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331.THROMBOTIC MICROANGIOPATHIES/THROMBOCYTOPENIAS AND COVID-19-RELATED THROMBOTIC/VASCULAR DISORDERS: CLINICAL AND EPIDEMIOLOGICAL

Initial Report of Povetacicept, an Enhanced Dual BAFF/APRIL Antagonist, in Autoimmune Cytopenias: The RUBY-4 Study

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Introduction: BAFF and APRIL are cytokines with key roles in B cell development, survival, differentiation into antibody-secreting cells (ASCs; plasmablasts and plasma cells), and production of antibodies, making them promising targets for the treatment of autoantibody-associated diseases such as immune thrombocytopenia (ITP), warm autoimmune hemolytic anemia (wAIHA), and cold agglutinin disease (CAD). Patients with ITP or AIHA have elevated serum BAFF and APRIL levels and belimumab, a BAFF inhibitor, has exhibited encouraging efficacy in the treatment of lupus-associated ITP as well as alone or in combination with rituximab for the treatment of primary ITP. Due to their overlapping but non-redundant roles, inhibition of both BAFF and APRIL may be required for optimal efficacy in autoimmune cytopenias. In preclinical studies, dual BAFF/APRIL inhibition achieved superior suppression of ASCs and immunoglobulin levels vs inhibitors of BAFF or APRIL alone or an anti-CD20 antibody, suggesting the potential of this novel mechanism to modify the underlying pathogenesis of autoimmune cytopenias. Povetacicept (ALPN-303) is a TACI-Fc fusion protein engineered for potent dual BAFF/APRIL inhibition. In a mouse model of AIHA, povetacicept suppressed anti-erythrocyte autoantibodies and increased hematocrit (ASH 2022 abstract #3763). In a first-in-human study in healthy volunteers, povetacicept was well tolerated and reduced levels of circulating ASCs and immunoglobulins. This is an initial report of an open-label study of povetacicept in autoimmune cytopenias (RUBY-4; NCT05757570).
Methods: RUBY-4 is a phase 1b, group-sequential, parallel-cohort study evaluating povetacicept in participants aged ≥18 years with a documented diagnosis of primary ITP, wAIHA, or CAD of ≥12 weeks in duration (Figure). Eligible participants must have sustained thrombocytopenia (ITP cohort) or sustained symptomatic anemia (wAIHA/CAD cohorts)-i.e., platelet count $<30 \times 10^9$/L or hemoglobin ≤10 g/dL on 2 occasions ≥7 days apart during screening-and a history of failure or relapse on ≥2 prior treatments (including a thrombopoietin receptor agonist for the ITP cohort). Background therapy, including corticosteroids, is allowed but must remain at stable doses for the durations specified in the protocol. Participants receive povetacicept 240 mg subcutaneously once every 4 weeks for 24 weeks, with an optional 24-week treatment extension, followed by an 8-week off-treatment follow-up period. The primary objective is safety and tolerability; secondary objectives include pharmacokinetics, pharmacodynamics, immunogenicity, and efficacy.
Results: As of 31 July 2023, 1 participant with ITP has enrolled and received 2 doses of povetacicept 240 mg without incident. Initial, preliminary observations include expected reductions in B cells and immunoglobulin levels. The RUBY-4 study continues to enroll in the US, Canada, Australia, and Turkey. At the time of presentation, available data including safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy (e.g., platelet or hemoglobin response rate, duration of response, and time to response) findings will be reported.
Conclusions: To our knowledge, povetacicept is the first dual BAFF/APRIL inhibitor to be evaluated for the treatment of autoimmune cytopenias. Previous preclinical and healthy volunteer studies suggest the potential of povetacicept for suppression of the pathogenic autoimmunity that mediates platelet/erythrocyte destruction in ITP, wAIHA, and CAD, which may lead to more durable responses and improved outcomes for patients.

Disclosures Broome: *Alexion; Dianthus:* Consultancy; *Argenx; Incyte; Rigel; Sanofi; Star Therapeutics:* Research Funding. **Kuter:** *Rubius:* Current equity holder in publicly-traded company; *AIRx, Alexion (Syntimmune), Alnylam, Alpine, Amgen, argenx, BioCryst, Bristol Myers Squibb (BMS), Caremark, Cellularity, Cellphire, Chugai, CRICO, Daiichi Sankyo, Dianthus, Electra Therapeutics, Fuji, Hemopure, Hengrui. Immunovant, Incyte, Inmagenebio:* Consultancy; *AIRx, Alexion (Syntimmune), Alnylam, Alpine, Amgen, Argenx, BioCryst, Bristol Myers Squibb (BMS), Caremark, Cellularity, Cellphire, Chugai, CRICO, Daiichi Sankyo, Dianthus, Electra Therapeutics, Fuji, Hemopure, Hengrui, Immunovant, Incyte, Inmagenebio, Ke:* Honoraria; *UpToDate:* Patents & Royalties: UpToDate Chapters; *Platelet Disorder Support Association:* Membership on an entity's Board of Directors or advisory committees; *Kezar, Kyowa-Kirin, Merck Sharp & Dohme:* Honoraria; *Kezar, Kyowa-Kirin, Merck Sharp Dohme, Momenta, Novartis, Nuvig, Pfizer, Platelet Biogenesis, Platelet Disorder Support Association, Protagonist, Rigel, Sanofi (Bioveratif), Sanofi (Principia), Sanofi (Genzyme), Sobi (Dova), Takeda, UCB, Up-To-Date, Zafge:* Consultancy; *Alnylam, BioCryst, Novartis, Rigel, Sanofi (Principia), Takeda (Bioverativ), and UCB:* Research Funding. **Davies:** *Alpine Immune Sciences, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Enstrom:** *Alpine Immune Sciences, Inc.:* Current Employment, Current equity holder in publicly-traded company; *Tempest Therapeutics:* Current equity holder in publicly-traded company, Ended employment in the past 24 months. **Chunyk:** *Alpine Immune Sciences, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Thomas:** *Alpine Immune Sciences, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Naumovski:** *Alpine Immune Sciences, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Lentz:** *Argenx:* Consultancy, Research Funding; *Novo Nordisk:* Consultancy, Research Funding.

OffLabel Disclosure: This abstract reports information on povetacicept, an investigational agent being developed for potential treatment of autoantibody-associated diseases.

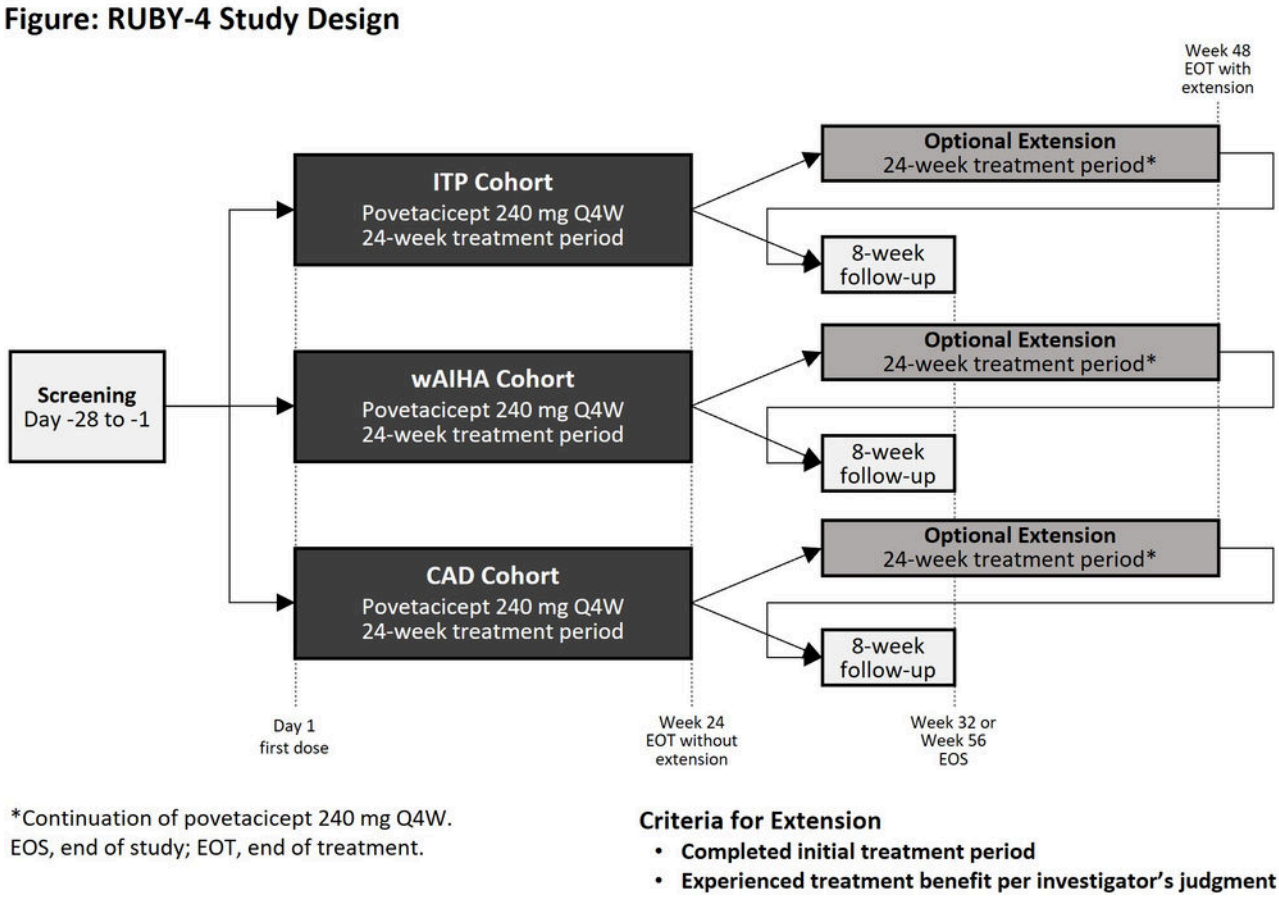

Figure 1

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