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# Povetacicept (ALPN-303), a Potent Dual BAFF/APRIL Antagonist, for the Treatment of Myasthenia Gravis (MG) and Other Antibody-Related Neurological Diseases

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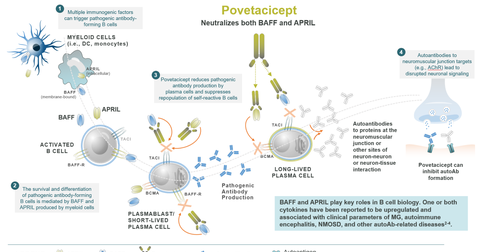
## Background

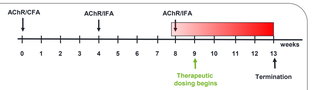
B cell activating factor (BAFF) of the TNF family and a proliferation-inducing ligand (APRIL), cytokines that bind and signal through BAFF-R, transmembrane activator and CAML interactor (TACI), and/or B cell maturation antigen (BCMA) on B cells, play overlapping and non-redundant roles in B cell development, proliferation, function, and survival. Therapeutic agents targeting B cell pathways, including BAFF and APRIL, have demonstrated promising clinical potential in the treatment of myasthenia gravis (MG), as well as other autoantibody-related neurological 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 has more potent inhibitory activity than wild-type (WT) TACI-Fc or BAFF- or APRIL-specific antibodies and demonstrates superiority to anti-CD20 therapeutics in preclinical models.[1] Povetacicept may therefore significantly improve clinical outcomes in MG 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.

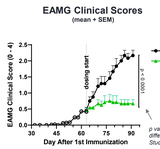
## Figure 1: Povetacicept is an Enhanced APRIL/BAFF Antagonist that Potently Modulates B Cells and Pathogenic Autoantibodies

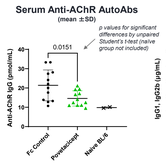


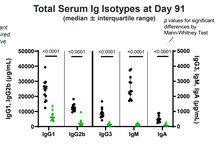

## Figure 2: Povetacicept Ameliorates Experimental Autoimmune Myasthenia Gravis (EAMG)

EAMG was induced in female C57BL/6 mice with immunizations of acetylcholine receptor (AChR) in either complete Freund's adjuvant (CFA) or incomplete Freund's adjuvant (IFA). The shaded red bar at right indicates onset and progression of disease (clinical scores ≥0.5). Intraperitoneal dosing with 10 mg/kg povetacicept or molar-matched amounts of Fc control began at Day 63 and continued twice weekly until Day 84. Mice were terminated on Day 91 (Week 13). Serum was collected on Days 63 (for total Igs) and 91 (total Igs; anti-AChR IgG). Clinical scores and serum Igs were similar across EAMG groups at Day 63.



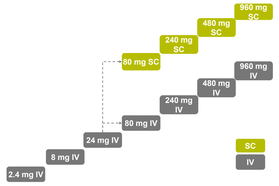




## Figure 3: RUBY-1 Study Design

### Study Design

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




### Demographics and Disposition

| Attribute | Participants (N=72) |
|---|---|
| Age (year)[1] | 31.0 (18, 64) |
| Female | 49 (68%) |
| Race<br>White<br>Asian<br>Other | <br>46 (64%)<br>14 (19%)<br>12 (17%) |
| BMI (kg/m²)[1] | 24.6 (18, 31) |
| eGFR[2]<br>≥90<br>60–89 | <br>59 (82%)<br>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, 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 |
| IgG<3 g/L | 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

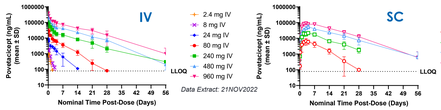
| Preferred Term (Any Grade) | All Placebo (N=22) | All Povetacicept (N=50) |
|---|---|---|
| **Headache or Migraine** | **4 (18%)** | **12 (24%)** |
| Grade 1 | 4 (18%) | 10 (20%) |
| Grade 2 | 0 | 2 (4%) |
| **Infections** | **6 (27%)** | **12 (24%)** |
| Grade 1 | 4 (18%)[2] | 4 (8%)[3] |
| Grade 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 and 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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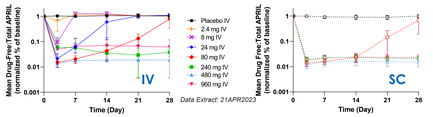
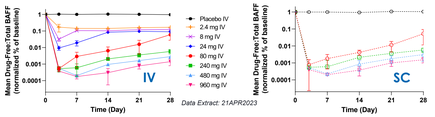
### Circulating Drug-Free APRIL : Total APRIL




Data Extract: 21APR2023

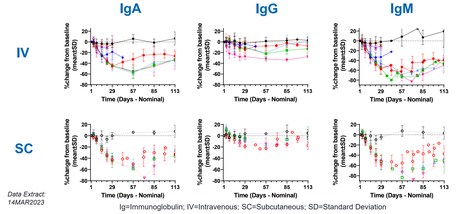
### Circulating Drug-Free BAFF*:Total BAFF




Data Extract: 21APR2023

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

## Figure 6: Povetacicept Dose-Dependently Reduces Circulating Immunoglobulins

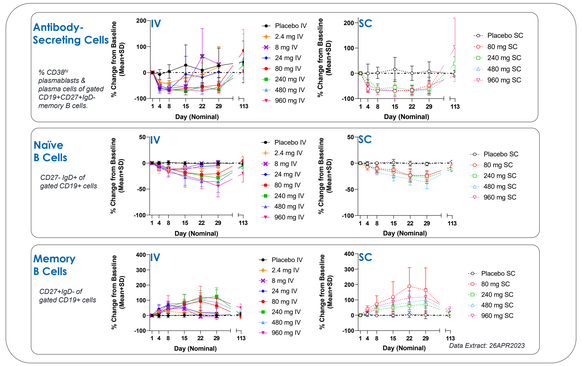



Data Extract: 14MAR2023

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




## Summary and Conclusions

- In the EAMG mouse model, povetacicept treatment initiated after disease onset led to statistically significant reductions, as compared to Fc control treatment, in clinical scores, anti-AChR IgG, and serum Ig of multiple isotypes.
- 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 serious or severe infections, IgG<3 g/L, or cytokine release were observed.
- Povetacicept demonstrates dose-dependent PK/PD. Preliminarily, coverage of circulating APRIL and BAFF appeared to be maintained 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 MG and other autoantibody-related neurological diseases is strongly supported. Studies in autoimmune glomerulonephritis (RUBY-3; NCT05732402) & cytopenias (RUBY-4; NCT05757570) are currently enrolling.

## References

1. Evans *et al.* (2023) *Arthr Rheumatol* 75:1187.
2. Uzawa *et al.* (2021) *Clin Exp Immunol* 203:366.
3. Ma *et al.* (2023) *Front Immunol* 13:1064007.
4. Ashida *et al.* (2022) *Front Neurol* 13:1012857.

## Acknowledgements

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