Supplemental Material

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

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Methods

Secondary endpoints

OTE trough FEV_1 during the 12-week studies was a key secondary endpoint of Studies 0126 and 0127. The OTE trough FEV_1 is a metric of both the persistence and consistency of the treatment effect over the 12-week treatment duration, placing emphasis on the entire dosing period, as opposed to only the last assessment day, at which point the number of subjects being evaluated is smallest due to drop out. Mathematically, the OTE is an inverse weighted mean of observed FEV_1 troughs that places a higher weight on more informative (e.g., less variance) time points, relative to using a single time point (end of study) to make an inference on treatment effect at the end of treatment, when the least number of subjects are still on study due to subject withdrawal.

Statistical Analyses

A mixed-effect repeated-measures model was used to evaluate the primary FEV_1 endpoint. The model included fixed effect class terms for treatment group, smoking status (current or former

smoker), reversibility status (not reversible to either ipratropium or albuterol, reversible to albuterol but not to ipratropium, reversible to ipratropium but not to albuterol or reversible to both ipratropium and albuterol), concomitant LABA use at baseline (yes or no), sex (male or female) and age at baseline (≤65 years or >65 years). Missing data were assumed to be missing at random. The missing at random assumption was evaluated using both 1- and 2-dimensional tipping point multiple imputation and found to be valid.

To evaluate the consistency of treatment effects on trough FEV_1 across a wide range of the ITT population, sub-group analyses were conducted on pooled Study 0126 and 0127 results. Trough FEV_1 sub-group analysis included patient segmentation by age group (≥65 years), LABA use, ICS use, 2011 GOLD category D[17] (indicating symptomatic patients with significant airflow limitation) and those scoring <2 on the Modified Medical Research Council dyspnea scale. A similar model used for trough FEV_1 was used for peak FEV_1. The OTE trough FEV_1 was computed by deriving a set of inverse-weights and applying those weights to the predicted values for trough FEV_1 from the primary analysis model. A t-test was used to derive statistical significance.
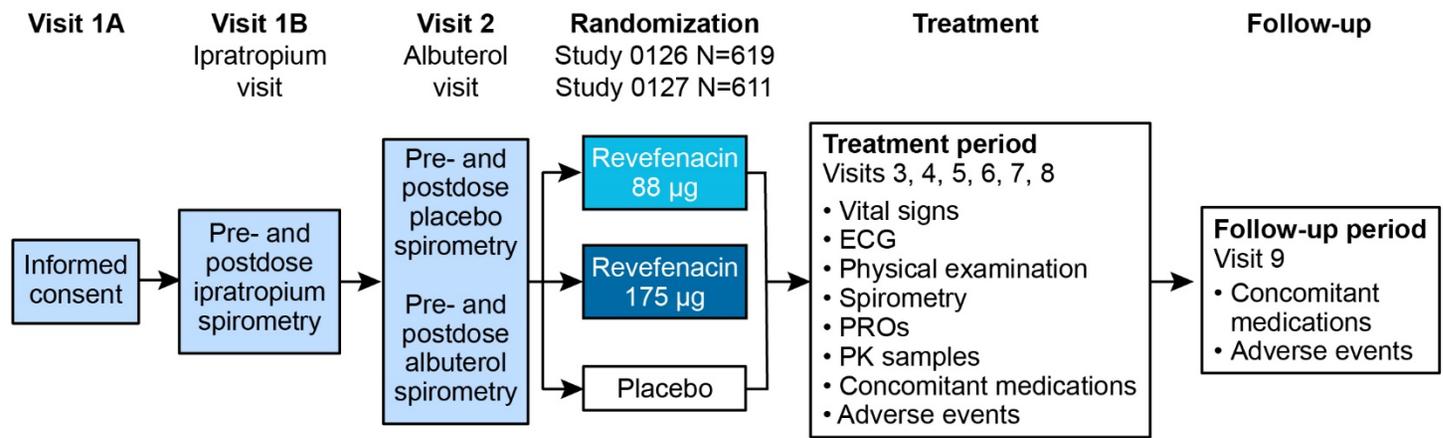
Supplemental Figure. 1 Study design. During Visit 1A, patients were issued study-specific rescue medication (an albuterol metered-dose inhaler) that they were permitted to use on an as-needed basis during the treatment period. Next, they underwent a washout period from prohibited medications, including all LAMA-containing products. Once sufficient patients receiving concomitant LABAs had been enrolled (up to 40% of the study population), the washout period for the remaining enrolled patients also pertained to all LABA-containing products. After the washout period, patients were required to attend 2 screening visits (Visits 1B and 2), 6 treatment visits (Visits 3-8) and a follow-up visit (Visit 9). Patients underwent ipratropium reversibility testing during Visit 1B and albuterol reversibility testing at Visit 2. ECG: electrocardiogram; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; PK: pharmacokinetic; PROs: patient-reported outcomes.
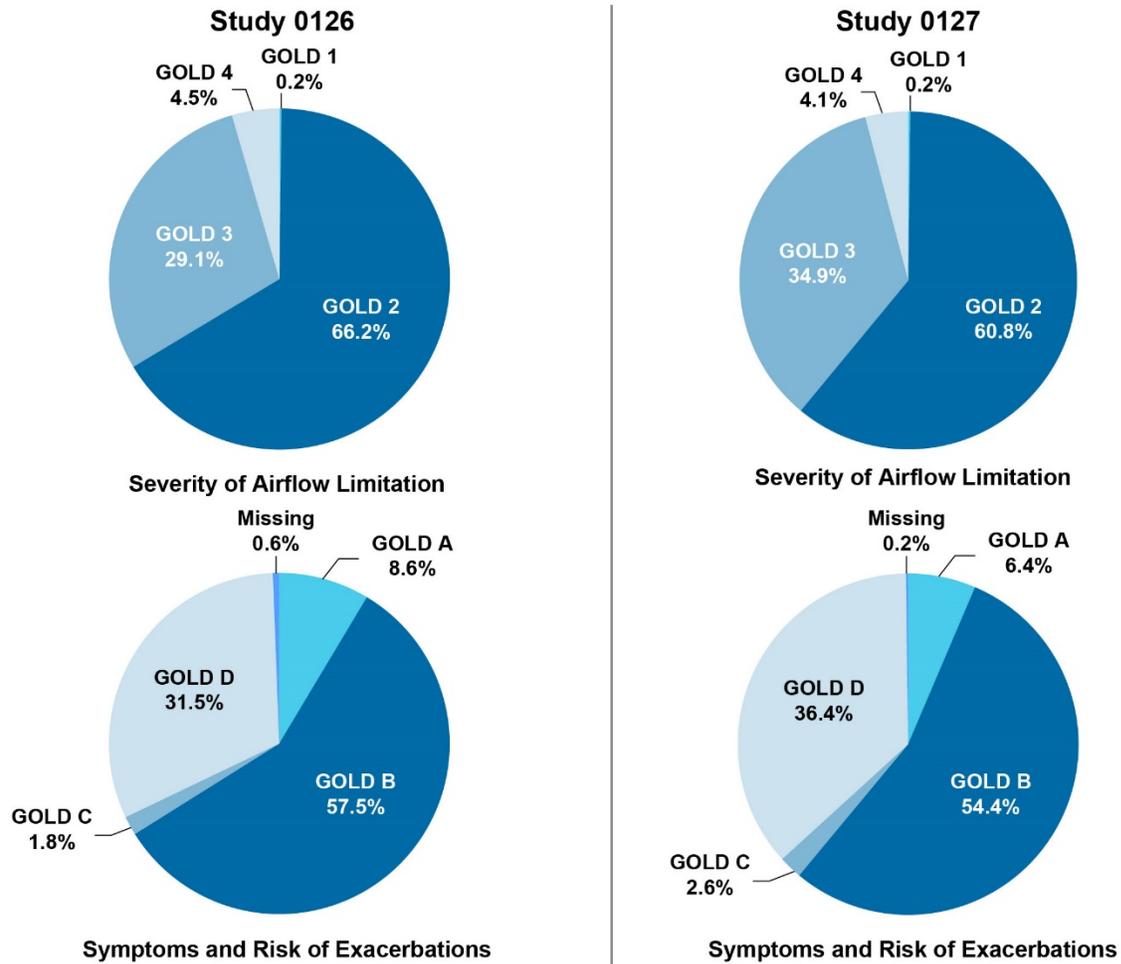
Supplemental Figure 2. Baseline COPD severity in Studies 0126 and 0127. COPD severity of participants in Studies 0126 and 0127 was determined according to severity of airflow limitation[a] (upper panels) and symptoms and risk of exacerbations[b] (lower panels) using 2011 GOLD criteria. [a]GOLD severity of airflow limitation: 1 = mild, 2 = moderate, 3 = severe, 4 = very severe. [b]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.