AUC_{0–12h}$) to be calculated. Most patients also provided sufficient assessments for FEV_1 AUC from 12 to 24 hours (FEV_1 $AUC_{12–24h}$) and FEV_1 AUC from 0 to 24 hours (FEV_1 $AUC_{0–24h}$) to be calculated.

Data Collection and Assessments

FEV_1 was assessed by spirometry using a flow-volume loop for all respiratory flow measurements. Trough FEV_1 and 0- to 2-hour postdose (peak) serial spirometry were conducted at Days 1, 15, 29, 57, and 84 (trough FEV_1 was also assessed on Day 85). Serial spirometry over 24 hours in the subgroup of patients started on Day 84 postdose. In these patients, spirometry was performed at 45 and 15 minutes predose and at 5, 15, and 30 minutes, and 1, 2, 4, 6, 8, 10, 12, 15, 21, 22, 23.25, and 23.75 hours postdose (the time window for spirometry was ±5 minutes for each nominal time point up to the 2-hour time point and a ±10 minute window for each of the later time points). Some patients were unable (based on advisement that it was clinically inappropriate) or unwilling to perform spirometry at every time point in the 24-hour period. Spirometry was performed according to techniques described in the Spirometry Manual, which reflects the ATS Guidelines for Spirometry.[28] A central spirometry vendor (CompleWare Corporation) was used to provide standardized training on spirometry, qualification of the spirometry technician, and quality control of the spirometry throughout the trials. Serial FEV_1 AUC data were collected separately from Trials 0126 and 0127 and then pooled together for this post hoc analysis.

Statistical Analysis

Spirometry endpoints were analyzed by fitting mixed-effects repeated-measures models (modeling details are provided in the Supplementary Materials). A patient must have had an available beginning, in-between, and end time point assessment for the calculation of AUCs (if any of these were missing, the AUC was set to missing). In addition, FEV_1 $AUC_{0–24h}$ was

set to missing if either FEV_1 $AUC_{0–12h}$ or FEV_1 $AUC_{12–24h}$ was missing. AUCs were calculated using the trapezoidal rule and converted to weighted means for analysis by dividing by interval duration (2, 12, or 24 hours). All statistical analyses were performed using base SAS software version 9.4 and SAS/STAT software version 15.1 (SAS Institute). *P*-values presented for these post hoc analyses were unadjusted for multiple testing and were nominal.

Results

Patient Population and Baseline Demographics and Characteristics

A total of 97 patients (50 who received revefenacin 175 µg and 47 who received placebo) from the 2 trials were included in the Day 84 24-hour serial spirometry substudy analysis set. Baseline demographics and characteristics of patients included in the substudy analysis set were similar and generally well balanced between the revefenacin and placebo arms (Table 1). Most common comorbid conditions included hypertension (60%), gastroesophageal reflux disease (53%), and depression (35%).

Table 1 Baseline Demographics and Clinical Characteristics

	Revefenacin 175 µg (n = 50)	**Placebo (n = 47)**
Age, years	64 (9)	64 (8)
Male, n (%)	26 (52)	18 (38)
Race, White, n (%)	42 (84)	39 (83)
BMI, kg/m^2	29 (7)	29 (7)
Current Smoker, n (%)	24 (48)	25 (53)
Pack-Years, median	42	45
Concurrent ICS/LABA Use, n (%)	22 (44)	11 (23)
Post-ipratropium % Predicted FEV_1	56 (13)	54 (12)
Post-ipratropium FEV_1 to FVC Ratio	0.53 (0.08)	0.52 (0.10)
FEV_1, L	1.31 (0.45)	1.25 (0.38)
Patients With mMRC ≥2, n (%)	28 (56)	26 (55)
Patients With CAT ≥10, n (%)	45 (90)	43 (91)
Exacerbations in the Prior Year, n (%)		
0	37 (74)	34 (72)
1	12 (24)	10 (21)
≥2	1 (2)	3 (6)
GOLD Airflow Limit Category, n (%)		
≥50, <80%	34 (68)	32 (68)
≥30%, <50%	13 (26)	14 (30)
<30%	3 (6)	1 (2)

Notes: Data are mean (standard deviation) unless otherwise specified. The substudy analysis set was defined as all patients for whom Day 84 weighted mean FEV_1 0–12 hours could be calculated. GOLD airflow limit category is based on post-ipratropium % predicted FEV_1.

Abbreviations: BMI, body mass index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; mMRC, Modified Medical Research Council Dyspnea Scale.

The median number of years smoked was 41, and the median pack-years was 42. A higher proportion of patients who received revefenacin were male and were on a concurrent ICS/LABA regimen. ICS/LABA regimens included budesonide and formoterol fumarate, fluticasone propionate and salmeterol, mometasone furoate and formoterol fumarate, or fluticasone furoate and vilanterol, all at their FDA-approved doses. An ad hoc sensitivity analysis comparing FEV_1 AUC results adjusted and not adjusted for sex and concurrent ICS/LABA showed that the net effect of these imbalances was minimal.

Lung Function Efficacy

This post hoc analysis of pooled substudy data from Trials 0126 and 0127 showed that revefenacin improved lung function in patients with moderate to very severe COPD when assessed by FEV_1 AUC. In these patients, bronchodilation onset with revefenacin was rapid with a least squares (LS) mean difference (95% confidence interval [CI]) of 145 mL (99, 191; P <0.001) between revefenacin 175 µg vs placebo at 15 minutes postdose on Day 1, and this difference was maintained through 2 hours postdose; Figure 1; Supplementary Table 1). At Day 84, improvements in bronchodilation were sustained over 24 hours in the revefenacin treated arm vs placebo (Figure 2), with LS mean differences (95% CI) between revefenacin 175 µg vs placebo being 282 mL (181, 383) for FEV_1 $AUC_{0–2h}$, 220 mL (134, 305) for FEV_1

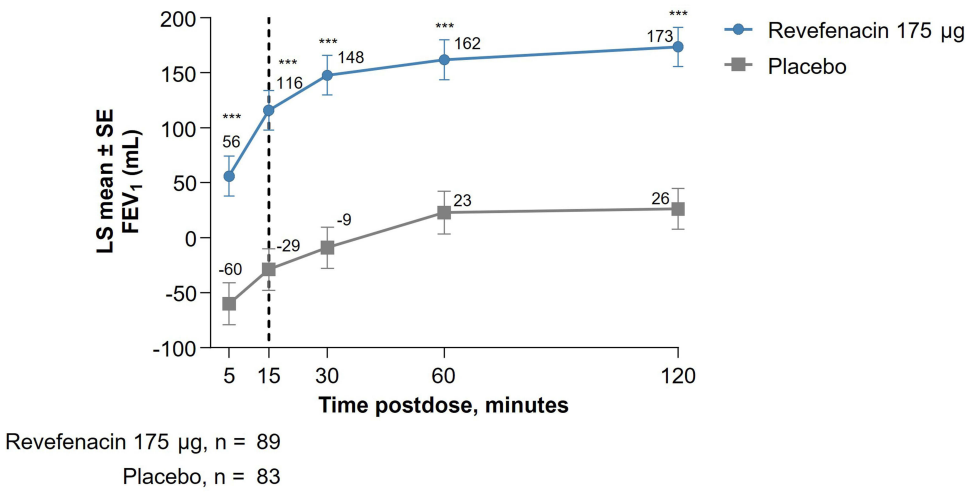

Figure 1 Short-Term (0 to 2 Hours) Increase in FEV_1 of Revefenacin at Day 1.
Notes: ***P<0.001 vs placebo. The vertical line signifies time point of bronchodilation onset with revefenacin. LS mean values at each time point are shown. The number of patients in each group at 15 minutes postdose is reported.
Abbreviations: FEV_1, forced expiratory volume at 1 second; LS, least squares; SE, standard error.

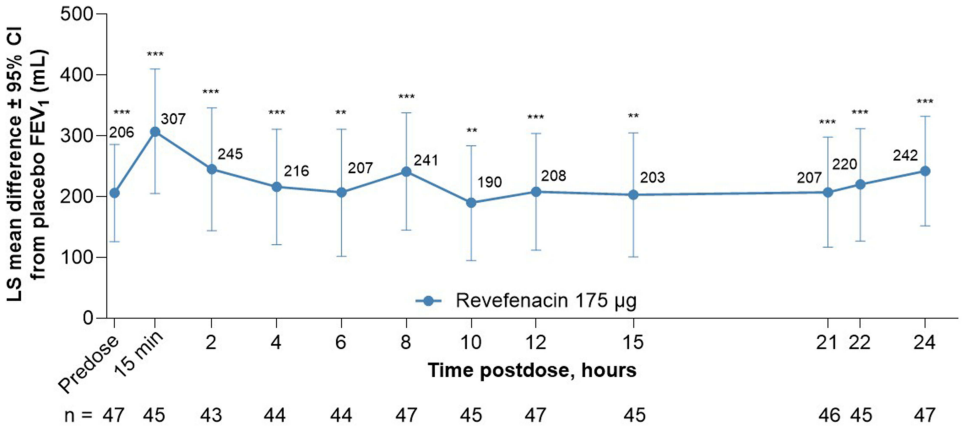

Figure 2 LS Mean Difference of Revefenacin from Placebo in Serial Spirometry Over 24 Hours at Day 84.
Notes: ***P<0.0001 vs placebo. **P<0.001 vs placebo. LS mean differences from placebo values at each time point are shown.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume at 1 second; LS, least squares; min, minute.

Table 2 Weighted Mean FEV_1 Lung Function Endpoints of Revefenacin from Placebo at Day 84

Parameters	Revefenacin 175 µg	Placebo
FEV_1 $AUC_{0–2h}$ (mL)		
Evaluable n	45	42
LS Mean Difference (SE)	282 (51)	–
95% CI for LS Mean Difference (SE)	(181, 383)	–
P-value	<0.001	–
FEV_1 $AUC_{0–12h}$ (mL)		
Evaluable n	50	47
LS Mean Difference (SE)	220 (43)	–
95% CI for LS Mean Difference (SE)	(134, 305)	–
P-value	<0.001	–
FEV_1 $AUC_{12–24h}$ (mL)		
Evaluable n	48	47
LS Mean Difference (SE)	205 (43)	–
95% CI for LS Mean Difference (SE)	(119, 291)	–
P-value	<0.001	–
FEV_1 $AUC_{0–24h}$ (mL)		
Evaluable n	48	47
LS Mean Difference (SE)	212 (42)	–
95% CI for LS Mean Difference (SE)	(129, 296)	–
P-value	<0.001	–
Peak FEV_1 0–2 hours (mL)		
Evaluable n	50	47
LS Mean Difference (SE)	264 (46)	–
95% CI for LS Mean Difference (SE)	(172, 355)	–
P-value	<0.001	–
Trough FEV_1 (mL)		
Evaluable n	50	47
LS Mean Difference (SE)	197 (38)	–
95% CI for LS Mean Difference (SE)	(122, 273)	–
P-value	<0.001	–

Notes: Evaluable n is the number of patients included in the analysis.

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume at 1 second; FEV_1 AUC, area under the FEV_1 vs time curve; FEV_1 $AUC_{0\text{-}2h}$, FEV_1 AUC from 0 to 2 hours; FEV_1 $AUC_{0\text{-}12h}$, FEV_1 AUC from 0 to 12 hours; FEV_1 $AUC_{0\text{-}24h}$, FEV_1 AUC from 0 to 24 hours; FEV_1 $AUC_{12\text{-}24h}$, FEV_1 AUC from 12 to 24 hours; LS, least squares; SE, standard error.

$AUC_{0–12h}$, 205 mL (119, 291) for FEV_1 $AUC_{12–24h}$, and 212 mL (129, 296) for FEV_1 $AUC_{0–24h}$ (all P <0.001; Table 2). Differences in LS mean (95% CI) in trough and peak FEV_1 at Day 84 between revefenacin 175 µg vs placebo were 197 (122, 273) mL and 264 (172, 355) mL (both P <0.001), respectively.

Discussion

When assessing FEV_1 AUC in this post hoc analysis from two Phase 3 trials where patients underwent 24-hour serial spirometry, sustained and robust bronchodilation at Day 84 was observed over 24 hours postdose in patients who received revefenacin, reflected by a FEV_1 $AUC_{0–24h}$ LS mean difference vs placebo of 212 mL. Furthermore, improvements in lung function also favored revefenacin vs placebo when assessed by FEV_1 $AUC_{0–2h}$, $AUC_{0–12h}$, and $AUC_{12–24h}$, demonstrating that the action of revefenacin is persistent regardless of the observed time interval. In addition, within 15 minutes, revefenacin exhibited an effect on mean FEV_1 which with approximately 97.5% confidence exceeded the MCID of 100 mL (LS mean difference vs placebo [95% CI] of 145 [99, 191] mL).[8,21,22]

FEV_1 AUC is normalized as a time-adjusted calculation (ie, by dividing the observed FEV_1 AUC value by the interval duration to obtain a time-normalized value).[29,30] The time-adjustment enables a relative comparison of bronchodilator effect across various postdose intervals. In this analysis, the Day 84 LS mean FEV_1 $AUC_{0–12h}$, FEV_1 $AUC_{12–24h}$, and FEV_1 $AUC_{0–24h}$ improvements for revefenacin over placebo were remarkably similar, demonstrating that the consistent and sustained effect revefenacin has during the daytime was carried over through the nighttime, and indeed over the full 24 hours postdose. In this manner, FEV_1 AUC analyses have utility in describing the profile of long-acting bronchodilators. Indeed, when combined with the early and late assessments of peak and trough FEV_1, respectively, a full-time profile of a bronchodilator's effectiveness over the dosing interval is achieved. Thus, each of these lung function parameters play a role in the reporting of spirometry outcomes from bronchodilators in clinical trials.

According to the FDA, if the goal of a trial is to reduce airflow obstruction, the primary efficacy endpoint should be the change in postdose FEV_1 for a bronchodilator.[31] For bronchodilators, serial postdose FEV_1 assessments should be performed to characterize a time profile curve to estimate the time to and duration of the effect.[31] In this context, the FEV_1 AUC measure would appear to have utility in characterizing the time-averaged patient response. Nevertheless, in recent Phase 3 registrational trials of new COPD agents, FEV_1 AUC has been used less frequently than trough FEV_1 as the primary efficacy endpoint.[11,12,32] Trough FEV_1, which measures the extent of bronchodilation at the end of the dosing period[33] (ie, 24 hours for once-daily drugs and 12 hours for twice-daily drugs), is a highly sensitive measure of a drug's duration, and has effectively distinguished agents appropriate for once-daily dosing vs those more suited for twice-daily administration (Table 3). A placebo-adjusted difference in trough FEV_1 of 100 mL or greater vs baseline (predose) is considered an MCID.[8,21,22] Changes in trough FEV_1 of 100 mL have been correlated with fewer relapses following COPD exacerbations.[8,21,22,34] Given the above guidance and findings, trough FEV_1 became the primary lung function endpoint reported in long-acting bronchodilator clinical trials as this reflects lung function improvements over 12 to 24 hours as well as morning lung function when patients awaken.[8]

Despite the emergence of trough FEV_1 as a predominant measure for bronchodilator effect, FEV_1 AUC can still provide valuable complementary information as illustrated by revefenacin data in this post hoc analysis.[6,8] Despite limitations, each time interval endpoint provides useful information regarding the effect profile (Table 3). Different measures of FEV_1 can vary on the same day and be susceptible to diurnal changes (spirometry parameters tend to be lower in the morning vs evening).[8,36,37] Assessing bronchodilation over a 24 hour period (FEV_1 $AUC_{0–24h}$) obviously aligns best with once-daily dosing, and assessments such as FEV_1 $AUC_{0–12h}$ can examine daytime treatment effects. Therefore, with time averaging, this allows the comparison of effect from a once-daily drug dosed in the first part of the day vs the entire 24-hour period. Time averaging may also enable comparisons of drugs dosed once vs twice daily. Finally, FEV_1 $AUC_{12–24h}$ can assess the efficacy of a drug dosed once daily during the nighttime period[35] and show contrast to daytime FEV_1 $AUC_{0–12h}$.

A principal shortcoming of FEV_1 AUC is the potential to mask drastic differences between peak and trough measurements. For example, similar FEV_1 $AUC_{0–12h}$ values cannot distinguish between a modest yet consistent bronchodilation over a 12-hour interval vs a high peak-to-trough profile where a robust acute effect wanes to a low, clinically ineffective level at the 12-hour trough. This scenario supports the importance of reporting peak and trough

Table 3 Lung Function Endpoints to Assess Bronchodilator Efficacy in COPD

Endpoint	Description	Limitations
Peak FEV_1	• Measures the maximum degree of bronchodilation postdose • Often defined as within 2 to 4 hours postdose[24,32,35]	• Does not give information on the duration of bronchodilation
FEV_1 AUC (General)	• Provides a time-weighted measure of bronchodilation over a time interval • Based on serial spirometry at multiple points during a time interval	• Limited information on the consistency of bronchodilation from peak (maximum) to trough (end of dose interval) measures • Validity depends upon the number of FEV_1 measurements over a time interval • Does not inform peak effect • Does not inform trough effect or duration of bronchodilation
FEV_1 $AUC_{0–2h}$	• Measures acute bronchodilation over first 2 hours postdose	
FEV_1 $AUC_{0–12h}$	• Measures bronchodilation over first 12 hours postdose (often during daytime while patient is most active)[35] • A common endpoint for drugs dosed twice daily	
FEV_1 $AUC_{12–24h}$	• Measures bronchodilation during nighttime[35] • Useful measure for drugs administered once daily combined with FEV_1 AUC_{0-12h} to assess consistency of bronchodilation during daytime vs nighttime	
FEV_1 $AUC_{0–24h}$	• Measures bronchodilation over 24 hours postdose • Useful measure for drugs dosed once daily	
Trough FEV_1	• Measures bronchodilation at the end of the dosing period (ie, 24 hours for once-daily drug; 12 hours for twice-daily drug) • Differences in trough FEV_1 of 100 mL or greater are considered highly sensitive to a robust duration of effect (ie, MCID = 100 mL)[8,21,22]	• Typically assessed within a narrow window of time postdose (ie, at or near 24 hours postdose for drugs administered once daily)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FEV_1 AUC, area under the FEV_1 vs time curve; MCID, minimal clinically important difference.

FEV_1 alongside FEV_1 AUC values from bronchodilators in clinical trials. Each lung function endpoint has its own strengths and limitations. In practice, all of the above lung function parameters are recommended to assess a drug's full bronchodilation profile. Therefore, it is recommended that clinicians utilize multiple lung function endpoints in order to better understand the potential bronchodilation of a patient during the dosing interval.

Limitations with this post hoc analysis should be noted. The principal limitation was the low number of patients who underwent serial spirometry in the substudy (approximately 50 per treatment group), yielding imprecise treatment effect estimates; nonetheless, the 95% CI lower limits exceeded 100 mL at 30 minutes and 2 hours postdose.

Conclusion

Revefenacin, an approved LAMA administered once daily for the maintenance treatment of moderate to very severe COPD, demonstrated robust, stable, and sustained improvements in lung function compared with placebo over 24 hours as measured by FEV_1 AUC. These FEV_1 AUC substudy results support previous peak and trough FEV_1 findings[11] indicating a consistent revefenacin response that was sustained for the entire 24-hour postdose period. Lung function endpoints used in clinical trials for COPD have their benefits and limitations. Combining peak and trough FEV_1 with time-averaged FEV_1 AUC measures from clinical trials allows for full profiling of a bronchodilator's efficacy response. Clinicians should be aware of the information that each lung function endpoint is conveying, and that the synthesis of multiple lung function endpoints is optimal to assess the consistency of bronchodilation that a patient may receive.

Abbreviations

COPD, chronic obstructive pulmonary disorder; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta-agonist; ICS, inhaled corticosteroids; FEV_1, forced expiratory volume in 1 second; FEV_1 AUC, area under the FEV_1 vs time curve; MCID, minimal clinically important difference; ATS, American Thoracic Society; FDA, US Food and Drug Administration; FEV_1 $AUC_{0\text{-}2h}$, FEV_1 AUC from 0 to 2 hours; FEV_1 $AUC_{0\text{-}12h}$, FEV_1 AUC from 0 to 12 hours; FEV_1 $AUC_{12\text{-}24h}$, FEV_1 AUC from 12 to 24 hours; FEV_1 $AUC_{0\text{-}24h}$, FEV_1 AUC from 0 to 24 hours; LS, least squares; CI, confidence interval; PRO, patient-reported outcome.

Data Sharing Statement

Theravance Biopharma (and its affiliates) will not be sharing individual deidentified patient data or other relevant trial data documents at this time.

Ethics Approval

All patients provided written informed consent and the protocol was reviewed and approved by an institutional review board (Quorum Review IRB, Seattle, Washington). This study was conducted according to the principles of Good Clinical Practice, following the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline and the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Corey J. Witenko is a current employee of Theravance Biopharma US, Inc. and owns stock. Melinda K. Lacy is a current employee of Theravance Biopharma US, Inc. and owns stock. Ann W. Olmsted is a paid consultant for Theravance Biopharma US, Inc. and owns stock. Edmund J. Moran is a current employee of Theravance Biopharma US, Inc. and owns stock. In addition, Edmund J. Moran has a patent US11484531 licensed to Viatris. Donald A. Mahler serves on the advisory boards of AstraZeneca, Boehringer Ingelheim, Theravance, Verona, and Viatris and receives royalties from pharmaceutical companies (Elpen Pharmaceutical Company and University of Aberdeen) for the use of baseline dyspnea index/transition dyspnea index. The authors report no other conflicts of interest in this work.

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