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Clinical Pharmacokinetic/Pharmacodynamic Modeling of Povetacicept, a Potent Dual BAFF/APRIL Antagonist, to inform Dose Selection in Autoimmune Diseases

Rupert H. Davies[1], Jeffrey R. Proctor[2], Stacey R. Dillon[1], Russell J. Sanderson[1], Allison G. Chunyk[1], and Stanford L. Peng[1]

[1]Alpine Immune Sciences Inc., Seattle, United States of America and [2]Prosiga Consulting, Vancouver, Canada

ALPINEImmuneSciences

Abstract/Background

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 play key roles in pathogenesis of multiple autoimmune diseases via their roles in the activation, differentiation and/or survival of B cells, particularly antibody-secreting cells, as well as T cells and innate immune cells.

Therapeutic agents targeting BAFF and/or APRIL have demonstrated promising clinical efficacy and proof-of-concept in systemic lupus erythematosus, lupus nephritis, IgA nephropathy, Sjogren's syndrome, and myasthenia gravis; 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 mediates potent inhibitory activity. Povetacicept may therefore significantly improve clinical outcomes in autoimmune and/or autoantibody or B cell-related diseases.

In a 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. This study provided the PK/PD data for model fitting, and simulations of these models were used to inform dose selection in subsequent clinical trials in autoimmune patients.

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

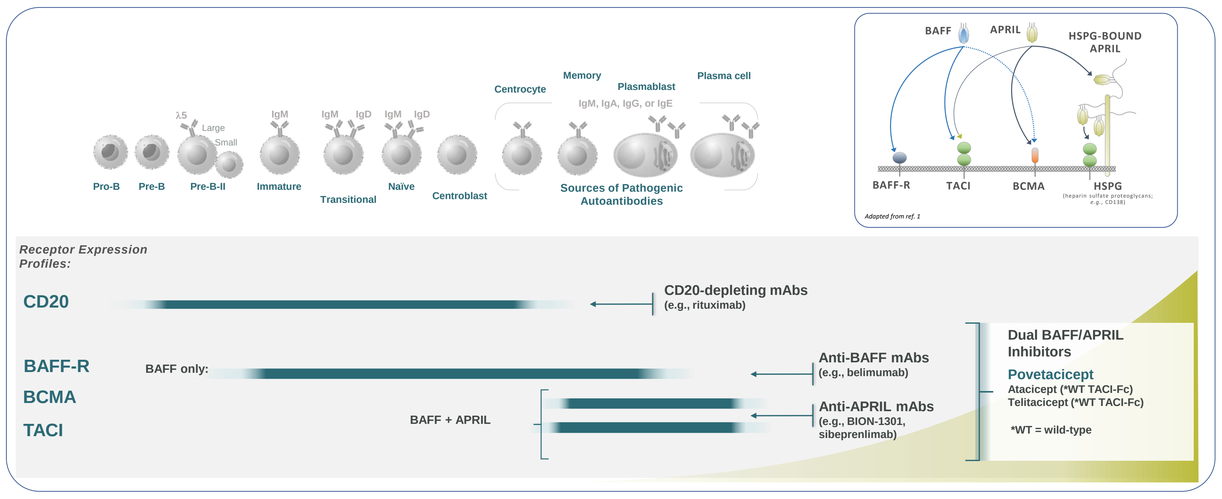


Figure 2: Povetacicept is an Enhanced APRIL/BAFF Antagonist that Potently Modulates B Cells and Pathogenic Autoantibodies

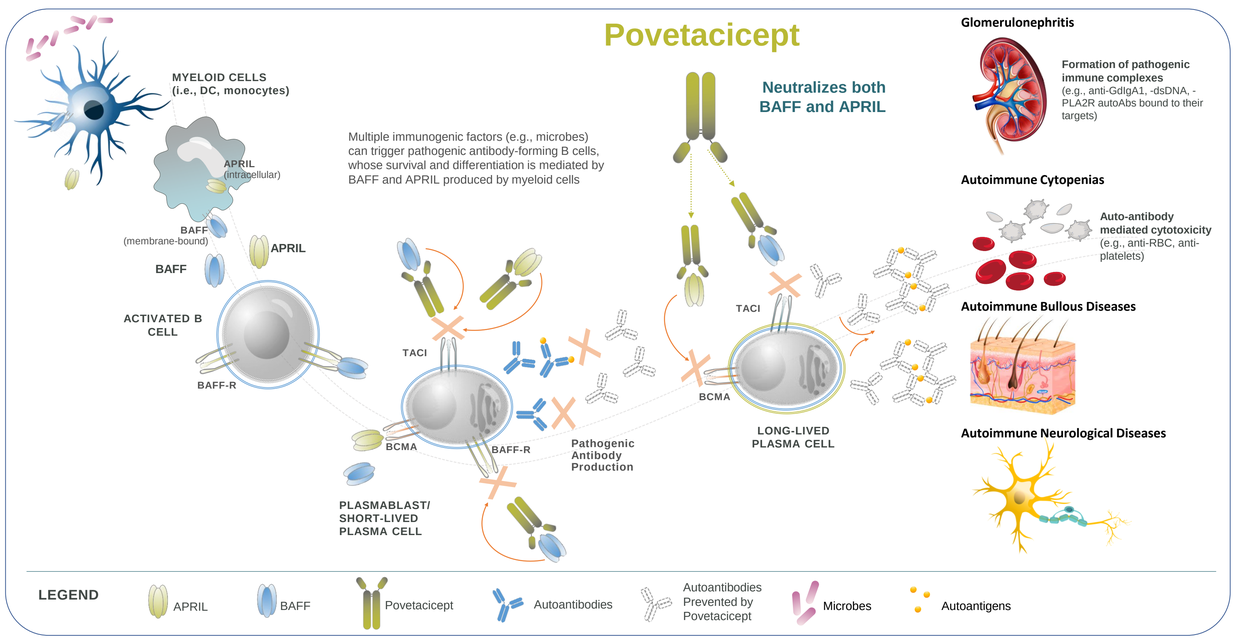


Figure 3: RUBY-1 Study Design

Study Design

- RUBY-1 (NCT05054484) was a Phase 1 trial evaluating single ascending doses of 2.4 to 960 mg povetacicept administered IV or SC to healthy volunteers.
- PK/PD models (direct and indirect) were fit to exposure and PD data.
- Monte Carlo simulations of these models were used to predict the APRIL and BAFF target coverage and decreases in immunoglobulin G (IgG) and galactose-deficient IgA1 as surrogate PD and efficacy biomarkers, respectively.
- Repeat-dose stimulations were performed out to 24 weeks with 16 weeks of recovery.

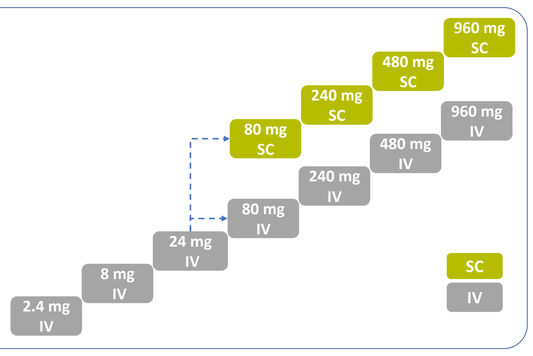
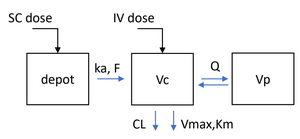


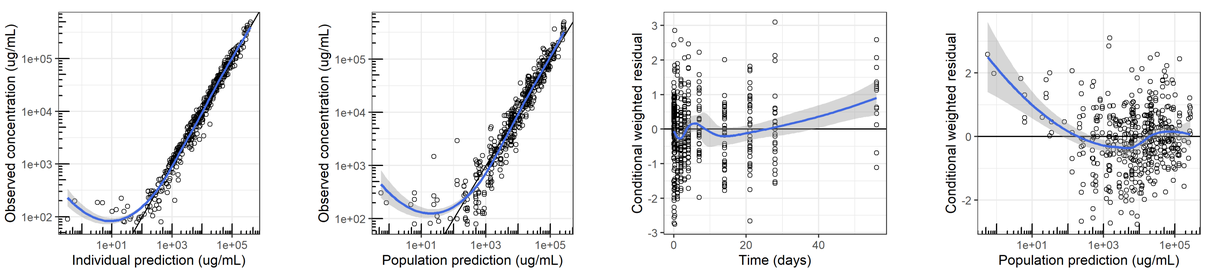
Figure 4: Povetacicept PK Model Structure, Model Diagnostic Plots and Visual Predictive Assessment

PK Model Structure



- Two compartment model with first order absorption
- Parallel linear and non-linear (Michaelis-Menten) clearance
- Inter-individual variability estimated on CL, Vc
- All parameters estimated with RSE < 40%
- < 20% shrinkage in PK model

PK Model Diagnostic Plots



PK Visual Predictive Assessment

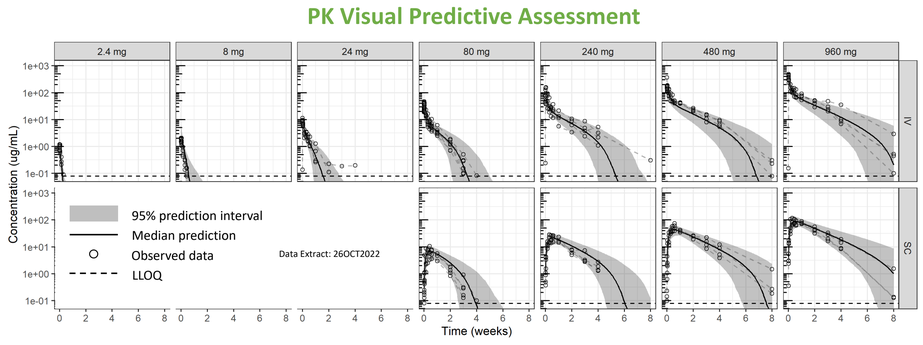
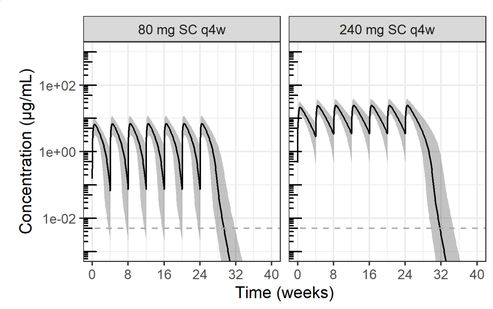


Figure 5: Povetacicept PK Simulation

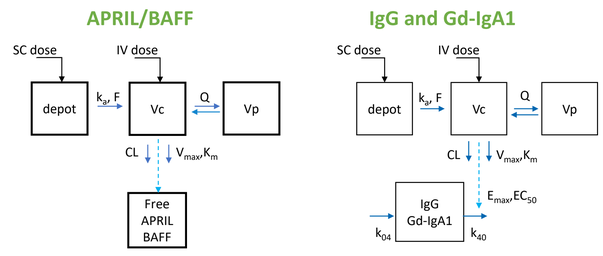


- Based on NCA, the half-life of povetacicept at 80 and 240 mg SC is 3.7 days and 7.4 days, respectively.
- Repeat dosing of povetacicept, at dose intervals of 4 weeks or more, is predicted to have little to no accumulation.
- For doses below 240 mg Q4W, non-linear clearance dominates.
- Steady state is reached by the second dose due to the rapid clearance.

95% prediction interval
Median prediction
LLOQ

Figure 6: Povetacicept PK/PD Model Structures and Visual Predictive Assessments and Summary of Simulations

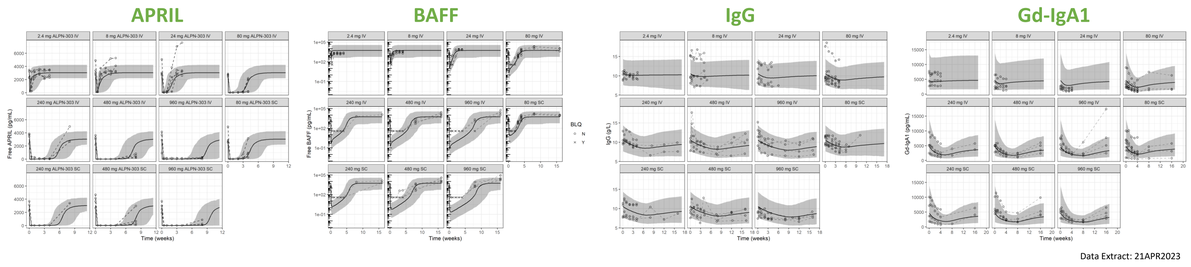
PK/PD Model Structures



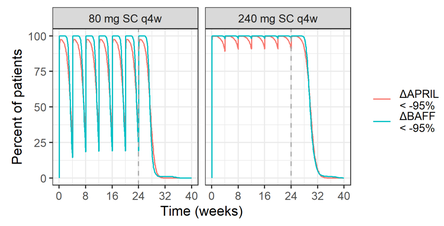
- APRIL, BAFF, IgG and Gd-IgA1 PK/PD models were all fitted individually and had specific parameters.
- Free APRIL/BAFF concentrations are best described with direct models.
- IgG and Gd-IgA1 concentrations are best described by indirect models with a saturable effect.

95% prediction interval
Median prediction
Observed data

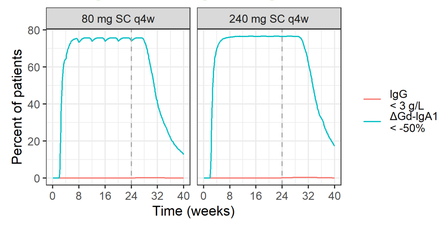
PK/PD Visual Predictive Assessments



APRIL/BAFF Target - 95% Coverage



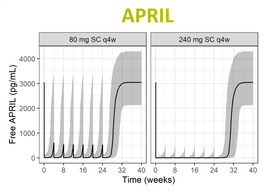
IgG and Gd-IgA1 Targets



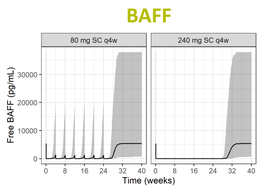
- The dose regimens of 80 and 240 mg SC Q4W are predicted to enable greater than 75% and 90% of patients with target coverage for 3 and 4 weeks at steady state, respectively.
- These dose regimens will not likely (< 1%) be associated with hypogammaglobulinemia (IgG < 3 g/L).
- Gd-IgA1 simulations predict greater than 70% of patients will have decreases in Gd-IgA1 greater than 50%.
- These dose regimens of 80 and 240 mg SC Q4W are anticipated to provide adequate APRIL/BAFF target coverage while minimizing risk of hypogammaglobulinemia.

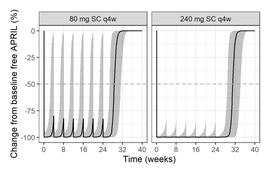
Figure 7: Povetacicept PK/PD Simulations

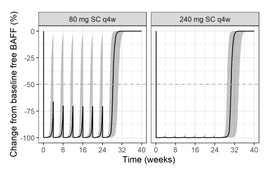
APRIL



BAFF



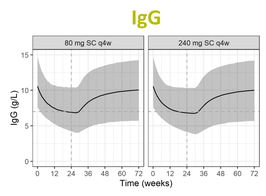


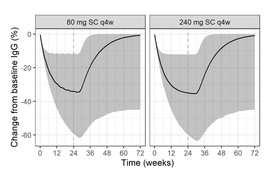


- Simulations show that APRIL/BAFF are quickly reduced by both 80 and 240 mg dose regimens within <1 day and the median APRIL/BAFF recovers to baseline levels within 8 to 10 weeks, respectively.
- APRIL/BAFF simulations predict that median patient dosed 80 and 240 mg SC Q4W will have 70% and >95% reductions in APRIL/BAFF for entire dosing period, respectively.

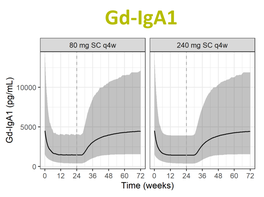
95% prediction interval
Median prediction

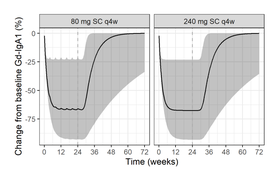
IgG





Gd-IgA1





- IgG simulations of 80 and 240 mg SC Q4W dose regimens predict an estimated reduction of 35% on average (ranging from 11% to 62% [95% prediction interval]) from baseline.
- Gd-IgA1 simulations of 80 and 240 mg SC Q4W dose regimens estimate a mean reduction of greater than 65%.
- The povetacicept doses of 80 and 240 mg Q4W are similarly predicted to result in meaningful reductions in other immunoglobulins (IgA: -60% and IgM: -80%) that may further correlate with activity.

95% prediction interval
Median prediction

Summary and Conclusions

- Povetacicept exposure is best described by a PK model with parallel linear and nonlinear clearance.
- APRIL/BAFF and immunoglobulin concentrations are best described by direct and indirect models with a saturable effect, respectively.
- Dose regimens of 80 and 240 mg SC Q4W are anticipated to provide adequate APRIL/BAFF target coverage while minimizing risk of hypogammaglobulinemia.
- Simulations of these PK/PD models support investigating the dose regimens of 80-240 mg SC every 4 weeks in future studies within autoimmune diseases.

References

1. Sakai *et al*. Clin Microbiol Rev. 2017. Oct; 30(4): 991-1014.
2. Hébert and Joly. Immunotherapy. 2018 Jan; 10(1): 27-37.

Acknowledgements

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