Glycopyrronium Improves Health Status, Lung Function in COPD

BY SHARON WORCESTER

DENVER — Twice-daily treatment with the long-acting muscarinic antagonist glycopyrronium improved health status and lung function in patients with chronic obstructive pulmonary disorder and moderate to severe airflow limitation in the randomized, double-blind, placebo-controlled GEM2 (Glycopyrronium Effect on Symptoms and Lung Function) study.

In patients with stable symptomatic COPD with moderate to severe airflow limitation, twice-daily 12.5-mcg dosing of glycopyrronium provides clinically meaningful improvement in lung function over the 12-hour dosing interval, has early onset, and is sustained over 12 weeks when compared with placebo. It is also associated with significant improvements in COPD symptoms, health status, and rescue medication use, as well as numerical improvement in dyspnea scores, Edward Kerwin, MD, of the Clinical Research Institute of Southern Oregon, PC, Medford, and his colleagues reported in a poster at an international conference of the American Thoracic Society.

Lung function — as measured by forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 12 hours (AUC 0-12h) — was significantly better both at day 1 and at week 12 of treatment in 216 patients who were randomized to receive a 12.5 mcg twice daily dose of the fast-onset, long-acting muscarinic antagonist (Novartis), compared with 216 patients who received placebo; there was a "significant and clinically meaningful between-treatment difference of 119 and 123 mL, respectively," the researchers wrote.

"Glycopyrronium also showed consistently significant improvements in trough FEV_1 vs. placebo at all assessed time points," they said, adding that glycopyrronium showed an early onset of bronchodilation with significant improvements in FEV_1 at 5 and 15 minutes post dose, compared with placebo at day 1 and week 12.

The least squares mean treatment differences for glycopyrronium vs. placebo for change from baseline in trough forced vital capacity (FVC) were 171 mL on day 2, and 130 mL at week 12. Peak FEV_1 and peak FVC were significantly improved with glycopyrronium vs. placebo on day 1 (least squares mean treatment differences of 137 and 223 mL, respectively) and at week 12 (least squares mean treatment differences of 148 and 201 mL, respectively).

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Patients in the study needed fewer daily puffs and had less need for rescue medications.

Health status was improved at week 12, with both significant and clinically meaningful improvements in St. George's Respiratory Questionnaire total score in the treatment vs. placebo group (–6.4 vs. –1.2), and the percentage of patients achieving minimal clinically important differences (MCID), defined as at least 4 units, was significantly higher in the treatment vs. placebo group (54.9% vs. 42.3%), the investigators said.

Additionally, numerical improvements in transition dyspnea index total score and percentage of patients achieving a MCID, defined as at least one unit, were observed at week 12 in the glycopyrronium vs. placebo group.

Wide-Ranging Improvement

Patients in the glycopyrronium group showed improvement on all symptoms scores and endpoints, according to data recorded in patient e-diaries, and those in the treatment group also were able to perform usual daily activities significantly more often than those in the placebo group.

"A statistically significant decrease in daily, daytime, and nighttime number of puffs, and a significant increase in the percentage of days with no rescue medication use were observed," the investigators noted.

Patients included in the multicenter GEM2 study were adults aged 40 years and older with moderate to severe airflow limitation (GOLD 2011 strategy level 2 or 3), who were either current or former smokers with a smoking history of at least 10 pack-years. All had postbronchodilator FEV_1 of at least 30% and less than 80% of the predicted value, and postbronchodilator FEV_1/forced vital capacity ratio of less than 0.70 at a run-in visit.

They also all had a modified Medical Research Council grade of 2 or greater at the run-in visit. Patients with a history of asthma or with a COPD exacerbation requiring treatment with antibiotics and/or systemic corticosteroids, and/or with hospitalization within 6 weeks of the screening and run-in periods were excluded, as were those with a history of long QT syndrome or whose corrected QT was greater than 450 ms at the run-in visit.

All underwent an initial 1- to 7-day washout period and a 2-week run-in period prior to randomization, as well as a safety follow-up period. Patients received either glycopyrronium 12. 5 mcg or placebo twice daily delivered via the Neohaler device for 12 weeks.

Well Tolerated

Treatment was generally well tolerated; of the 430 patients included in the safety set, 44 permanently discontinued treatment due to adverse events (4.6% and 4.2% in the treatment and placebo groups, respectively). The number who experienced at least one adverse event during the treatment period was similar in the two groups; COPD was the most common adverse event, occurring in 20.8% of those in the treatment group and 21.5% in the placebo group.

A nonfatal myocardial infarction occurred in one patient in the treatment group.

Laboratory parameters and vital sign findings were comparable in the two groups.

Based on the findings of the GEM studies, Novartis has submitted a New Drug Application to the Food and Drug Administration; glycopyrronium is already approved in more than 70 countries, including countries in Latin America and the European Union, as a once-daily treatment marketed as the Seebri Breezhaler.

The GEM2 study was sponsored by Novartis Pharmaceuticals. Two of the study researchers are Novartis employees.

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Umeclidinium Triple Therapy Improves Lung Function

DENVER — Lung function and health-related quality of life improved for patients with chronic obstructive pulmonary disorder who received the long-acting muscarinic agent (LAMA) umeclidinium with fixed-dose inhaled corticosteroid/long-acting beta antagonist (LABA) therapy, based on a post hoc analysis of pooled data from four phase III trials.

Compared with inhaled corticosteroid (ICS)/LABA therapy alone, the triple therapy increased the number of rescue-free days, Thomas Siler, MD, a pulmonologist with Midwest Chest Consultants, St. Charles, MO, reported at an international conference of the American Thoracic Society.

The analysis involved 819 patients treated with 62.5 mcg of umeclidinium (Ellipta) — an approved maintenance treatment for COPD — plus ICS/LABA, 821 patients treated with 125 mg umeclidinium plus ICS/LABA, and 818 who received placebo and ICS/LABA. Statistically significant improvements were seen with active triple therapy vs. dual therapy plus placebo in forced expiratory volume in 1 second (FEV_1) at day 85 (0.130 L) and at all other time points, as well as in 0 to 6 h weighted mean FEV_1 at day 84 (0.152 L), Dr. Siler said.

With active triple therapy vs. dual therapy plus placebo, overall rescue use was reduced by 0.3 puffs/day, and the number of rescue-free days increased by 7.1%. Also, St. George's Respiratory Questionnaire (SGRQ) score at day 84 decreased by 1.55 vs. placebo, and the proportion of SGRQ responders was 41% vs. 31% for umeclidinium vs. placebo (odds ratio, 1.6).

Moderate/severe COPD exacerbations were experienced by 88 patients: 31 (4%) of the umeclidinium group patients and 57 (7%) of the placebo group patients.

The findings were similar in the patients who received off-label 125-mg dosing of umeclidinium, and the incidence of adverse events and serious adverse events was similar across treatment groups, Dr. Siler noted.

Data on the benefits of LAMAs in triple therapy in patients with moderate to very severe COPD are limited. This pooled analysis of data from four randomized, double-blind, parallel-group 12-week trials of once-daily add-on umeclidinium included COPD patients who entered a 4-week run-in on open-label ICS/LABA (either fluticasone furoate/vilanterol 100/25 mcg or fluticasone propionate/salmeterol 250/50 mcg), and who were then randomized to receive 62.5 or 125 mcg of umeclidinium or placebo.

GlaxoSmithKline funded the study.

—Sharon Worcester