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Phase 1 Study in Healthy Adults of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Povetacicept (ALPN-303), a Dual BAFF/APRIL Antagonist for the Treatment of Autoimmune Glomerulonephritides

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Objectives: B cell activating factor of the TNF family (BAFF) and a proliferation-inducing ligand (APRIL), play overlapping and non-redundant roles in B cell development, proliferation, function, and survival. Povetacicept (ALPN-303) is an Fc fusion protein of an engineered TACI variant TNFRSF domain with enhanced affinity for APRIL and BAFF. In preclinical studies, povetacicept demonstrated enhanced pharmacokinetics (PK) and immunomodulatory properties. Povetacicept also suppressed autoantibodies, renal IgG deposition, and nephritis in mouse models. This study assessed the safety, tolerability, PK, pharmacodynamics (PD), and immunogenicity of povetacicept in adult healthy volunteers (HV).

Methods: In this first-in-human study (NCT05034484), 66 adult HV were randomized 4:2 into single ascending dose cohorts of intravenous (IV) or subcutaneous (SC) povetacicept or placebo. Safety, PK, circulating immunoglobulins (Ig), galactose-deficient IgA1 (Gd-IgA1), and circulating leukocyte populations were assessed.

Results: Povetacicept has been well tolerated in all cohorts evaluated as single IV or SC doses of up to 960 mg. Overall, it exhibits dose-related PK and expected PD effects, including dose-related reductions in serum IgA, IgM, IgG, and Gd-IgA1 (Figure 1), and in circulating antibody-secreting cells (plasmablasts and plasma cells) (Figure 2). In the same setting, these PD effects appear greater than those reported for WT TACI-Fc molecules and appear to be saturated at doses ≥80 mg. Coverage of free APRIL was maintained for 2-3 weeks with 80 mg and ≥4 weeks with 240 mg, respectively. To date, there have been no serious AEs, no imbalances of infections between placebo and povetacicept groups, no administration-related reactions other than mild injection site pain, and no adverse trends in safety laboratories.

Conclusions: To date, povetacicept has demonstrated acceptable safety and tolerability as single IV or SC doses. The observed PD effects suggest dose regimens of 80-240 mg SC every 4 weeks for future studies. Clinical development of povetacicept for multiple autoantibody-related glomerulonephritides is strongly supported.

Fig 1