Pharmacokinetic and Pharmacodynamic Properties of Lulizumab Pegol, an Anti-CD28 Antagonistic Domain Antibody, in Normal Healthy Volunteers and Patients with Systemic Lupus Erythematosus

Rong Shi, Nilay Takkar, Bindu Murthy, Johanna Mora, Diane Shevell, Lara Pupim, Dominique Duchesne, John Throup, and Ihab G. Girgis

Bristol-Myers Squibb, Lawrenceville, NJ

Objectives: Lulizumab is a domain antibody with antagonistic activity against CD28 T-cell co-stimulation. Phase 1 studies have demonstrated that Lulizumab has a favorable safety and PK/PD profile, thereby supporting further dose-ranging evaluation in systemic lupus erythematosus (SLE) patients. To that end, the Phase 2 proof of concept study studied 4 SC dosing regimens: 12.5 mg weekly, and 12.5 mg, 5 mg, and 1.25 mg every 2 weeks. The dosing regimens were selected based on the PK/PD modeling for peripheral receptor occupancy (RO) of first in human trials to provide a range of RO to span the PK-RO curve. The primary objective of this work was to confirm whether the PK/RO relationship was translatable from healthy volunteers to SLE patients.

Methods: A population PK model was developed to fit the PK data from the first-in-human study: a two-compartment PK model with first-order absorption. A sequential population PK/PD model approach was used to fit the RO data with a maximum effect (Emax) model. NONMEM 7.3 was used to execute data analysis. During the Phase 2 interim analysis, the population PK and RO models were updated with data from SLE patients.

Results: The population PK and RO model adequately describe the data from healthy subjects and SLE patients. Lulizumab Cmin at steady state is approximately 25% lower in SLE patients than in healthy subjects. A wide range of RO (>40% to >90%) at steady state Cmin is believed to provide sufficient data to adequately characterize the dose/exposure-response relationship for efficacy and safety in SLE patients (Figure).

Conclusions: Observed Lulizumab RO in SLE patients was consistent with the model predictions based on healthy subject data. As a result, a wide range of RO was elicited by the dosing regimens selected for Phase 2 investigation.

Figure. Receptor Occupancy and Cmin Relationship at Steady State in SLE patients

![Figure](image-url)