first study visit. At the end of the 4-week run-in period during which they received FF/VI 100/25 mcg once daily, patients were randomized 1:1:1 to once-daily UMEC 62.5 mcg, UMEC 125 mcg, or placebo, and open-label FF/VI for 12 weeks. All patients were followed for an additional week. The primary end point was trough FEV_1 on day 85. Other end points included weighted mean FEV_1 over 0 to 6 hours on day 84, serial FEV_1, rescue use, and St George's Respiratory Questionnaire (SGRQ) score. Safety was measured by on-treatment adverse events (AEs) and serious AEs.

Both doses of UMEC + FF/VI in both studies produced statistically significant and clinically meaningful improvements in trough FEV_1 at day 85 ($P \leq .001$) and 0 to 6-hour weighted mean FEV_1 at day 84 ($P \leq .001$).

Both doses of UMEC + FF/VI increased the percentage of rescue-free days vs baseline (range, 5.9% to 14.2%) vs placebo (2.3% and 3.8%). There was a significant reduction in puffs per day in both studies for UMEC 62.5 mcg + FF/VI dose and for the UMEC 125 mcg + FF/VI in study 1 (but not study 2). SGRQ scores at day 84 were significantly improved with UMEC 62.5 mcg + FF/VI. The incidence of on-treatment AEs was similar across all groups in both studies (30% to 39%).

Compared with placebo + FF/VI in patients with COPD, once-daily UMEC (62.5 or 125 mcg) added to once-daily FF/VI resulted in improvements in lung function and rescue use, with consistent safety profiles across all treatment groups.

New Bronchodilation Treatments for COPD

Written by Phil Vinall

The muscarinic antagonist tiotropium when combined with the β-2 agonist olodaterol provided significant bronchodilation above that achieved with tiotropium alone in patients with chronic obstructive pulmonary disease (COPD). Richard ZuWallack, MD, St. Francis Hospital and Medical Center, Hartford, Connecticut, USA, presented the results of ANHELTO 1 [NCT01694771] and 2 [NCT01696058], studies that evaluated the effectiveness of tiotropium (18 µg QD administered with HandiHaler) + olodaterol (5 µg QD administered with Respimat) in clinically stable patients with COPD.

Both were double-blind, randomized, 12-week studies carried out in 184 centers. Patients with post-bronchodilator forced expiratory volume at 1 second (FEV_1) ≥ 30% and < 80% of predicted normal, with post-bronchodilator FEV_1/forced vital capacity (FVC) < 70%, ≥ 40 years of age, and who are current or ex-smokers with a smoking history of > 10 pack-years were included in the studies. Primary end points were the changes from baseline to 12 weeks in FEV_1 area under the curve from 0 to 3 hours (AUC_{0-3}) and trough FEV_1 response. Secondary end points included St. George's Respiratory Questionnaire (SGRQ) score, peak FEV_1, FVC AUC_{0-3}, peak and trough FVC responses, and rescue medication use.

The mean ages of the 1132 patients enrolled in the studies were 64.6 (study 1) and 64.1 years (study 2); 49.8% and 53.6%, respectively, were men. The mean duration of COPD diagnosis ranged from 7.1 to 8.5 years.

Compared with tiotropium plus placebo, the combined treatment produced significant improvement in FEV_1 AUC_{0-3} response at treatment days 1, 29, and 85 in both studies ($P < .0001$).

Trough FEV_1 response to treatment was also significantly improved by combination therapy compared with tiotropium alone in both studies ($P < .01$). Significant improvements with combined treatment were noted in all secondary end points. Combining olodaterol and tiotropium provided significant improvements in lung function compared with tiotropium + placebo after 12 weeks.

SUN-101 is a long-acting muscarinic antagonist formulation of glycopyrrolate delivered by the eFlow vibrating mesh nebulizer, and it was shown to be as safe and effective as once-daily dosing in patients with moderate-to-severe COPD [GOLDEN-1; NCT01426009]. Edward Kerwin, MD, Sunovion Pharmaceuticals Inc., Marlborough, Massachusetts, USA, presented the results of a recent study [GOLDEN-2; NCT01706536] that evaluated the efficacy and safety of twice-daily treatment.

GOLDEN-2 was a 28-day, randomized, double-blind, placebo-controlled, parallel-arm study that included 282 patients with COPD aged 35 to 75 years, with baseline FEV_1 ≥ 30% and ≤ 70% of predicted, and ≥ 10 pack-year smoking history. Patients were randomized to SUN-101 (12.5 mcg, n = 55; 25 mcg, n = 54; 50 mcg, n = 57; or 100 mcg, n = 59) or placebo (n = 57) twice daily. Inhaled corticosteroids and roflumilast were permitted throughout the study. The primary end point was change from baseline in morning trough FEV_1 on day 28. The main secondary end point was change from baseline in AUC_{0-12} FEV_1 on day 28. Safety was assessed by adverse events (AEs).

All doses of SUN-101 were associated with significant increases in trough FEV_1 on day 28 ($P < .005$). After each dosing, there was rapid onset of bronchodilation, which persisted throughout the dosing interval.

Significant improvements were also seen in FEV_1 AUC_{0-12} on day 28 for all doses versus placebo ($P < .0001$). All doses of SUN-101 were well tolerated, with no deaths and a low incidence of serious AEs. The most

commonly reported AEs were exacerbations (3.2%), headache (2.8%), diarrhea (1.8%), and back pain (1.4%). Anticholinergic AEs were infrequent. A comparison of trough FEV_1 improvements with once- and twice-daily dosing showed twice-daily dosing to be more effective.

Twice-daily treatment with SUN-101 produced dose-dependent increases in trough FEV_1 and FEV_1 AUC_{0-12} that were better than once-daily treatment, suggesting this approach is an additional treatment option for patients with moderate-to-severe COPD.

Two randomized clinical trials using aclidinium bromide to treat moderate-to-severe COPD reported significant improvement in bronchodilation, dyspnea, and health-related quality of life and symptoms [Jones PW et al. *Eur Respir J.* 2012; Rennard SI et al. *Clin Drug Investig.* 2013]. Stephen Rennard, University of Nebraska Medical Center, Omaha, Nebraska, USA, presented results from LAS-MD-38, a long-term safety, tolerability, and efficacy study [NCT01045161] treating patients with moderate-to-severe COPD with twice-daily aclidinium bromide.

This was an open-label, 40-week extension study of ACCORD COPD II, the 12-week double-blind lead-in trial [Rennard SI et al. *Clin Drug Investig.* 2013]. At 12 weeks, patients (n = 448) were transitioned from placebo (Group 1), 200 µg aclidinium (Group 2), and 400 µg aclidinium (Group 3) to open-label aclidinium (400 µg twice daily). The primary end point was change from baseline in morning pre-dose trough FEV_1 at week 52. Additional end points were trough FEV_1 at all time points, dyspnea status (Transition Dyspnea Index [TDI] focal score), and health-related quality of life (SGRQ total score). No statistical comparisons were made. Safety, the primary outcome, was assessed via AEs of new or increased intensity during this extension study. Patients were mean age 62.7 years; 54.6% were men. Mean smoking pack-years was 54.2; mean pre- and post-bronchodilator FEV_1 were 1.37 and 52.7 mL, respectively; and 53.6% of patients had COPD of moderate severity.

Aclidinium (400 mg) is well tolerated and an effective, long-term therapeutic option in moderate-to-severe COPD.