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

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Background

B cell activating factor (BAFF) of the tumor necrosis factor (TNF) family and a proliferation-inducing ligand (APRIL), cytokines which bind and signal through BAFF receptor, 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 and/or APRIL have demonstrated promising clinical potential in autoantibody-related glomerulonephritides (GN) such as lupus nephritis (LN), IgA nephropathy (IgAN), membranous nephropathy, and other B-cell-related diseases such as systemic lupus erythematosus (SLE); however, there is still need for more safe and efficacious therapies. Povetacicept (ALPN-303) is an Fc fusion protein of an engineered TACI variant TNF receptor superfamily domain (vTD) with enhanced affinity for APRIL and BAFF which mediates more potent inhibitory activity than wild type TACI-Fc or BAFF- or APRIL-specific antibodies. Povetacicept may therefore significantly improve clinical outcomes in autoantibody-mediated GNs and other B-cell-related diseases. In this first-in-human study (NCT05034484), human volunteers (HV) were treated in single ascending dose cohorts of intravenous (IV) or subcutaneous (SC) povetacicept or placebo. Participants were followed to assess safety and pharmacokinetics (PK), circulating immunoglobulins (Ig), galactose-deficient IgA1 (Gd-IgA1), and circulating leukocyte populations by flow cytometry.

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

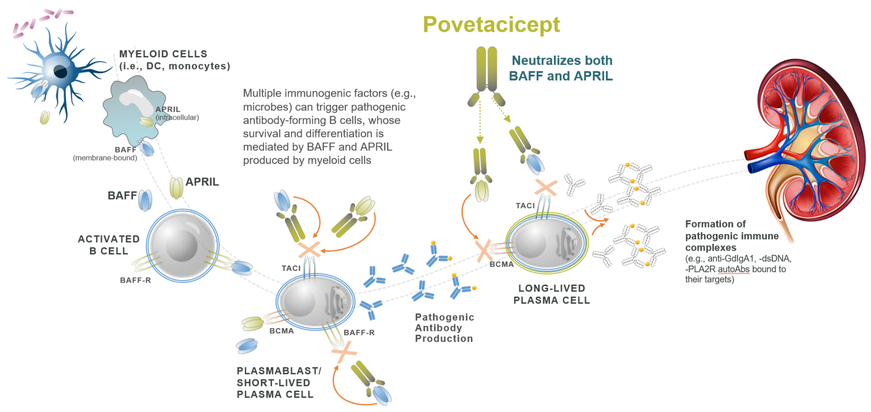
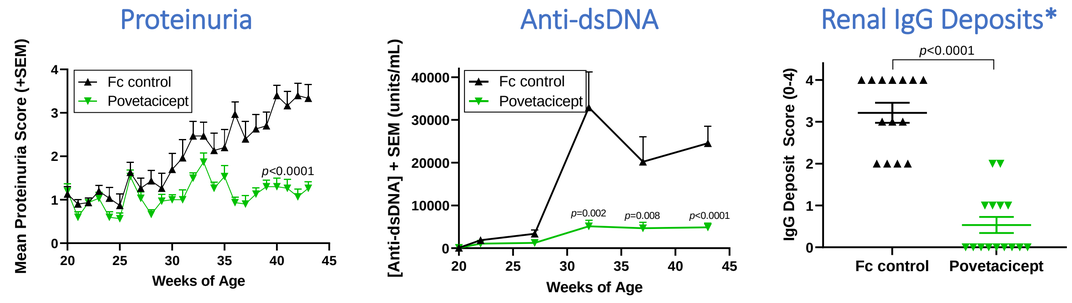


Figure 2: Povetacicept Significantly Suppresses Disease in the (NZB/NZW)F_1 Lupus Nephritis Model



(NZBxNZW)F_1 mice were dosed with povetacicept 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.* Above: Anti-dsDNA=Anti-double stranded DNA; Ig=Immunoglobulin

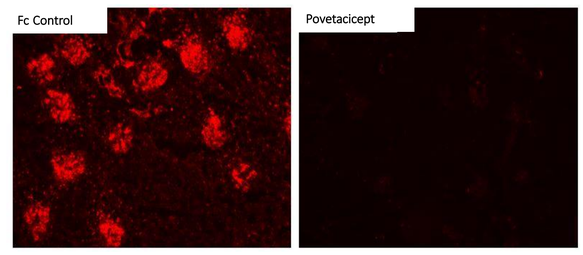
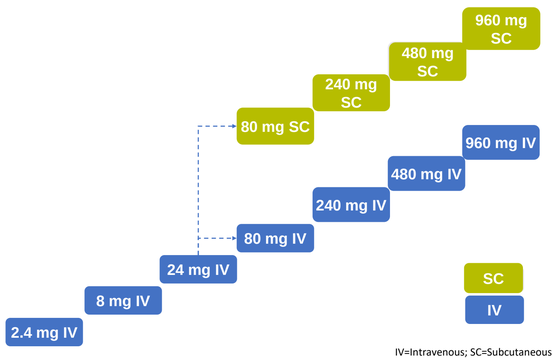


Figure 3: RUBY-1 Study Design

Study Design

- First-in-human Phase 1, evaluating single ascending doses of 2.4 to 960 mg povetacicept administered IV or SC to adult healthy volunteers.
- Randomized, double-blind, placebo-controlled.
- NCT05034484.



IV=Intravenous; SC=Subcutaneous

Demographics and Disposition

Attribute	Subjects (N=72)
Age (year)[1]	31 (18, 64)
Female	49 (68%)
Race	
White	46 (64%)
Asian	14 (19%)
Other	12 (17%)
BMI (kg/m²)[1]	25 (18, 31)
eGFR[2]	
≥90	59 (82%)
60–89	13 (18%)
Completed	68 (94%)

[1] Median (min, max) *Data Extract: 03FEB2023*
[2] mL/min/1.73 m²

BMI=Body Mass Index
eGFR=Estimated Glomerular Filtration Rate

Figure 4: Povetacicept is Well-Tolerated Overall

- Povetacicept has been well-tolerated overall; the most common adverse events (AEs) has been mild (G1) headache or migraine. Asymptomatically decreased Ig, an expected pharmacodynamic (PD) effect, has been noted, primarily of the IgM isotype, with no hypogammaglobulinemia of total IgG. The incidence of infection has not been significantly different 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) have been observed.

Povetacicept is Well-Tolerated Overall

Data Extract: 03FEB2023

Treatment-Emergent Adverse Event (TEAE)	All Placebo (N=22)	All Povetacicept (N=50)
Any TEAE	**12 (55%)**	**35 (70%)**
Grade 1	8 (36%)	25 (50%)
Grade 2	3 (14%)[1]	9 (18%)[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 (n=1 each).
[2] Back pain, headache, migraine, nausea, URTI, or urinary tract infection (n=1 each); lipase increased (n=2); or presyncope (n=3).
[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: 03FEB2023

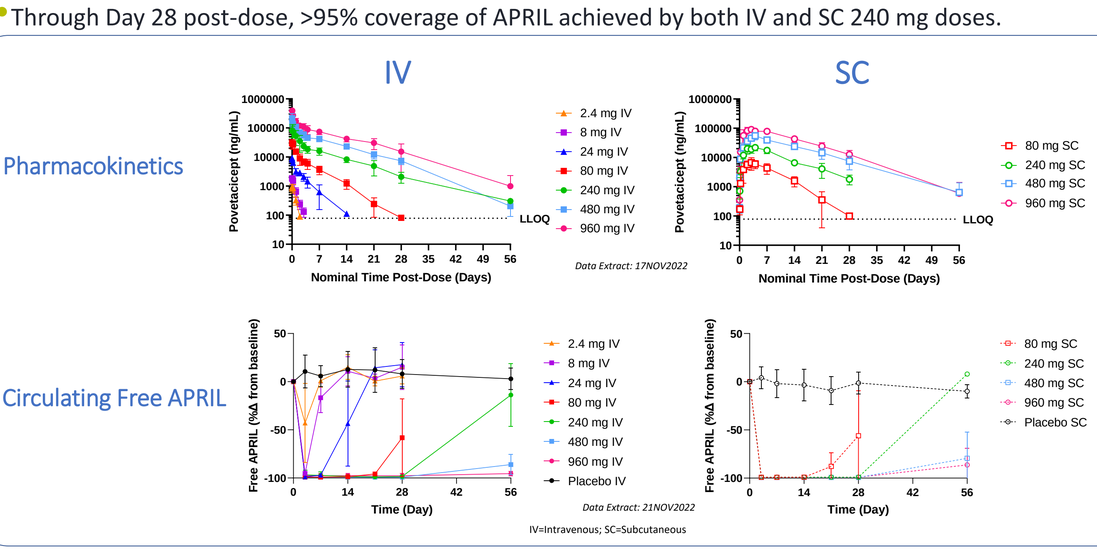
Preferred Term (Any Grade)	All Placebo (N=22)	All Povetacicept (N=50)
Headache or Migraine	**4 (18%)**	**11 (22%)**
Grade 1	4 (18%)	9 (18%)
Grade 2	0	2 (4%)
Immunoglobulin(s) decreased		**10 (20%)**
Blood immunoglobulin M decreased		9 (18%)
Grade 1	0	9 (18%)
Immunoglobulins decreased		1 (2%)
Grade 1		1 (2%)
Infections	**4 (18%)**	**6 (12%)**
Grade 1	3 (14%)[2]	4 (8%)[3]
Grade 2	1 (5%)[4]	2 (4%)[5]
Dizziness[6]	**1 (5%)**	**6 (12%)**
Grade 1	1 (5%)	3 (6%)
Grade 2	0	3 (6%)

[1] Observed in > 10% of povetacicept-treated participants.
[2] COVID-19 (n=1) or URTI (n=2).
[3] Furuncle or URTI (n=1) each, or COVID-19 (n=2).
[4] URTI.
[5] URTI or urinary tract infection (n=1 each).
[6] 'Dizziness,' 'dizziness postural,' 'presyncope,' or 'vertigo'.

URTI=Upper Respiratory Tract Infection

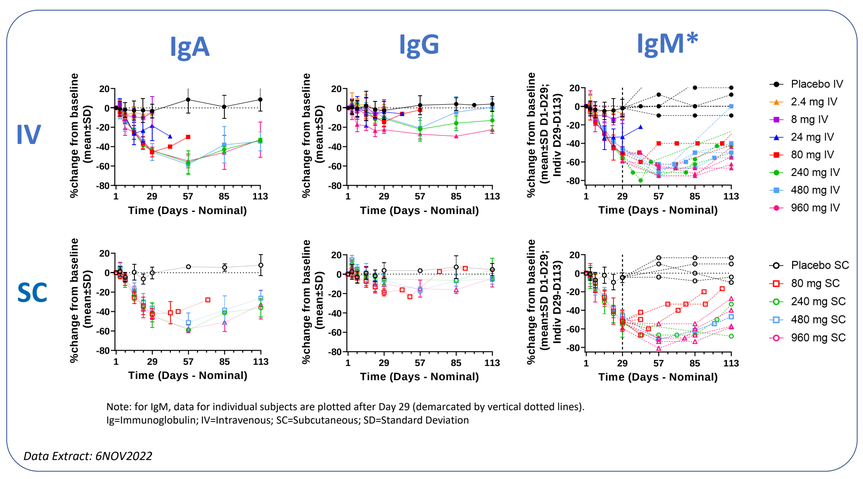
Figure 5: Povetacicept Provides Dose-Dependent Pharmacokinetics and Target Coverage

- Dose-dependent PK is observed by both IV and SC routes with good bioavailability (70 to 81% at 80 to 960 mg). Estimated half-life ($t_{1/2}$) at 80 to 240 mg SC is 3.7 to 7.4 days, respectively.
- Through Day 28 post-dose, >95% coverage of APRIL achieved by both IV and SC 240 mg doses.



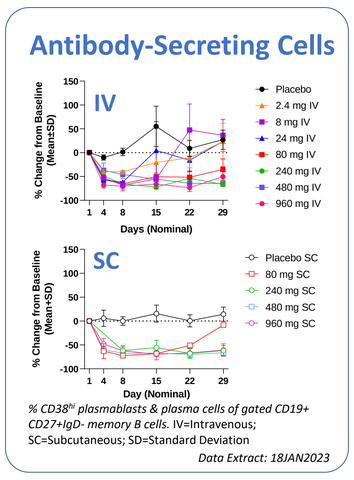
IV=Intravenous; SC=Subcutaneous

Figure 6: Povetacicept Dose-Dependently Reduces Circulating Immunoglobulins and Antibody-Secreting Cells



Note: for IgM, data for individual subjects are plotted after Day 29 (demarcated by vertical dotted lines).
Ig=Immunoglobulin; IV=Intravenous; SC=Subcutaneous; SD=Standard Deviation

Data Extract: 6NOV2022

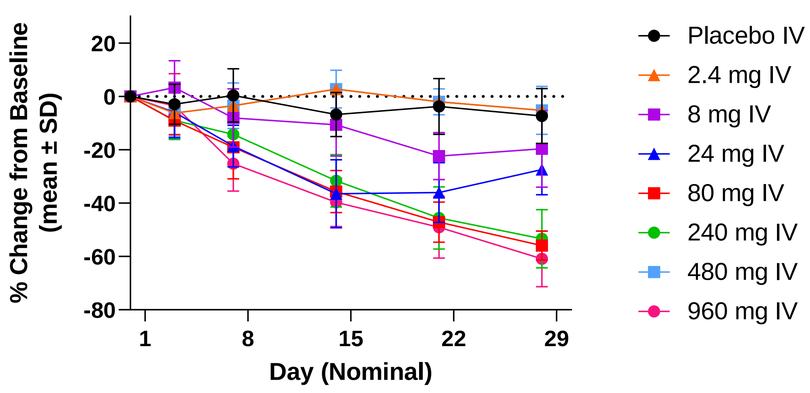


% $CD38^{hi}$ plasmablasts & plasma cells of gated CD19+ CD27+IgD- memory B cells. IV=Intravenous; SC=Subcutaneous; SD=Standard Deviation

Data Extract: 18JAN2023

Effects generally appear saturated ≥ 80 mg for ≥ 4 weeks

Figure 7: Povetacicept Dose-Dependently Decreases Gd-IgA1 Levels



Serum galactose-deficient IgA1 (Gd-IgA1) levels were measured using an ELISA kit (Immuno-Biological Laboratories) 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 lower limit of quantification and upper limit of quantification set at 1.56 and 50 ng/mL, respectively. The % change from baseline (predose) values are plotted. IV=Intravenous; SD=Standard Deviation

Data Extract: 08SEPT2022

Summary and Conclusions

- In this first-in-human study, povetacicept 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.
- Povetacicept demonstrates dose-dependent PK/PD. Coverage of free APRIL is maintained for 2-3 and ≥4 wks 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 povetacicept in autoimmune GNs and other autoantibody-related diseases is strongly supported.
- A clinical study (RUBY-3) of povetacicept in patients with GN, including IgAN, LN, or primary membranous nephropathy, is now open for enrollment (NCT05732402).
- Other studies in related disorders, including autoimmune cytopenias (NCT05757570) and systemic lupus, are also open for enrollment or in preparation.

Acknowledgements

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