

**Background** Povetacept (ALPN-303) is an Fc fusion protein of a variant, engineered TACI domain, which mediates significantly more potent inhibitory activity than WT TACI-Fc or BAFF- or APRIL-specific monoclonal antibodies, with enhanced pharmacokinetic (PK) and immunomodulatory properties versus WT TACI-Fc in preclinical studies. Povetacept may therefore significantly improve clinical outcomes in systemic lupus erythematosus (SLE) and other B-cell-related diseases. This study was designed to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of povetacept in adult healthy volunteers (HV).

**Methods** In this first-in-human study (NCT05034484), 66 adult HV were randomized 4:2 into single ascending dose cohorts of intravenous (IV) or subcutaneous (SC) povetacept or placebo. Participants were followed to assess safety and PK, circulating immunoglobulins (Ig), and circulating leukocyte populations.

**Results** Povetacept has been well tolerated in all cohorts evaluated as single IV or SC doses of up to 960 mg. Overall, it exhibits dose-related PK and expected PD effects, including dose-related reductions in serum IgA, IgM, IgG (figure 1), and in circulating antibody-secreting cells (plasmablasts and plasma cells). These PD effects appear greater than those reported for WT TACI-Fc molecules in HV and appear to be saturated at doses  $\geq 80$  mg. Coverage of free APRIL was maintained for 2–3 weeks with 80 mg and  $\geq 4$  weeks with 240 mg, respectively. The most frequent adverse event (AE) has been mild headache. To date, there have been no imbalances of infections between the placebo and dosed groups, no treatment-related serious AEs, no administration-related reactions other than mild injection site pain, and no adverse trends in safety laboratories (table 1).

**Conclusions** To date, povetacept has demonstrated acceptable safety and tolerability and exhibits expected PD effects on circulating Ig. These findings support future clinical development

of povetacept in patients with SLE and/or other B-cell- and/or autoantibody-related diseases.

### LSO-091 STUDY DESIGN OF ENERGY: A PHASE 2/3 TRIAL TO ASSESS THE EFFICACY AND SAFETY OF NIPOCALIMAB IN WARM AUTOIMMUNE HEMOLYTIC ANEMIA

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**Background** Patients with systemic lupus erythematosus may develop secondary warm autoimmune hemolytic anemia (wAIHA). wAIHA is a rare condition characterized by the premature destruction of red blood cells (RBCs) mainly in the presence of pathogenic immunoglobulin G (IgG) autoantibodies that preferentially bind to RBCs at 37°C, resulting in extravascular hemolysis of these RBCs in the spleen (or liver). Nipocalimab is a high affinity, fully human, aglycosylated, effectorless monoclonal antibody that targets the neonatal Fc receptor (FcRn) to lower circulating IgG levels, including pathogenic autoantibodies. Here we describe the rationale and study design of ENERGY, an ongoing, adaptive, phase 2/3 multicenter, randomized, double-blind, placebo-controlled study that will evaluate the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of nipocalimab compared with placebo in patients with wAIHA (NCT04119050).

**Methods** Subjects  $\geq 18$  years of age who have been diagnosed with primary idiopathic or secondary wAIHA and are currently receiving treatment for wAIHA or have previously received treatment for wAIHA will be included in the study. Stable doses of corticosteroids or immunosuppressants will be allowed. Approximately 111 patients will be randomized 1:1:1 to receive nipocalimab at two different dose schedules or placebo. Following completion of 24 weeks of double-blind treatment, patients may enter an open-label extension period to receive nipocalimab for 144 weeks with a follow-up period of 6 weeks after last assessment.

**Results** ENERGY will include over 170 sites across nearly 20 countries. The primary endpoint is percentage of participants achieving durable response of improvement in hemoglobin (Hgb). The secondary endpoints include change from baseline in the total score from the Functional Assessment of Chronic Illness Therapy-Fatigue Scale, corticosteroid dose reduction from baseline, and normalization of hemolytic markers.

**Conclusions** The results of ENERGY have the potential to identify a novel treatment option to address the significant unmet needs of patients with wAIHA. Enrollment is ongoing in this clinical trial.

**Abstract LSO-090 Table 1 Treatment-Emergent Adverse Events**

Treatment-Emergent Adverse Event (TEAE)	All Placebo (N=22)	All Povetacept (N=44)
Any TEAE	12 (55%)	27 (61%)
Grade 1	7 (32%)	20 (45%)
Grade 2	4 (18%)	6 (14%)
Grade 3	1 (5%)	1 (2%)
<b>Any Adverse Event of Interest</b>	<b>1 (5%)</b>	<b>1 (2%)</b>
Administration-Related Reaction	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
<b>Most Common TEAEs</b>		
Preferred Term (Any Grade)	All Placebo (N=22)	All Povetacept (N=44)
Headache or Migraine	4 (18%)	11 (25%)
Grade 1	4 (18%)	9 (20%)
Grade 2	0	2 (5%)
Infections	4 (18%)	6 (14%)
Grade 1	3 (14%)	5 (11%)
Grade 2	1 (5%)	1 (2%)
Dizziness	1 (5%)	5 (11%)
Grade 1	1 (5%)	4 (9%)
Grade 2	0	1 (2%)
Hypogammaglobulinemia	0	4 (9%)
Grade 1	0	4 (9%)

Data Extract: July 29, 2022