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Updated Results from the RUBY-3 Study of Povetacicept, an Enhanced Dual BAFF/APRIL Antagonist, in Autoantibody-Associated Glomerulonephritis

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Objectives : Inhibition of BAFF and/or APRIL has shown promise in IgA nephropathy (IgAN), systemic lupus erythematosus (SLE), lupus nephritis (LN), and primary membranous nephropathy (pMN), and may exert a disease-modifying effect. Povetacicept (ALPN-303) is an Fc fusion protein of a variant TACI domain engineered for more potent dual BAFF/APRIL inhibition than wild-type TACI or anti-BAFF or anti-APRIL antibodies. Previous results showed povetacicept 80 mg every 4 weeks was initially well tolerated and demonstrated promising, clinically meaningful reductions in urine protein to creatinine ratio (UPCR) and Gd-IgA1 in participants with IgAN.
Methods : RUBY-3 is an open-label, multiple ascending dose, phase 1b/2a study of povetacicept 80 or 240 mg administered subcutaneously once every 4 weeks. Eligible participants are aged ≥18 years with biopsy-confirmed IgAN, LN, or pMN and on maximally tolerated ACE inhibitor/ARB therapy, with well-controlled blood pressure, and disease-specific immunosuppressive therapy where applicable. The primary objective is safety; secondary objectives include pharmacokinetics, pharmacodynamics, immunogenicity, biomarkers, and efficacy.
Results : As of 1 Dec 2023, 12 participants with IgAN have enrolled and received povetacicept 80 mg, with 7 (58%) having received ≥24 weeks of treatment. Povetacicept continues to be well tolerated, with the majority of treatment-emergent adverse events being of low grade. There have been no incidences of severe hypogammaglobulinemia (IgG <3 g/L) or severe infections. Povetacicept 80 mg was associated with a UPCR reduction of 52.6% at 24 weeks (n=7). Reductions in Gd-IgA1, stable renal function, and pharmacodynamically expected decreases in immunoglobulin levels were also observed. Additional results from the 80 mg cohort with longer duration of follow-up, as well as initial results from the 240 mg dosing cohort, are planned to be presented.
Conclusions : Povetacicept remains well tolerated with multiple dosing and continues to demonstrate very promising activity in IgAN, strongly supporting further study in IgAN as well as other glomerulonephritis and autoantibody-associated diseases.