A PLACEBO-CONTROLLED PHASE 1 STUDY IN HEALTHY ADULT VOLUNTEERS OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ALPN-303, A POTENT DUAL BAFF/APRIL ANTAGONIST, FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

Keywords: Systemic lupus erythematosus, Randomized control trial, Clinical Trials


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Background: Povetacicept (ALPN-303) is an Fc fusion protein of a variant, engineered transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) domain which mediates significantly more potent inhibitory activity than wild type (WT) TACI-Fc or B cell activating factor (BAFF)- or a proliferation inducing ligand (APRIL)-specific monoclonal antibodies, with enhanced pharmacokinetic (PK) and immunomodulatory properties versus WT TACI-Fc in preclinical studies. Povetacicept may therefore significantly improve clinical outcomes in systemic lupus erythematosus (SLE) and other B cell-related diseases.

Objectives: This study was designed to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of povetacicept in adult healthy volunteers (HV).

Methods: In this first-in-human study (NCT05034484), 66 HV were randomized 4:2 into 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 leukocyte populations.

Results: Povetacicept 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 (ASC; plasmablasts and plasma cells). These PD effects appear greater than those reported for WT TACI-Fc molecules and in circulating antibody-secreting cells (ASC; plasmablasts and plasma cells). PD effects, including dose-related reductions in serum IgA, IgM, IgG, and/or other B-cell- and/or autoantibody-related diseases.

Conclusion: These findings support future clinical development of povetacicept in patients with SLE and/or other B-cell- and/or autoantibody-related diseases.


Disclosure of Interests: Tobias Alexander Grant/research support from: Amgen, Miltenyi, Janssen, Robert Biesen: None declared, Gerd Rüdiger Burmester: None declared, Andreas Radbruch: None declared, Renate Arnold: None declared, Falk Hiepe: None declared.

DOI: 10.1136/annrheumdis-2023-eular.5531

Table 1. Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event (TEAE)</th>
<th>All Placebo (N=22)</th>
<th>All Povetacicept (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache or Migraine</td>
<td>5 (18%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>4 (18%)</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>6 (27%)</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6 (27%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (5%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>1 (5%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

Most Common TEAEs:

<table>
<thead>
<tr>
<th>Preferred Term (Any Grade)</th>
<th>All Placebo (N=22)</th>
<th>All Povetacicept (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration-Related Reaction Site Pain</td>
<td>Grade 1</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

Acknowledgements: NIL.


DOI: 10.1136/annrheumdis-2023-eular.382

Figure 1. Povetacicept Dose-Dependently Reduces Circulating Immunoglobulins.

Effects generally appear saturated ≥ 80 mg for ≥ 4 weeks.

Acknowledgements: NIL.

Disclosure of Interests: Falk Hiepe: None declared.

Acknowledgements: NIL.


DOI: 10.1136/annrheumdis-2023-eular.382

Acknowledgements: NIL.

Disclosure of Interests: Falk Hiepe: None declared.

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Acknowledgements: NIL.

Disclosure of Interests: Falk Hiepe: None declared.