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COPD Exacerbations in the Phase 3 Revefenacin Clinical Trial Program

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INTRODUCTION

- Revefenacin is a novel once-daily (QD), lung-selective, long-acting muscarinic antagonist (LAMA) under development for the nebulized long-term maintenance treatment of chronic obstructive pulmonary disease (COPD)[1]
- Increased trough forced expiratory volume in 1 second was demonstrated of nebulized revefenacin 88 µg and 175 µg QD in patients with moderate to very severe COPD over 12 weeks[2]
- Safety and tolerability were demonstrated of nebulized revefenacin 88 µg and 175 µg QD for up to 52 weeks in patients with moderate to very severe stable COPD[3]

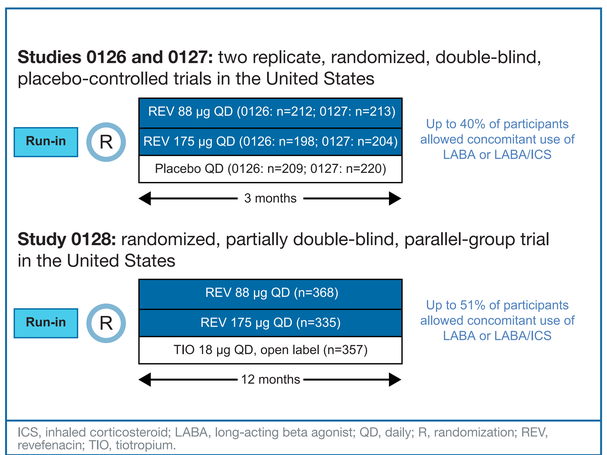
OBJECTIVE

- This was a *post hoc* analysis to assess COPD exacerbation data associated with revefenacin 88 µg and 175 µg QD in patients with moderate to very severe COPD participating in a phase 3 revefenacin clinical trial program

METHODS

- These were phase 3 studies of patients with moderate to very severe COPD administered revefenacin 88 µg and 175 µg QD via standard jet nebulizer. The study designs for studies 0126 (NCT02459080), 0127 (NCT02512510), and 0128 (NCT02518139) are shown in **Figure 1**

Figure 1. Study designs

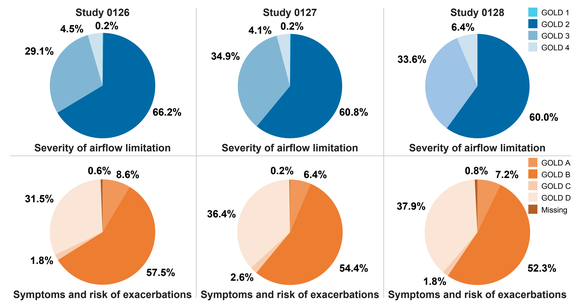


ICS, inhaled corticosteroid; LABA, long-acting beta agonist; QD, daily; R, randomization; REV, revefenacin; TIO, tiotropium.

RESULTS

- Participants had moderate to very severe COPD with similar percentages of patients with exacerbations across all 3 trials (**Figure 2**)

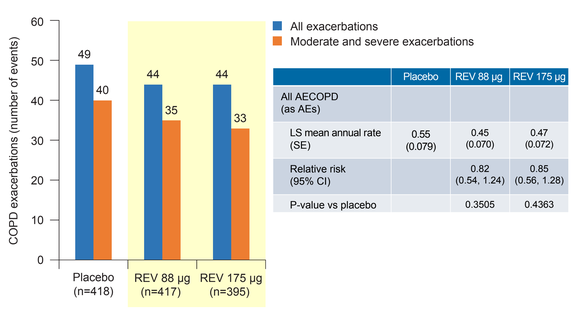
Figure 2. COPD severity, and symptoms and risk of exacerbations



COPD severity of participants in Studies 0126, 0127, and 0128 was determined according to severity of airflow limitation (upper panels) and symptoms and risk of exacerbations (lower panels) using 2011 GOLD criteria.[4] GOLD severity of airflow limitation: 1 = mild, 2 = moderate, 3 = severe, 4 = very severe; GOLD symptoms and risk of exacerbations: A = less symptoms, low risk; B = more symptoms, low risk; C = less symptoms, high risk; D = more symptoms, high risk. COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

- Pooled data analysis from Studies 0126 and 0127 (3-month trials) showed revefenacin 88 µg and 175 µg nominally reduced COPD exacerbation relative to placebo (**Figure 3**)

Figure 3. COPD exacerbations. Pooled data analysis from Studies 0126 and 0127

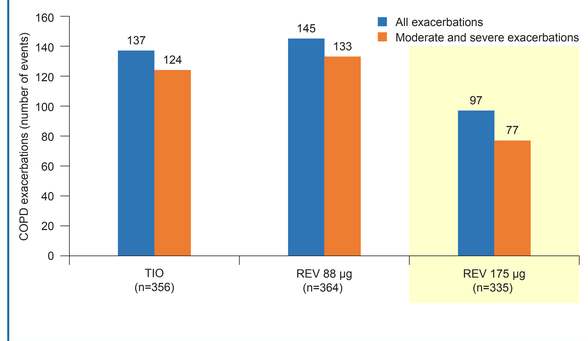


	Placebo	REV 88 µg	REV 175 µg
All AECOPD (as AEs)			
LS mean annual rate (SE)	0.55 (0.079)	0.45 (0.070)	0.47 (0.072)
Relative risk (95% CI)		0.82 (0.54, 1.24)	0.85 (0.56, 1.28)
P-value vs placebo		0.3505	0.4363

AE, adverse event; AECOPED, acute exacerbation of COPD; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LS, least squares; REV, revefenacin; SE, standard error.

- In Study 0128 (12-month trial), revefenacin 175 µg was associated with numerically fewer COPD exacerbations than revefenacin 88 µg and tiotropium 18 µg (**Figure 4**)

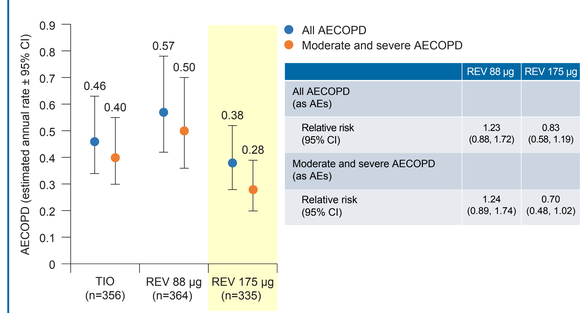
Figure 4. COPD exacerbations in Study 0128



COPD, chronic obstructive pulmonary disease; REV, revefenacin; TIO, tiotropium.

- In Study 0128, the revefenacin 175 µg group had the lowest COPD exacerbation rates (**Figure 5**)
  - Overall exacerbation rates decreased by approximately 17%, and moderate and severe exacerbation rates decreased by approximately 30% relative to tiotropium

Figure 5. Exacerbation rate in Study 0128



	REV 88 µg	REV 175 µg
All AECOPD (as AEs)		
Relative risk (95% CI)	1.23 (0.88, 1.72)	0.83 (0.58, 1.19)
Moderate and severe AECOPD (as AEs)		
Relative risk (95% CI)	1.24 (0.89, 1.74)	0.70 (0.48, 1.02)

AEs, adverse events; AECOPED, acute exacerbation of chronic obstructive pulmonary disease; CI, confidence interval; REV, revefenacin; TIO, tiotropium.

DISCLOSURES

JFD: consultant and advisory committee member for Mylan Inc., Theravance Biopharma US, Inc., and Sunovion Pharmaceuticals.

SS: research support from AstraZeneca and Mylan; advisory committee member, consultant, and/or speaker for Aradigm, AstraZeneca, Bayer Schering Pharma, Boehringer Ingelheim, Cempra, CSL, Behring, GlaxoSmithKline, Merck, Invacare, Pulmonx, Sunovion, and Theravance Biopharma US, Inc.

CNB, EJM, SP, GDC, BH: employees of Theravance Biopharma US, Inc.

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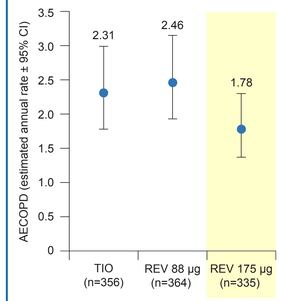
- COPD exacerbations data based on AEs were supported by the Exacerbations in COPD Tool patient-reported outcome measure, confirming that the revefenacin 175 µg group had the lowest COPD exacerbation rates (**Figure 6**)

Figure 6. Study 0128 COPD exacerbations based on the EXACT patient-reported outcome measure



All AECOPD (as EXACT)	REV 88 µg	REV 175 µg
Relative risk (95% CI)	1.07 (0.78, 1.47)	0.77 (0.55, 1.08)

AECOPED, acute exacerbation of COPD; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EXACT, Exacerbations in COPD Tool; REV, revefenacin; TIO, tiotropium.

LIMITATIONS

- The design of the 12-month trial was open label, and thus, differential withdrawal may have biased the results
- The absence of selection for exacerbation-prone patients, small sample sizes, and therefore the lack of statistical power, must be accounted for when interpreting these positive trends

CONCLUSIONS

- Analyses of phase 3 data indicate that revefenacin 175 µg QD for up to 52 weeks was associated with a reduction in COPD exacerbation in patients with moderate to very severe COPD, with revefenacin providing additional benefit over tiotropium
- LAMAs have been shown to have an effect on reducing COPD exacerbations.[5] While the sample size was small, nebulized revefenacin 175 µg QD reduced the frequency of exacerbations similar to other LAMAs in this class

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