Abstract: PB2059

Title: SENSITIVITY AND SUBGROUP ANALYSES FURTHER SUPPORT CLINICAL SIMILARITY IN EFFICACY BETWEEN ABP 959 AND ECULIZUMAB REFERENCE PRODUCT IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

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Background:

ABP 959, a biosimilar to eculizumab reference product (RP), binds to the human complement C5 protein to inhibit progression of the complement cascades. Excessive activation or insufficient control of C5 plays a role in the pathogenesis of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), generalized myasthenia gravis (gMG), and neuromyelitis optical spectrum disorder (NMOSD). Eculizumab RP is approved for these indications. Analytical and non-clinical similarities of ABP 959 with eculizumab RP as well as clinical pharmacokinetic (PK) and pharmacodynamic (PD) similarities in healthy volunteers, and clinical efficacy and safety similarities in patients with PNH have been previously reported.

Aims:

Our aim is to further support the previously demonstrated clinical similarity of ABP 959 with RP in patients with PNH, utilizing: 1) sensitivity analyses on hemolysis to assess the potential impact of including previously excluded lactate dehydrogenase (LDH) values; and 2) age and gender subgroup comparisons at week 27.

Methods:

This multicenter, randomized, double-blind, active-controlled, 2-period crossover study evaluated the clinical similarity of ABP 959 compared with RP in adult patients with PNH. Patients were randomized 1:1 to receive each investigational product (900 mg of ABP 959 or RP IV q14d) in one of two treatment sequences (ABP 959/RP or RP/ABP 959); the primary efficacy endpoint was hemolysis, measured by LDH at week 27 for a parallel comparison. LDH values impacted by confounding events unrelated to efficacy of investigational product, as determined by the LDH Review Committee, were excluded from the primary analysis. To assess the robustness of the parallel comparison primary analysis and the potential impact of the LDH exclusions, a sensitivity analysis was conducted without excluding these values. The parallel comparison of LDH at week 27 was also examined in subgroups by baseline covariates including age (≤54 years old vs >54 years old) and gender.

Results:

Forty-two patients (20 in ABP 959/RP group; 22 in RP/ABP 959 group) were randomized across 25 centers. The primary efficacy endpoint of LDH at week 27 for the previously reported parallel comparison excluded six LDH values (4 LDH values in 4 patients in the ABP 959/RP group and 2 LDH values in 2 patients in the RP/ABP 959 group). The values were excluded due to hemolysis in the tube (4 LDH values), cholecystitis (1 LDH value), and upper respiratory tract infection (1 LDH value). The result of the current sensitivity analysis performed without excluding these values was similar to the result of the primary efficacy analysis, with a 1-sided 97.5% upper CI of 1.170 and was also contained within the non-inferiority margin of 2.873. Additional results of the subgroup (age and gender) analyses were also consistent with the results of the primary efficacy analysis for the parallel comparison.

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Summary/Conclusion:

These additional analyses support the findings of the key primary efficacy analysis between ABP 959 and RP in

patients with PNH. The results of this study, along with previously demonstrated analytical, non-clinical, and clinical similarity, validate the robustness of similarity in clinical efficacy and are consistent with the conclusion of no clinically meaningful differences between ABP 959 and eculizumab RP.

Table. Sensitivity Analysis of LDH (U/L) at Week 27 - Parallel Comparison Without Excluding LDH Values Impacted by Confounding Events Between Week 13 and Week 27 (Full Analysis Set)

Statistics	ABP 959 (n = 20)	Eculizumab (n = 22)
Week 27 geometric LS mean[a]	203.91	198.35
95% confidence interval	(182.67, 227.61)	(178.96, 219.86)
Ratio of Week 27 geometric LS mean (ABP 959/Eculizumab)[a]	1.0280	
97.5% upper confidence interval limit	1.1703	
95% confidence interval	(0.9030, 1.1703)	

Note: LS= Least squares.

n = Number of subjects included in the mixed model.

LDH values impacted by confounding events determined by the blinded independent LDH review committee were included.

[a] The point estimate and corresponding confidence limits for the log-transformed LDH values are 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 subject as a random effect.

A within subject variance-covariance structure of compound symmetry is used. Degree of freedom method is Kenward-Roger. Point estimates and corresponding confidence limits for the geometric LS means and the ratio of geometric LS means are calculated by transforming back to the original scale. LDH values from all assessed time points from week 13 to week 27 are included in the mixed model.

Keywords: Paroxysmal nocturnal hemoglobinuria (PNH), PNH