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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 Blistering Diseases (RUBY-1)

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#42273

Introduction

B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) are tumor necrosis factor superfamily (TNFSF) members that bind transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI), B cell maturation antigen (BCMA), and/or BAFF receptor (BAFF-R) on B cells and together support B-cell development, survival, and differentiation into antibody-secreting cells (ASC). In preclinical studies, co-neutralization of BAFF and APRIL can directly suppress ASC and reduce circulating immunoglobulins (Ig).

Autoimmune blistering diseases (ABDs) are characterized by autoantibodies targeting structural skin proteins. Treatments are limited: rituximab is the only biologic approved for pemphigus vulgaris[1,2], but may be associated with frequent relapses, often accompanied by elevations in the cytokine BAFF[3]. BAFF and its related cytokine APRIL play key roles in B-cell activation across a broader spectrum of B cells than rituximab and are elevated in ABDs, correlating with disease activity[4-6]. BAFF/APRIL inhibition may lead to more durable autoantibody reductions, improving clinical outcomes. Povetacicept (ALPN-303) is an Fc fusion of an engineered TACI domain and a dual BAFF/APRIL antagonist that is more potent preclinically than other BAFF and/or APRIL inhibitors evaluated (i.e., belimumab, atacicept, telitacicept); some are approved and/or demonstrate promising potential for related diseases like lupus, particularly its cutaneous manifestations.

In this first-in-human study (NCT05034484), adult healthy volunteers (HV) were randomized into single-ascending-dose cohorts of intravenous (IV) or subcutaneous (SC) povetacicept or placebo. Assessments include safety, pharmacokinetics (PK), free and total APRIL and BAFF, and circulating Ig and leukocyte populations.

Figure 1: APRIL and BAFF are Critical Survival and Differentiation Factors Throughout B Cell Development

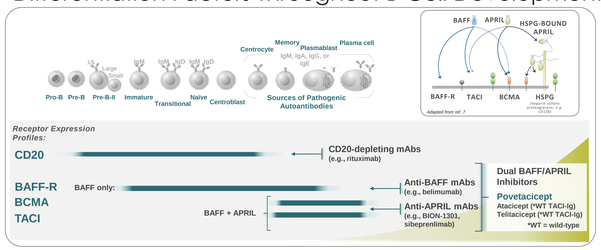
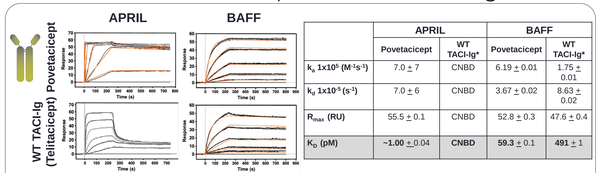


Figure 2: Povetacicept is an Fc Fusion of an Engineered TACI Domain with Enhanced Affinity for APRIL and BAFF as Compared to WT TACI-Ig



	APRIL		BAFF	
	Povetacicept	WT TACI-Ig*	Povetacicept	WT TACI-Ig*
K_a 1x10^5 ($M^{-1}s^{-1}$)	7.0 ± 7	CNBD	6.19 ± 0.01	1.75 ± 0.01
K_d 1x10^5 (s^{-1})	7.0 ± 6	CNBD	3.67 ± 0.02	8.63 ± 0.02
R_{max} (RU)	55.5 ± 0.1	CNBD	52.8 ± 0.3	47.6 ± 0.4
K_D (pM)	~1.00 ± 0.04	CNBD	59.3 ± 0.1	491 ± 1

Affinity measurements of povetacicept and WT TACI-Ig (telitacicept) binding to recombinant human BAFF and APRIL as determined by surface plasmon resonance (SPR). SPR sensorgrams are shown in black lines and results from non-linear least squares regression analysis of the data in orange lines. CNBD, could not be determined; the WT TACI-Ig/APRIL interaction displayed multiple on- and off-rates, preventing an accurate data fit using a 1:1 model. *Telitacicept commercial drug product (Tai'ai®).

Figure 3: Povetacicept Targets Both BAFF and APRIL, Two Key Cytokines that may Drive Pathogenic Autoantibodies in Autoimmune Blistering Diseases

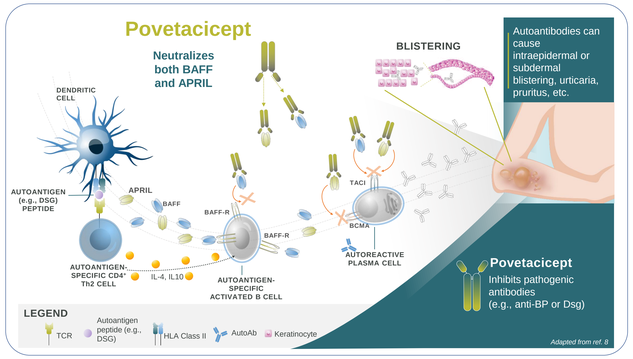
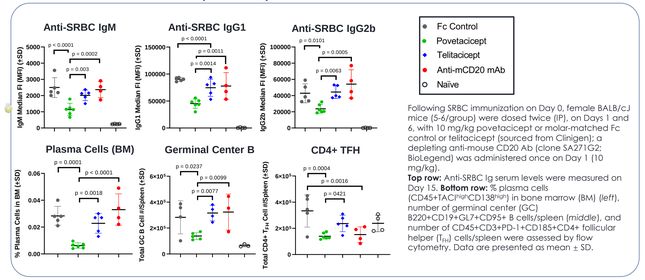


Figure 4: Povetacicept is Superior to Anti-CD20 Antibody and WT TACI-Ig (Telitacicept) in a Sheep Red Blood Cell (SRBC) Mouse Immunization Model

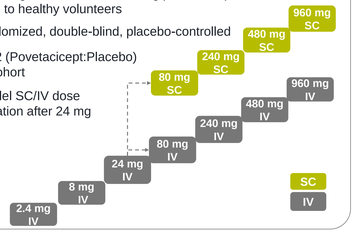


Following SRBC immunization on Day 0, female BALB/cJ mice (5-6/group) were dosed twice (IP), on Days 1 and 6, with 10 mg/kg povetacicept or molar-matched Fc control or telitacicept (sourced from Clinigen); a depleting anti-mouse CD20 Ab (clone SA271G2; BioLegend) was administered once on Day 1 (10 mg/kg).
Top row: Anti-SRBC Ig serum levels were measured on Day 15. **Bottom row:** % plasma cells (CD45+TACI^{high}CD138^{high}) in bone marrow (BM) (*left*), number of germinal center (GC) B220+CD19+GL7+CD95+ B cells/spleen (*middle*), and number of CD45+CD3+PD-1+CD185+CD4+ follicular helper (T_{FH}) cells/spleen were assessed by flow cytometry. Data are presented as mean ± SD.

Figure 5: RUBY-1 Study Design

Study Design

- RUBY-1 (NCT05054484) is a Phase 1 trial evaluating single ascending doses of 2.4 to 960 mg povetacicept administered IV or SC to healthy volunteers
- Randomized, double-blind, placebo-controlled
- N=4:2 (Povetacicept: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/m^2)[1]	25 (18, 31)
eGFR[2]	
≥90	53 (80%)
60–89	13 (20%)
Completed[3]	39 (59%)

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

Data Extract: 29JUL2022

Table 1: Povetacicept is Well-Tolerated Overall

- Povetacicept 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).

Treatment-Emergent Adverse Event (TEAE)	All Placebo (N=22)	All Povetacicept (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]
Any 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 Povetacicept (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	0	4 (9%)

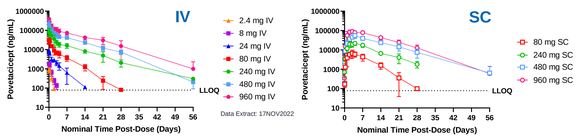
[1] Experienced by more than 5% of subjects treated with povetacicept.
[2] Events coded in system organ class of Infections and Infestations including COVID-19, nasopharyngitis, viral URTI (all G1); URTI (G2) in subjects in the placebo group and COVID-19 (n=2), URTI (n=2), furuncle (all G1); urinary tract infection (G2) in subjects treated with povetacicept.
[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 6: Povetacicept Provides Dose-Dependent Pharmacokinetics and Target Coverage

- Dose-dependent PK was 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 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.

Pharmacokinetics



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Circulating Free APRIL

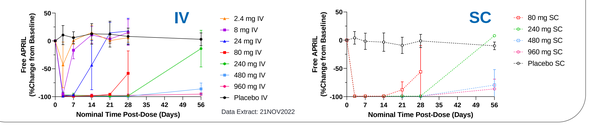

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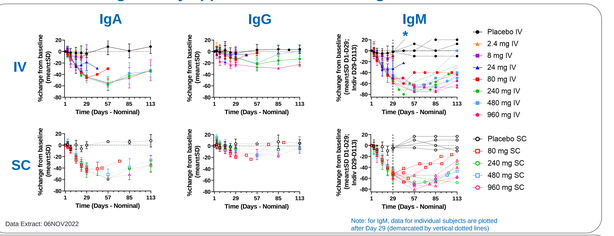
Figure 7: Povetacicept Dose-Dependently Reduces Circulating Immunoglobulins and Antibody-Secreting Cells

Effects generally appear saturated ≥ 80 mg for ≥ 4 weeks



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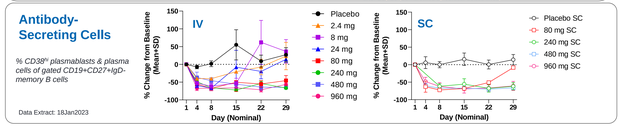
Note: for IgM, data for individual subjects are plotted after Day 29 (demarcated by vertical dotted lines)

Antibody-Secreting Cells

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



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Summary and Conclusions

- Povetacicept is an engineered variant TACI-Ig fusion with enhanced affinity as compared to WT TACI-Ig for both APRIL and BAFF and demonstrates preclinical superiority against CD20 depleting antibodies, as well as WT TACI-Ig and inhibitors of BAFF and/or APRIL alone.
- 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 wk 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 or longer in future studies.
- Povetacicept may differentiate from B cell depleting therapies and other inhibitors of BAFF and/or APRIL by potency and/or dose durability.
- Further clinical development of povetacicept in multiple autoantibody-mediated disorders, including autoimmune blistering diseases, is strongly supported.

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Acknowledgements

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