POS0114

A Placebo-Controlled Phase 1 Study in Healthy Adult Volunteers of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Povetacicept (ALPN-303), a Potent Dual BAFF/APRIL Antagonist, for the Treatment of Systemic Lupus Erythematosus and Other B Cell-Related Disorders (RUBY-1)

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Background

B cell activating factor of the TNF family (BAFF) and a proliferation-inducing ligand (APRIL), cytokines which bind and signal through BAFF-R, transmembrane activator and CAML interactor (TACI), and/or B cell maturation antigen (BCMA) on B cells, play overlapping and non-redundant roles in B cell development, proliferation, function, and survival. Therapeutic agents targeting BAFF +/- APRIL have demonstrated promising clinical potential in the treatment of systemic lupus erythematosus (SLE) and lupus nephritis, as well as other autoantibody-related diseases; however, there is still need for more safe and efficacious therapies. Povetacicept (ALPN-303) is an Fc fusion protein of an engineered TACI variant TNFRSF domain (vTD) with enhanced affinity for APRIL and BAFF, which demonstrates more potent inhibitory activity than WT TACI-Fc or BAFF- or APRIL-specific antibodies. Povetacicept may therefore significantly improve clinical outcomes in SLE and other B cell-related diseases. In this first-in-human study (NCT05034484), 72 healthy adult volunteers were treated in single ascending dose cohorts of intravenous (IV) or subcutaneous (SC) povetacicept or placebo. Participants were followed to assess safety and PK, circulating immunoglobulins (Ig), and circulating lymphocyte populations by flow cytometry.

Figure 1: Povetacicept is an Enhanced APRIL/BAFF Antagonist that Potently Modulates B Cells and Pathogenic Autoantibodies

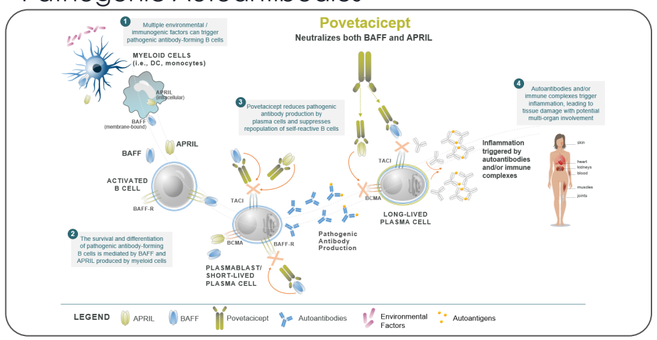
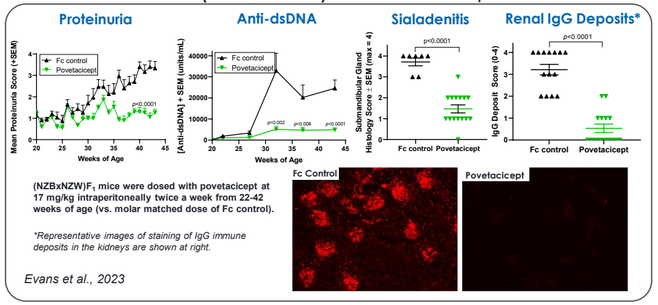


Figure 2: Povetacicept Significantly Suppresses Disease in the (NZB/NZW)F_1 Murine Lupus Model

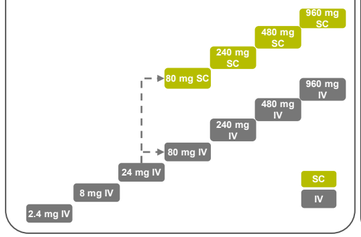


Evans et al., 2023

Figure 3: RUBY-1 Study Design

Study Design

Single ascending doses of 2.4 to 960 mg povetacicept administered IV or SC to adult healthy volunteers



Demographics and Disposition

Attribute	Subjects (N=72)
Age (year)[1]	31.0 (18, 64)
Female	49 (68%)
Race	
White	46 (64%)
Asian	14 (19%)
Other	12 (17%)
BMI (kg/m²)[1]	24.6 (18, 31)
eGFR[2]	
≥90	59 (82%)
60–89	13 (18%)
Completed	71 (99%)

[1] Median (min, max)
[2] mL/min/1.73 m²

Data Extract: 14MAR2023

BMI = body mass index
eGFR = estimated glomerular filtration rate

Figure 4: Povetacicept is Well-Tolerated Overall

- The most common non-laboratory adverse events (AEs) have included mild (grade 1) headache and dizziness.
- No serious or severe infections, severe hypogammaglobulinemia (IgG < 3g/L) or cytokine release syndrome were observed.

Povetacicept is Well-Tolerated Overall

Data Extract: 14MAR2023

Treatment-Emergent Adverse Event (TEAE)	All Placebo (N=22)	All Povetacicept (N=50)
Any TEAE	**12 (55%)**	**40 (80%)**
Grade 1	7 (32%)	24 (48%)
Grade 2	4 (18%)[1]	15 (30%)[2]
Grade 3	1 (5%)[3]	1 (2%)[3]
Adverse Event of Interest	**1 (5%)**	**1 (2%)**
Administration-Related Reaction[4]	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] Dyspepsia, iron deficiency anemia, lipase increased, URTI, COVID-19 (n=1 each; 1 participant had 2 different Grade 2 events).
[2] Back pain, COVID-19, headache, migraine, nausea, Staphylococcal infection, urinary tract infection (URTI), or Varicella zoster virus infection (n=1 each); lipase increased (n=2); presyncope (n=3); URTI (n=4). 2 participants had 2 different Grade 2 events.
[3] Blood creatine phosphokinase increased, attributed to strenuous exercise.
[4] Infusion-related reaction, injection-related reaction, injection site pain, or injection site reaction.

Most Common[1] TEAEs

Data Extract: 14MAR2023

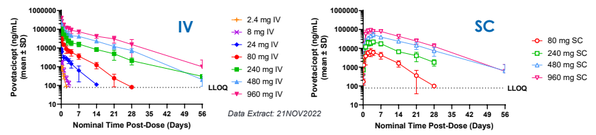
Preferred Term (Any Grade)	All Placebo (N=22)	All Povetacicept (N=50)
Headache or Migraine	**4 (18%)**	**12 (24%)**
Grade 1	4 (18%)	10 (20%)
Grade 2	0	2 (4%)
Infections	**6 (27%)**	**12 (24%)**
Grade 1	4 (18%)[2]	4 (8%)[3]
Grade 2	2 (9%)[4]	8 (16%)[5]
Dizziness[6]	**1 (5%)**	**6 (12%)**
Grade 1	1 (5%)	3 (6%)
Grade 2	0	3 (6%)

[1] Non-Ig TEAEs observed in > 10% of povetacicept-treated participants.
[2] COVID-19 (n=2) or URTI (n=2).
[3] Furuncle (n=1), or COVID-19 (n=3).
[4] URTI or COVID-19 (n=1) each.
[5] COVID-19, Staphylococcal infection, urinary tract infection, Varicella zoster virus infection (n=1) each; URTI (n=4).
[6] Dizziness, dizziness postural, presyncope, or vertigo.

Figure 5: Povetacicept Exhibits Dose-Dependent Pharmacokinetics and Target Engagement

- Dose-dependent PK is observed with good bioavailability (70 to 81% at 80 to 960 mg).
- Estimated half-life ($t_{1/2}$) at 80 or 240 mg SC is 3.7 to 7.4 days, respectively.
- Ratios of drug-free to total APRIL and BAFF* rapidly diminished and remained low for 2–3 and ≥4 wks after dosing with 80 and 240 mg, respectively.

Pharmacokinetics



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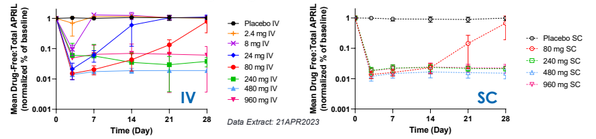
Circulating Drug-Free APRIL : Total APRIL



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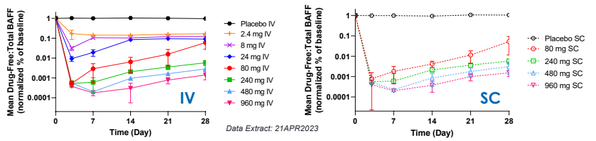
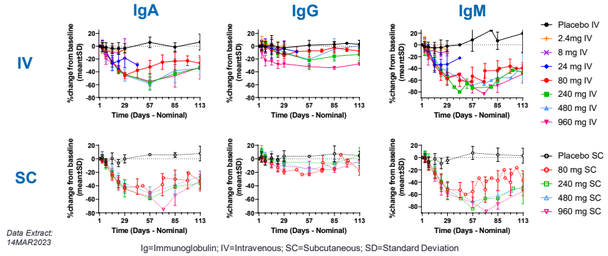
Circulating Drug-Free BAFF*:Total BAFF



Data Extract: 21APR2023

*Current assay for drug-free BAFF does not detect BAFF-soluble TACI complexes

Figure 6: Povetacicept Dose-Dependently Reduces Circulating Immunoglobulins

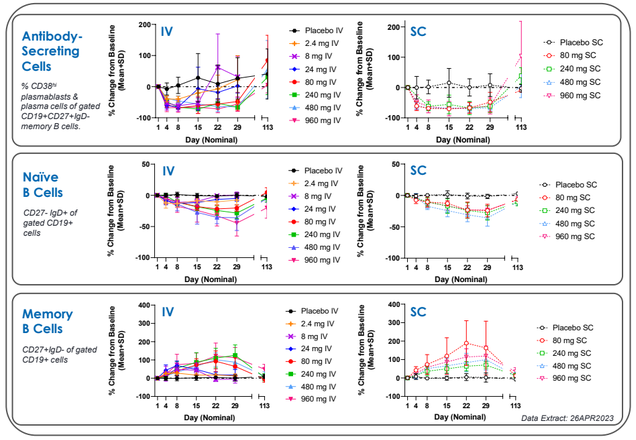


Data Extract: 14MAR2023

Ig=Immunoglobulin; IV=Intravenous; SC=Subcutaneous; SD=Standard Deviation

Post-dose reductions in IgM < LLN (0.5 g/L) were observed in 26/50 (52%) versus 1/22 (5%) of povetacicept- versus placebo-treated participants, respectively. No incidences of total IgG < LLN (6.1 g/L) were observed. A statistical relationship between dose and incidence of post-treatment Ig reductions < LLN could not be confirmed.

Figure 7: Povetacicept Impacts Naïve & Memory B Cells and Antibody-Secreting Cells (ASC)



Data Extract: 26APR2023

Summary and Conclusions

- In this first-in-human study, povetacicept was well-tolerated as single IV or SC doses of up to 960 mg in adult healthy volunteers. The most frequent adverse event was mild headache. No severe infections, severe IgG hypogammaglobulinemia (IgG<3 g/L), or cytokine release were observed.
- Povetacicept demonstrates dose-dependent PK/PD. Preliminarily, ratios of drug-free to total APRIL and BAFF* rapidly diminished and remained low for 2–3 and ≥4 wks after dosing with 80 and 240 mg, respectively, corresponding to anticipated reductions in serum Ig, naïve B cells, and antibody-secreting cells, supporting dose regimens of 80–240 mg SC every 4 wks in future studies.
- Dose-related increases in circulating memory B cells were also observed, consistent with reported effects of prior BAFF inhibitors (Tak 2008; Stohl 2012; Eslami 2022).
- Future clinical study of povetacicept in SLE is strongly supported and is in preparation. Studies in autoimmune glomerulonephritis (RUBY-3; NCT05732402) & cytopenias (RUBY-4; NCT05757570) are open for enrollment.

References

- Tak *et al.* (2008) *Arthr Rheumatol* 58:61.
- Stohl *et al.* (2012) *Arthr Rheumatol* 64:2328.
- Eslami *et al.* (2022) *Front Immun* 13:1035556.
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Acknowledgements

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