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PO6:131

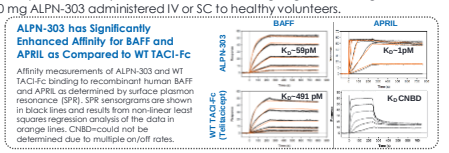
A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ALPN-303, A POTENT DUAL BAFF/APRIL INHIBITOR, IN ADULT HEALTHY VOLUNTEERS (RUBY-1)

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

[1]Alpine Immune Sciences Inc., Seattle, United States of America
[2]Nucleus Network, Melbourne, Australia

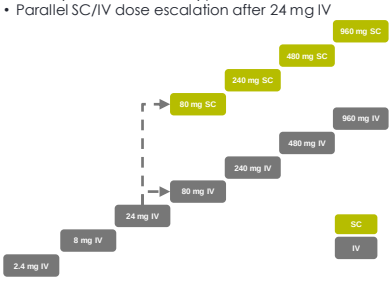
Background

- In rheumatic diseases like systemic lupus erythematosus (SLE) and other autoantibody-related disorders, current treatments fail to achieve remission in the majority of patients. 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 such diseases.
- ALPN-303 is an Fc fusion protein of a variant, engineered TACI domain which 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.
- 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.



Study Design

- 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%)

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

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, 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

Data Extract: 29JUL2022

Most Common[1] TEAEs

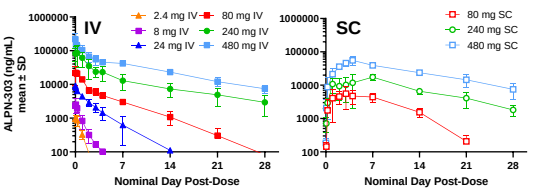
Preferred Term (Any Grade)	All Placebo (N=22)	All ALPN-303 (N=44)
Headache or Migraine	4 (18%)	11 (25%)
Grade 1	4 (18%)	9 (20%)
Grade 2	0	2 (5%)
Infections[2]	4 (18%)	6 (14%)
Grade 1	3 (14%)	5 (11%)
Grade 2	1 (5%)	1 (2%)
Dizziness[3]	1 (5%)	5 (11%)
Grade 1	1 (5%)	4 (9%)
Grade 2	0	1 (2%)
Hypogammaglobulinemia[4]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

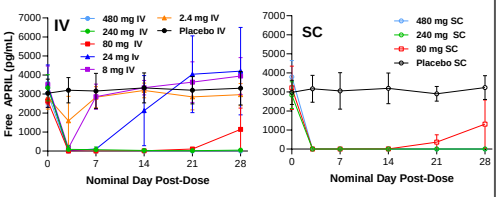
- ALPN-303 has been well-tolerated overall; most common adverse events (AEs) include mild (G1) headache, dizziness, low Ig (an expected pharmacodynamic [PD] effect), or back pain. Incidence of infection has not significantly differed from placebo.
- No G4-5 AEs, serious AEs, serious or severe infection,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

Dose-Dependent Pharmacokinetics



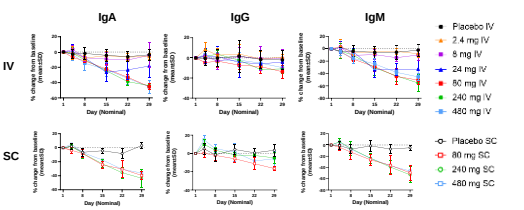
- Dose-dependent PK (preliminary) is observed by both IV and SC routes with good bioavailability (60 to >100% at 80 to 240 mg)
- Estimated half-life ($t_{1/2}$) at 80 to 240 mg: 3.1 to 7.7 days

Target Coverage: Circulating Free APRIL



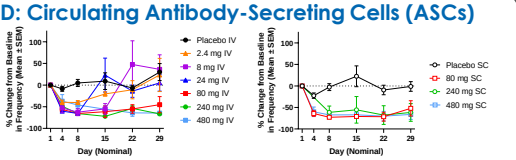
- Dose-dependent reductions, and durations thereof, in free APRIL observed
- Through Day 28 post-dose, >95% coverage achieved by both IV and SC 240 mg doses (preliminary)

PD: Circulating Immunoglobulins (Ig)



- Dose-dependent, on-target reductions in circulating IgM>IgA>IgG (preliminary)
- Maximal negative slope observed at doses ≥ 80 mg, suggesting saturated PD

PD: Circulating Antibody-Secreting Cells (ASCs)



- Dose-dependent, on-target reductions in the frequency of circulating CD19+CD38+CD27+IgD- ASCs (includes plasmablasts, plasma cells; preliminary)
- Maximal reductions observed at doses ≥ 80 mg, suggesting saturated PD

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, hypogammaglobulinemia, or cytokine release have been observed.
- ALPN-303 demonstrates dose-dependent PK/PD. Coverage of free APRIL is maintained for ≥4 weeks with a 240 mg dose IV or SC, corresponding to reductions in serum Ig and antibody-secreting cells (ASCs).
- 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, bullous disorders), are in preparation.

Sponsor: Alpine Immune Sciences, Inc.

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