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POSTER ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

Efficacy of Parallel and Crossover Analysis As Well As Pharmacokinetic Similarity Were Confirmed between ABP 959 and Eculizumab Reference Product in Patients with PNH

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Introduction: ABP 959, a biosimilar to eculizumab reference product (RP), binds to the human complement component 5 protein to inhibit terminal complement activation. Eculizumab RP is approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome, generalized myasthenia gravis, and neuromyelitis optical spectrum disorder. Regulatory approval of biosimilars is based on a totality of evidence approach which includes demonstration of similarity in analytical and non-clinical characteristics, and in comparative clinical studies. Analytical and non-clinical similarities of ABP 959 with eculizumab RP and clinical pharmacokinetics (PK)/pharmacodynamics (PD) and safety similarities in healthy adults have been previously reported. Similarity of the primary efficacy and safety results from the parallel and crossover comparisons in patients with PNH have also been previously reported. Here, we report together the primary efficacy results from both the parallel and the cross-over comparisons along with additional PK analyses in patients with PNH to further support the demonstration of similarity of ABP 959 with eculizumab RP.

Methods: A multicenter, randomized, double-blind, active-controlled, 2-period crossover study evaluated the clinical similarity of ABP 959 compared with eculizumab RP in adult patients with PNH. Patients were randomized 1:1 to receive each investigational product (900 mg of ABP 959 or eculizumab RP IV q14d) in 1 of 2 treatment sequences (ABP 959/eculizumab RP or eculizumab RP/ABP 959). Primary efficacy determined by hemolysis, measured by lactate dehydrogenase (LDH), was analyzed for both the parallel and crossover comparisons. The parallel comparison endpoint was measured at week 27 and clinical similarity was assessed by comparing the 1-sided 97.5% upper confidence interval (CI) limit for the geometric least squares (LS) mean ratio of LDH between ABP 959 treatment group and eculizumab RP treatment group with a non-inferiority (NI) margin of 2.873. The crossover comparison endpoint was measured by the time-adjusted area under the effect curve (AUEC) of LDH from weeks 13 to 27, 39 to 53, and 65 to 79. The similarity of efficacy between treatment groups was assessed by comparing the 2-sided 90% CI for the geometric mean ratio (GMR) of the time-adjusted AUEC of LDH with a similarity margin of (0.77, 1.30). The total and unbound PK area under the curve (AUC) of ABP 959 and eculizumab RP from week 13 to week 15 and trough PK were identified as secondary endpoints in this study.

Results: Forty-two patients (20 in ABP 959/eculizumab RP group; 22 in eculizumab RP/ABP 959 group) were randomized across 25 centers. Similarity of efficacy was established in both the parallel and crossover comparisons. In the parallel comparison, the ratio of the geometric LS means of LDH at week 27 (ABP 959 vs eculizumab RP) was 1.0628, with a 1-sided 97.5% upper CI of 1.1576 was contained within the NI margin of 2.873. In the crossover comparison, a point estimate of the GMR of time-adjusted AUEC of LDH (ABP 959 vs eculizumab RP) of 0.9812 with a 2-sided 90% CI of (0.9403-1.0239) was contained within the prespecified margin of similarity. The GMR (90% CI) for the total and unbound PK AUC from week 13 to week 15 was 0.9122 (0.7586, 1.0968) and 0.9508 (0.7454, 1.2130), respectively. Geometric mean values for trough total and unbound concentrations of ABP 959 and eculizumab RP were similar between the treatment groups at all time points tested over the entire study.

Conclusions: Similarity in clinical efficacy in both parallel and crossover comparisons as determined by hemolysis in patients with PNH was established between ABP 959 and eculizumab RP. Additionally, analyses of serum total and unbound PK concentrations for patients with PNH further demonstrated PK similarity between ABP 959 and eculizumab RP. The results of this study, along with previously demonstrated analytical, non-clinical, clinical PK/PD in healthy adults, and efficacy and safety

evaluations in PNH patients, further support a demonstration of no clinically meaningful differences between ABP 959 and eculizumab RP.

Disclosures Kulasekararaj: *Achillion:* Consultancy; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *F. Hoffmann-La Roche Ltd:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Celgene/BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Samsung:* Consultancy; *Alexion, AstraZeneca Rare Disease:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *BioCryst:* Consultancy; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Akari Therapeutics:* Consultancy. **Arvanitakis:** *Ablynx/Sanofi:* Consultancy, Speakers Bureau; *Sobi:* Consultancy, Speakers Bureau; *Shire:* Research Funding; *Takeda:* Research Funding; *Chiesi:* Consultancy, Speakers Bureau; *Amgen:* Consultancy, Speakers Bureau; *Grifols:* Consultancy, Speakers Bureau. **Chonat:** *Takeda Pharmaceuticals:* Consultancy, Research Funding; *Roche/Genentech:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Amgen:* Consultancy, Research Funding; *GBT/Pfizer:* Consultancy, Research Funding; *Agios:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Alexion:* Consultancy, Other, Research Funding. **Cao:** *Amgen Inc:* Current Employment. **Chow:** *Amgen Inc:* Current Employment. **Henary:** *Amgen Inc:* Current Employment.

Panel 1 – Table 1 – Parallel and Crossover Primary Efficacy and Pharmacokinetic Analysis

Statistics	ABP 959	Eculizumab RP
Parallel Efficacy LDH (U/L) at week 27 Geometric LS mean [a] 95% CI GMR (ABP 959 vs. eculizumab RP)[a] 97.5% upper CI limit	 205.69 (191.23, 221.24) 1.0628 1.1576	 193.53 (180.80, 207.17)
Crossover Efficacy Time-adjusted AUEC (U*day/L/week) of LDH Geometric LS mean[b] 95% CI GMR (ABP 959 vs. eculizumab RP)[b] 90% CI	 1445.76 (1295.63, 1613.28) 0.9812 (0.9403, 1.0239)	 1473.44 (1321.86, 1642.41)
Total PK AUC (µg*day/mL) From Week 13 to Week 15 Geometric LS mean[c] GMR (ABP 959 vs. eculizumab RP)[c] 90% CI	 3898.05 0.9122 (0.7586, 1.0968)	 4273.28
Unbound PK AUC (µg*day/mL) From Week 13 to Week 15 Geometric LS mean[c] GMR (ABP 959 vs. eculizumab RP)[c] 90% CI	 2761.19 0.9508 (0.7454, 1.2130)	 2903.93

AUC = area under the curve; CV = coefficient of variation; GMR = geometric mean ratio; LDH = lactate dehydrogenase; LS = least squares; PK = pharmacokinetic
[a] The point estimate and corresponding confidence limits for the log-transformed LDH values were estimated from a linear mixed effects model with treatment, stratification factor, week 1 LDH value, time (as a continuous variable), and treatment by time interaction term as fixed effects, and with subject as a random effect. A within subject variance-covariance structure of compound symmetry was used. Degree of freedom method was Kenward-Roger. Point estimates and corresponding confidence limits for the geometric LS means and the ratio of geometric LS means were calculated by transforming back to the original scale. Lactate dehydrogenase values from all assessed time points from week 13 to week 27 were included in the mixed model
[b] The point estimate and corresponding confidence limits for the log-transformed time-adjusted AUEC were estimated from a linear mixed effects model with treatment, stratification factor, period, and sequence as fixed effects, and subject as a random effect. A within subject variance-covariance structure of unstructured was used. Degree of freedom method was Kenward-Roger. Point estimates and corresponding confidence limits for the geometric LS means and the ratio of geometric LS means were calculated by transforming back to the original scale
[c] Estimated from an analysis of variance model
Note: The time-adjusted AUEC of LDH was calculated for week 13 to week 27, week 39 to week 53 and week 65 to week 79.

Panel 2 – Graph 1 – Crossover Primary Efficacy Result – Time-Adjusted AUEC (U*day/L/week) of LDH

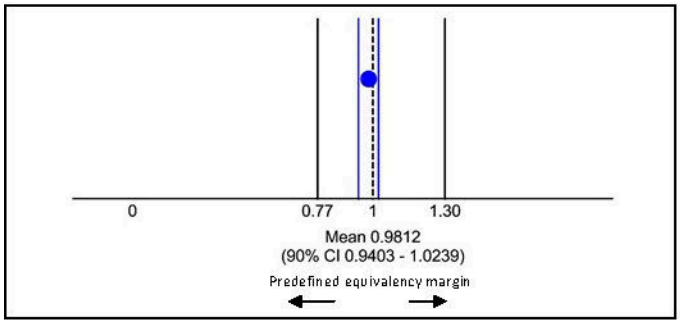

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Figure 1

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