A Randomized Placebo-Controlled Phase 1 Study in Healthy Adult Volunteers of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ALPN-303, a Potent Dual BAFF/APRIL Antagonist for the Treatment of Systemic Lupus Erythematosus and Other Autoantibody-Associated Diseases

Stacey R. Dillon[1], Rupert Davies[1], Jason D. Lickliter[2], Kristi McLendon[2], Kristi L. Manjarrez[1], Alina Smith[1], Mary C. Lessig[1], Lori Blanchfield[1], Russell J. Sanderson[1], Allison Chunyk[1], Amanda Enstrom[1], Tiffany Blair[1], Martin Wolfson[1], Mark Rixon[1], Hany Zayed[1], and Stanford L. Peng[1]

[1]Alpine Immune Sciences Inc., Seattle, United States of America

[2]Nucleus Network, Melbourne and Brisbane, Australia

Background

- Agents targeting the B-cell cytokines B-cell activating factor (BAFF) and/or a proliferation-inducing ligand (APRIL), including the monoclonal antibody belimumab and the wild-type (WT) transmembrane activator and calcium modulating cyclophilin ligand interactor (TACI)-Fc fusion proteins atacicept and telitacicept, have demonstrated promising clinical potential in rheumatic diseases like systemic lupus erythematosus (SLE) and other autoantibody-related disorders, though the majority of patients fail to achieve remission.
- ALPN-303 is an Fc fusion protein of a variant, engineered TACI domain with enhanced target affinity (see data at right).
- ALPN-303 mediates significantly more potent inhibitory activity than WT TACI-Fc or BAFF- or APRIL-specific monoclonal antibodies when evaluated head-to-head in preclinical studies, with enhanced pharmacokinetic (PK) and immunomodulatory properties.

ALPN-303 has Significantly Enhanced Affinity for BAFF and APRIL as Compared to WT TACI-Fc (Surface Plasmon Resonance)

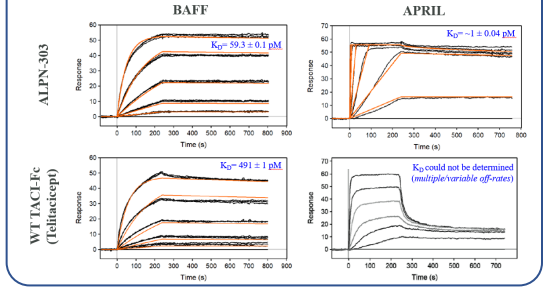
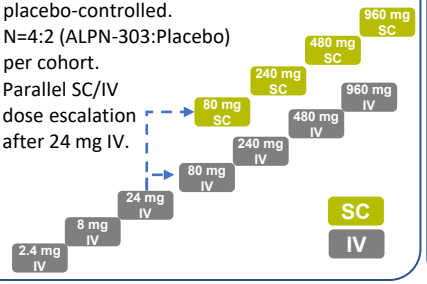


Figure 1: RUBY-1 Study Design

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	40 (61%)
Asian	13 (20%)
Other	13 (20%)
BMI (kg/m²)[1]	25 (18, 31)
eGFR[2]	
≥90	29 (69%)
60–89	13 (31%)
Completed[3]	39 (59%)

Data Extract: 29JUL2022

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

Figure 2: 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

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 (Grade 1)	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, hyperlipasemia, dyspepsia, fatigue and iron deficiency anemia (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.

Data Extract: 29JUL2022

Most Common[1] TEAEs

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.

Data Extract: 29JUL2022

Figure 3: 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.

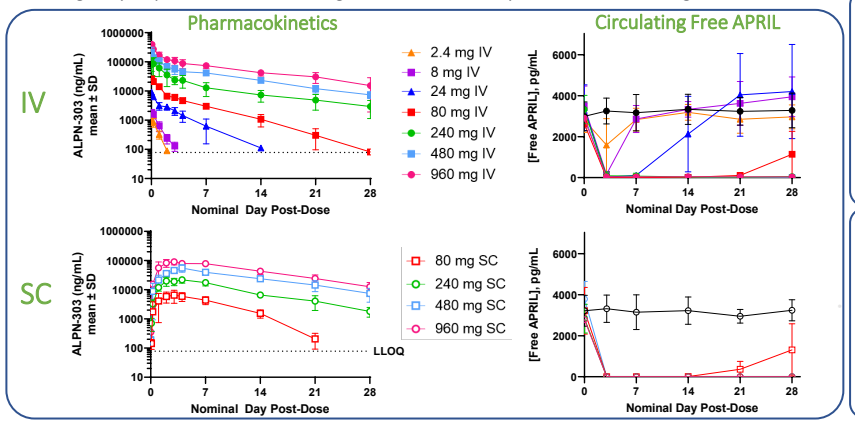
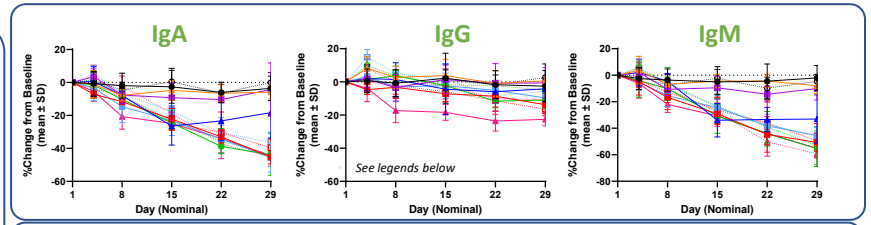
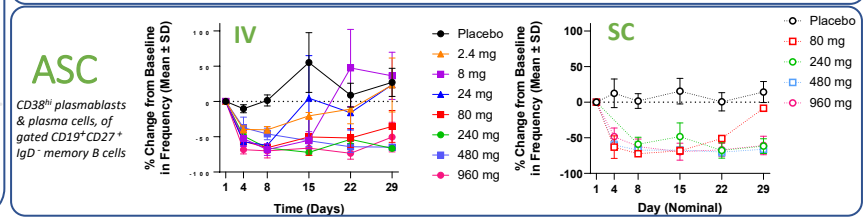


Figure 4: ALPN-303 Dose-Dependently Reduces Circulating Immunoglobulins and Antibody-Secreting Cells (ASC)

Effects appear generally saturated ≥80 mg for ≥4 weeks





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, severe hypogammaglobulinemia, or cytokine release have been observed.
- ALPN-303 demonstrates dose-dependent PK/PD. Coverage of free APRIL is maintained for 2-3 weeks and ≥4 weeks with 80 and 240 mg, respectively, corresponding to reductions in serum Ig 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 SLE and other autoantibody-related diseases is strongly supported. Clinical trials in SLE, as well as other related disorders (e.g., cytopenias, glomerulonephritides), are in preparation.