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

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Abstract

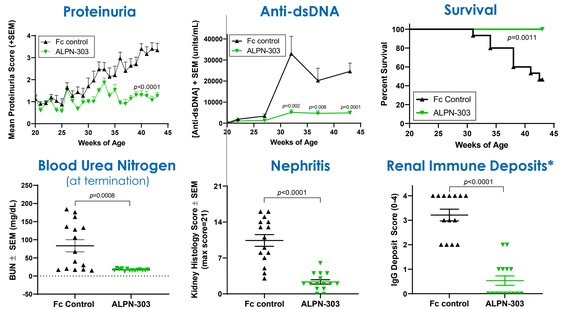
Background: Therapeutic agents targeting the B-cell cytokines BAFF and/or APRIL have demonstrated promising clinical potential in autoantibody-related GN such as lupus nephritis (LN) and IgA nephropathy (IgAN), and other B-cell-related diseases such as systemic lupus erythematosus; however, there is still need for more safe and efficacious therapies. ALPN-303 is an Fc fusion protein of an engineered TACI variant TNFRSF domain (vTD) which mediates more potent inhibitory activity than WT TACI-Fc or BAFF- or APRIL-specific antibodies. In preclinical studies, ALPN-303 demonstrated enhanced PK and immunomodulatory properties vs. WT TACI-Fc, which may translate to lower and/or less frequent doses in humans. ALPN-303 also suppressed autoantibodies, renal IgG deposition, and nephritis in mouse models. ALPN-303 may therefore significantly improve clinical outcomes in GN and other B-cell-related diseases.

Methods: In this first-in-human study (NCT05034484), adult healthy volunteers (HV) are randomized into single ascending dose cohorts of intravenous (IV) or subcutaneous (SC) ALPN-303 or placebo. Subjects are followed to assess safety and PK, circulating immunoglobulins (Ig), and circulating leukocyte populations by flow cytometry.

Results: ALPN-303 has been well tolerated as single IV or SC doses of up to 960 mg in adult HV, and overall exhibits dose-related PK and expected PD effects, including dose-related reductions in serum Ig. The most frequent adverse event has been mild headache. No severe infections or cytokine release have been observed.

Conclusions: ALPN-303 demonstrates dose-dependent PK/PD. Coverage of free APRIL is maintained for 2-3 weeks with an 80 mg and ≥4 weeks with a 240 mg dose IV or SC, corresponding to reductions in serum Ig and antibody-secreting cells (ASCs). These findings support future clinical development of ALPN-303 in multiple autoantibody-related GN, as well as other B-cell- and/or autoantibody-related diseases.

Figure 1: ALPN-303 Significantly Suppresses Disease in (NZB/NZW)F_1 Lupus Nephritis Model



(NZBxNZW)F_1 mice were dosed with ALPN-303 at 17 mg/kg intraperitoneally twice a week from 22-42 weeks of age (vs. molar matched dose of Fc control).

**Representative images of staining of IgG immune deposits in the kidneys are shown at right.*

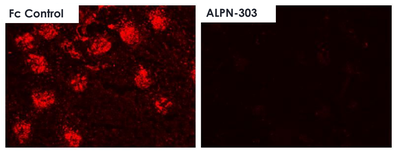
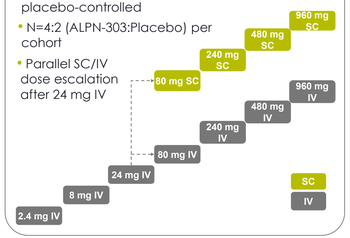


Figure 2: RUBY-1 Study Design

Study Design

- RUBY-1 (NCT05054484) is a Phase 1 trial evaluating single ascending doses of 2.4 to 960 mg ALPN-303 administered IV or SC to healthy volunteers
- Randomized, double-blind, placebo-controlled
- N=4:2 (ALPN-303:Placebo) per cohort
- Parallel SC/IV dose escalation after 24 mg IV



Demographics and Disposition

Attribute	Subjects (N=66)
Age (year)[1]	32 (18, 64)
Female	46 (70%)
Race White Asian Other	 40 (61%) 13 (20%) 13 (20%)
BMI (kg/m²)[1]	25 (18, 31)
eGFR[2] ≥90 60–89	 53 (80%) 13 (20%)
Completed[3]	39 (59%)

[1] Median (min, max)
[2] mL/min/1.73 m²
[3] As of 29JUL2022
BMI = body mass index
eGFR = estimated glomerular filtration rate

Figure 3: ALPN-303 is Well-Tolerated Overall

- ALPN-303 has been well-tolerated overall; most common adverse events (AEs) include mild (G1) headache, dizziness, low Ig (an expected pharmacodynamic [PD] effect), or back pain. Incidence of infection has not significantly differed from placebo.
- No G4-5 AEs, serious AEs, serious or severe infection, severe hypogammaglobulinemia, or cytokine release (no significant changes in: GM-CSF, IFNγ, IL-3, IL-5, IL-6, IL-7, IL-8, IL-10, IL-18, MIP-1α, MIP-1β, MCP-1, TNFα, or TNFβ)

ALPN-303 is Well-Tolerated Overall

Data Extract: 29JUL2022

Treatment-Emergent Adverse Event (TEAE)	All Placebo (N=22)	All ALPN-303 (N=44)
Any TEAE[1]	**12 (55%)**	**27 (61%)**
Grade 1	7 (32%)	20 (45%)
Grade 2	4 (18%)[2]	6 (14%)[3]
Grade 3	1 (5%)[4]	1 (2%)[4]
Adverse Event of Interest	**1 (5%)**	**1 (2%)**
Administration-Related Reaction[5]	1 (5%)	1 (2%)
Injection Site Pain (G1)	1 (5%)	1 (2%)
Serious or Severe Infection	0	0
Severe Hypogammaglobulinemia	0	0
Cytokine Release Syndrome	0	0

[1] Follow-up through day 29 post-dose
[2] Upper respiratory tract infection, hyperlipasaemia, dyspepsia, fatigue and iron deficiency anaemia (n=1 each)
[3] Urinary tract infection, headache, migraine, nausea, and back pain (n=1 each); lipase increased (n=2)
[4] Blood creatine phosphokinase increased, attributed to strenuous exercise
[5] Infusion-related reaction, injection-related reaction, injection site pain, or injection site reaction

Most Common[1] TEAEs

Data Extract: 29JUL2022

Preferred Term (Any Grade)	All Placebo (N=22)	All ALPN-303 (N=44)
Headache or Migraine	**4 (18%)**	**11 (25%)**
Grade 1	4 (18%)	9 (20%)
Grade 2	0	2 (5%)
Infections[2]	**4 (18%)**	**6 (14%)**
Grade 1	3 (14%)	5 (11%)
Grade 2	1 (5%)	1 (2%)
Dizziness[3]	**1 (5%)**	**5 (11%)**
Grade 1	1 (5%)	4 (9%)
Grade 2	**0**	1 (2%)
Hypogammaglobulinemia[4]	**0**	**4 (9%)**
Grade 1		4 (9%)

[1] Experienced by more than 5% of subjects treated with ALPN-303
[2] Events coded in system organ class of Infections and Infestations including COVID-19, nasopharyngitis, viral URTI (all G1); URTI (G2) in subjects in the placebo group and COVID-19 (n=2), URTI (n=2), furuncle (all G1); urinary tract infection (G2) in subjects treated with ALPN-303
[3] 'Dizziness,' 'dizziness postural' or 'presyncope'
[4] 'Blood immunoglobulin M decreased' or 'hypogammaglobulinemia'
G1 = Grade 1; G2 = Grade 2; URTI = upper respiratory tract infection

Figure 4: ALPN-303 Provides Dose-Dependent Pharmacokinetics and Target Coverage

- Dose-dependent PK is observed by both IV and SC routes with good bioavailability (60 to >100% at 80 to 960 mg). Estimated half-life ($t_{1/2}$) at 80 to 240 mg is 3.1 to 7.5 days
- Through Day 28 post-dose, >95% coverage of APRIL achieved by both IV and SC 240 mg doses

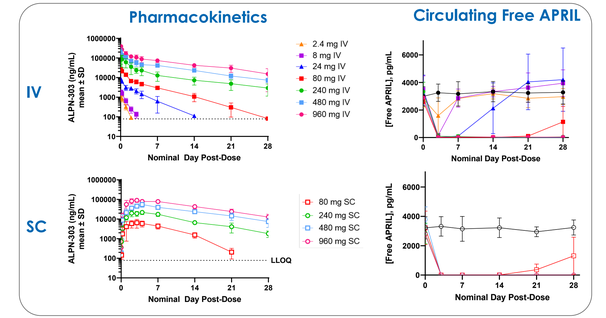
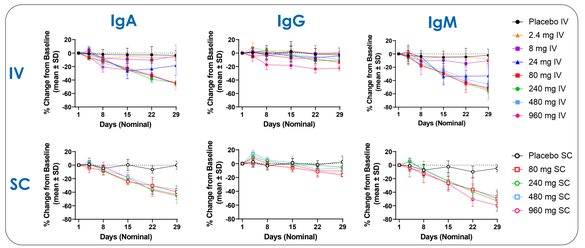


Figure 5: ALPN-303 Dose-Dependently Reduces Circulating Immunoglobulins and Antibody-Secreting Cells (ASC)

Effects generally appear saturated ≥ 80 mg for ≥ 4 weeks



Antibody-Secreting Cells

CD38^{hi} plasmablasts & plasma cells, of gated CD19+CD27+IgD- memory B cells

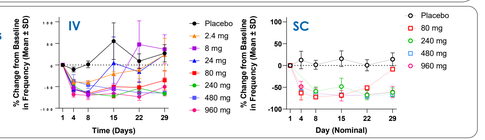
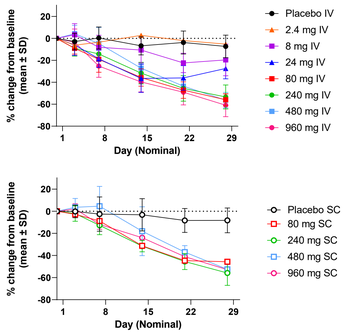


Figure 6: ALPN-303 Decreases Gd-IgA1 Levels



Serum galactose-deficient IgA1 (Gd-IgA1) levels were measured using an ELISA kit (Immuno-Biological Laboratories/IBL) per the manufacturer's protocol. Serum samples were diluted a minimum of 400-fold in assay diluent, and Gd-IgA1 was captured with a rat monoclonal antibody that specifically recognizes a hinge region in human Gd-IgA1 (KM55). The assay range was 1.56 to 100 ng/mL with the LLOQ and ULOQ set at 1.56 and 50 ng/mL, respectively. The % change from baseline (predose) values are plotted.

Summary and Conclusions

- In this first-in-human study, ALPN-303 has been well-tolerated as single IV or SC doses 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 of any grade, have been observed.
- ALPN-303 demonstrates dose-dependent PK/PD. Coverage of free APRIL is maintained for 2-3 and ≥4 wk with 80 and 240 mg, respectively, corresponding to reductions in serum Ig (including Gd-IgA1) and antibody-secreting cells. These data support dose regimens of 80-240 mg SC every 4 weeks in future studies.
- Further clinical development of ALPN-303 in autoimmune GNs and other autoantibody-related diseases is strongly supported. Clinical trials in GNs, including IgAN, LN, and membranous nephropathy, as well as other related disorders (e.g., lupus, cytopenias), are in preparation.

Acknowledgements

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