A Randomized, Placebo-Controlled, Phase 1 Study in Healthy Adult Volunteers of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ALPN-303, a Potent Dual BAF/FAPRIL Antagonist for the Treatment of Autoimmune Cytopenias

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Introduction

B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) are tumor necrosis factor superfamily (TNFSF) members that bind to transmembrane activator and costimulator-modulating cytokine (TACI), B-cell maturation antigen (BCMA), and immune thrombocytopenic purpura (ITP) are diseases characterized by autoantibodies directed against red blood cells and platelets, respectively. Significantly higher levels of both BAFF and APRIL have been observed in the serum of patients with AIHA and ITP compared to healthy subjects, and polymorphisms in BAFF and TACI have been associated with ITP.1 The cell-targeting agents currently used to treat AIHA or ITP, rituximab (anti-CD20) and belimumab (anti-BAFF), cannot directly deplete antibody-secreting plasma cells. To address these shortcomings, we have developed ALPN-303, an Fc fusion of an engineered TACI variant, TNFSF domain, which substantially improves a dose-limited affinity liabilities of wild-type (WT) TACI, resulting in highly potent dual BAFF/APRIL inhibition superior to WT TACI-Fc, or to BAFF- or APRIL-specific monoclonal Abs (mAb).

Figure 1: ALPN-303 is an Engineered TACI-Fc Fusion with Enhanced Affinity for BAFF and APRIL

Figure 2: ALPN-303 Inhibits Autoantibody Production to Disrupt Antibody-Driven Platelet Destruction in ITP

Figure 4: RUBY-1 Study Design

Table 1: ALPN-303 is Well-Tolerated Overall

Table: ALPN-303 Dose-Dependently Reduces Circulating Immunoglobulins and Antibody-Secreting Cells (ASC)

Effects generally appear saturated ≥ 80 mg for 3 to 4 weeks

Figure 6: ALPN-303 Dose-Dependently Reduces Circulating Immunoglobulins and Antibody-Secreting Cells (ASC)

Summary and Conclusions

ALPN-303 is an engineered variant TACI-Fc fusion with enhanced affinity as compared to WT TACI-Fc for both BAFF and APRIL.

ALPN-303 is efficacious in a mouse model of AIHA, significantly improving the hematocrit while reducing pathogenic anti-BCR autoantibodies.

In this first-in-human study, ALPN-303 has been well-tolerated as single Vs or 250 mg of up to 960 mg in adult healthy volunteers. The most frequent adverse event has been mild headache. No severe infections or hypogammaglobulinemia, or cytokine release events occurred.

ALPN-303 demonstrates dose-dependent PK/PD. Coverage of free APRIL is maintained for ≥4 wk with 240 mg, corresponding to reductions in serum IgG and antibody-secreting cells. These data support a regimen of up to 240 mg SC every 4 weeks in future studies.

Further clinical development of ALPN-303 in autoimmune cytopenias and other autoantibody-related diseases is strongly supported. Clinical trials in autoimmune cytopenias, including warfarin, cold agglutinin disease (CAD), and ITP, as well as other B cell-associated disorders (e.g., lupus, IgA nephropathy, lupus nephritis, and membranous nephropathy), are in preparation.