In PNH, a somatic mutation in the PIGA gene of one or more hematopoietic stem cells generates a clone of abnormal erythrocytes (RBCs) that lack alternative pathway (AP) regulatory complement proteins CD55 and CD59. This leads to uncontrolled complement activation on affected RBCs and membrane attack complex (MAC)-mediated intravascular hemolysis (IVH).  

Standard of care is C5 inhibition to prevent MAC formation thus MAC-mediated IVH. However, approximately 70% of patients receiving a C5 inhibitor remain anemic and more than one third were transfused more than once in the prior 12 months. This is presumably due to continuous extravascular hemolysis (EVH). 

Factor D (FD), a serine protease, catalyzes complement factor B cleavage, allowing formation of AP C3 convertase. By inhibiting FD, danicopan blocks C3 convertase formation, the control point for AP activation and amplification of all complement pathways. This leads to inhibition of EV C cleavage, C3 fragment deposition, terminal pathway activation and MAC formation. Thus, danicopan has the potential to control both EVH and IVH therefore, making FD a promising target in PNH.

**OBJECTIVES**

Demonstrate that danicopan is a potential treatment for PNH patients with an inadequate response to C5 inhibition.

**METHODS**

**RESULTS**

Twelve patients received at least one dose of danicopan. One discontinued after 2 doses, due to a serious adverse event of worsening of an underlying condition (pulmonary hypertension/edema), considered unlikely related to danicopan. The patient was excluded from the analysis. Eleven patients completed treatment. Benefits were observed in multiple laboratory markers of PNH, shown in Table 2. There was a mean increase in Hgb of 2.4 g/dL at 24 Weeks of treatment. FACIT Fatigue scores were reported, with a mean increase of 11 points at 24 Weeks relative to the baseline on danicopan. A 3-point change is clinically meaningful on this scale. In addition, total bilirubin was normalized while reticulocytes and direct bilirubin returned toward normal range.

**SAFETY**

Danicopan was generally well tolerated. All treatment emergent adverse events (TEAEs) were mild to moderate in severity except for events in 2 patients listed below.

### Table 2

<table>
<thead>
<tr>
<th>Lab Parameters</th>
<th>Baseline (n=12)</th>
<th>Week 12 (n=11)</th>
<th>Week 24 (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb (g/dL)</td>
<td>9.0 (± 0.2)</td>
<td>10.6 (± 0.5)</td>
<td>11.2 (± 0.6)</td>
</tr>
<tr>
<td>Alkaline phosphatase (mg/dL)</td>
<td>7.8 (± 0.2)</td>
<td>8.6 (± 0.3)</td>
<td>8.5 (± 0.3)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.5 (± 0.5)</td>
<td>0.5 (± 0.5)</td>
<td>0.4 (± 0.4)</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

Proof of concept is established with danicopan, an oral, small molecule FD inhibitor in the treatment of PNH on top of background CS inhibition. Meaningful improvement in Hgb, transfusion needs, FACIT-Fatigue and other parameters of interest were achieved. This demonstrates that further benefit can be achieved by blocking the AP at FD with danicopan, in patients on background CS inhibition. This benefit is likely due to the prevention of CS mediated EVH, in addition to control of IVH. Danicopan targets an unmet need in PNH and will be further evaluated in a pivotal trial with standard of care CS inhibition.

**ACKNOWLEDGMENTS**

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