Exposure-Response Analysis of Asthma Exacerbation Rate Confirmed Optimal 30 mg Q8W Benralizumab Dose for Treatment of Severe Asthma

Yen Lin Chia¹, Bing Wang¹, Binbing Yu², Peter Barker³, Mitch Goldman³, Lorin Roskos²

¹MedImmune, Mountain View, CA, United States; ²MedImmune, Gaithersburg, MD, United States; ³AstraZeneca, Gaithersburg, MD, United States

Objectives: To evaluate the dose regimen of 30 mg Q4W vs Q8W in asthma patients by modeling asthma exacerbation events and the impacts of covariates on efficacy.

Methods: A non-homogeneous Poisson mixed model was used to characterize the asthma exacerbation events in 8-wk interval up to 48 or 56 weeks in 2267 severe asthma patients from two pivotal Phase 3 studies, SIROCCO¹ and CALIMA². Both empirical assessment of exacerbation rate and population exposure-exacerbation event modeling were conducted. Pre-specified covariates such as region, number of prior exacerbation events, oral corticosteroid (OCS) usage were evaluated for significance. The impacts of anti-drug antibody (ADA), baseline blood eosinophil counts and other covariates of interest on benralizumab efficacy were assessed via clinical trial simulation.

Results: In empirical correlation with steady-state PK trough concentrations, AER ratios in SIROCCO ranged from 0.44 to 0.51, were similar across trough PK quartiles (Q1-Q4); however, low efficacy was observed in CALIMA Q1 in both 30 mg Q4W and Q8W. Low placebo exacerbation rate in CALIMA may have confounded the interpretation. In population modeling, the estimated benralizumab EC90 for AER was 927 ng/ml, slightly below the typical steady-state average PK concentration (1,066 ng/ml) for the Q8W regimen. Both 30 mg Q4W and 30 mg Q8W regimens exhibited similar efficacy.

Number of exacerbations in the past 12 months, Central/Eastern Europe region, and OCS use were significant covariates for base AER. There was a positive trend toward improved benralizumab efficacy for patients with higher baseline eosinophil counts albeit not statistically significant. The presence of ADA was found to have no impact on efficacy.

Conclusions: Both empirical and population-based analyses of AER confirmed 30 mg Q8W as the optimal ED90 of benralizumab for patients with severe asthma. Efficacy was observed over the entire range of baseline blood eosinophils counts.