Background

-B cell activating factor of the TNF family (BAFF) and a proliferation-inducing ligand (APRIL) are TNF superfamilly members that engage surface membrane activators and calcium-modulator and cyclophilin ligand (CAML) (TACI) receptor, B-cell maturation antigen (BCMA), and/or B-cell receptor (BCR) on B cells and together support B cell development, differentiation, and survival.

-ALPN-303 is an Fc fusion protein of a human TACI variant TNFRSF domain (VTD) engineered by directed evolution to have enhanced affinity for BAFF and APRIL.

-In preclinical studies, ALPN-303 mediates significantly improved inhibition of both BAFF and APRIL in vitro and enhanced pharmacokinetics (PK) and immunomodulatory properties in vivo (e.g., by reducing germinal center B cells, follicular helper T cells, and plasma cells), as compared to wild-type (WT) TACI-Fc molecules.

-B-cell targeting therapies like the WT TACI-Fc fusion atacicept and telitacicept, and belimumab

-ALPN-303, an Engineered Dual BAFF/APRIL Antagonist, Potently Inhibits Pathogenic Autoantibodies in Preclinical Models, and Demonstrates Tolerability in Healthy Volunteers.

-Background

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-Mice and Cynomolgus Monkeys

-Single Dose ALPN-303 Preliminarily Reduces Serum Ig in a Dose-Dependent Manner in Adult Healthy Volunteers

-Make and Female cynomolgus monkeys (n = 4/group) for dosing periods, n = 4/group for recovery) were dosed weekly for up to 5 doses at 25, 75, or 150 mg ALPN-303 via SC administration, or at 150 mg in 30 min IV infusion. No test-related adverse events occurred, and there were no test-related deaths at any dose in the cynomolgus monkey investigations.

-ALPN-303 Significantly Reduces Glomerular IgG Deposition in the bm12 Mice Model of Glomerulonephritis

-ALPN-303 Exhibits Higher Serum Exposure than WT TACI-Fc in Preclinical Models

-ALPN-303 exhibits higher serum exposures and more potent immunomodulatory activity and efficacy, including significant reversible

-Activities than WT TACI-Fc in preclinical models.

-ALPN-303 is well-tolerated in rodents and NHP and demonstrates encouraging immunomodulatory activity and efficacy, including significant reversible reductions in circulating IgG.

-ALPN-303 exhibits higher serum exposures and more potent immunomodulatory activities than WT TACI-Fc in preclinical models.

-In an ongoing Phase 1 trial in adult healthy volunteers (NCT05034484), subjects have been administered a single dose of 2, 8, 24, or 80 mg ALPN-303 (100 mg/mL) via 30 min IV infusion, or 80 mg via SC administration (each ALPN-303 group n = 4; placebo n = 10). To date, there have been no treatment-related serious adverse events, no infusion-related or injection site reactions, and no adverse trends in safety laboratory observations. Dose escalation beyond 80 mg is still in progress.

-To address a key limitation of WT TACI-Fc, which binds to APRIL relatively

-To bring this concept to clinical reality, an ALPN-303 dose escalation study in healthy volunteers is currently in progress.

-As a multivalent Fc fusion, ALPN-303 has the potential to inhibit both APRIL and BAFF at clinical relevant doses.

-Critical to the efficacy of this novel approach is the design of a dose escalation study in healthy volunteers that is planned to determine the relative clinical activity of ALPN-303 compared to the single-agent therapy, and in which the activity of ALPN-303 will be compared to the efficacy of similar Fc fusions.

-ALPN-303 is an attractive candidate development for the treatment of multiple autoimmune and inflammatory diseases.

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