BACKGROUND

• Sickle cell disease (SCD) is an autosomal recessive disorder caused by a mutation in the ε-chain of hemoglobin that leads to the production of sickle hemoglobin (HbS).

• When deoxygenated, HbS polymerizes and deforms red blood cells (RBCs) into a sickle shape and damages cell membranes. These deformed RBCs block capillaries and undergo hemolysis, which triggers downstream effects of extreme fatigue, tissue ischemia, vaso-occlusive crisis (VOC), vascular injury, and organ damage, leading to a spectrum of complications.

• More than 300,000 infants are born with SCD worldwide each year.

• Voxelotor (previously called GBT440-007) is a first-in-class, oral, once-daily therapy that is designed to modulate HbS affinity for oxygen and to in clinical development for the treatment of SCD.

• With the potential to improve RBC function and reduce VOC, it is hypothesized that voxelotor will modify the course of SCD.

• GBT440-007-001 is an ongoing phase 2a study in pediatric patients aged 6 to 17 years with SCD. The data presented are a summary of the analysis of a cohort of adolescents (aged 12-17 years) receiving 900 mg voxelotor for up to 24 weeks.

OBJECTIVES AND STUDY DESIGN

• The primary objective was to evaluate the efficacy of voxelotor 900 mg/d in adolescents with SCD, most of whom were on stable hydroxyurea treatment, demonstrated sustained and durable improvements in Hb and reduction in clinical measures of hemolysis in adolescents were consistent with results in adults.

• The TSS is the sum of 9 questions (related to pain, energy level, and ability to concentrate), with each question having a score ranging from 0 (no symptoms) to 3 (severe symptoms).

• Clinical measures of hemolysis improved concordantly; the median reductions in reticulocytes and unconjugated bilirubin were 23% and 30%, respectively (Table 3).

• Overall, 1 of 20 patients had a numerical decrease at week 24.

• No patient had a transfusion within 8 weeks of week 24. One patient was excluded due to a Hb response based on laboratory data with no confounding factors (ie, transfusion or VOC).

RESULTS

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>N</th>
<th>Dosed</th>
<th>Discontinued dosing prior to 24 weeks</th>
<th>Completed 24 weeks of dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voxelotor 900 mg/d</td>
<td>25</td>
<td>25</td>
<td>3</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 2. Dose Dispersions (900 mg/d)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (25th, 75th Percentile) Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, g/dL</td>
<td>–38.6 (–57.8, –27.1)</td>
</tr>
<tr>
<td>Reticulocytes, % change</td>
<td>–22.9 (–31.4, –3.8)</td>
</tr>
<tr>
<td>Unconjugated bilirubin, % change</td>
<td>–38.6 (–57.8, –27.1)</td>
</tr>
</tbody>
</table>

Table 3. Change in Hemolysis Measures from Baseline to Week 24

CONCLUSIONS

• Voxelotor 900 mg/d was well tolerated for up to 24 weeks of dosing.

• There were no drug discontinuations due to AEs.

• Voxelotor 900 mg/d was well tolerated for up to 24 weeks of dosing.

• Voxelotor was generally safe and well tolerated, consistent with results in adults.

• Most hemoglobin responders (88%) showed reduction in TSS from baseline to week 24.

• There was a 39% median reduction in TSS from baseline.

• 1 patient had a mean TSS of 0 at baseline and week 24.

Figure 4. Hb Responders/Nonresponders: TCD Changes at Week 24 (n=20)

SAFETY AND TOLERABILITY

Table 4. Drug-Related Adverse Events Occurring in ≥2 Patients

<table>
<thead>
<tr>
<th>AE</th>
<th>Voxelotor 900 mg/d (n=25)</th>
<th>Grade ≥3 (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, n (%)</td>
<td>10 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Headache, n (%)</td>
<td>6 (24)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash, n (%)</td>
<td>12 (48)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

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Disclosures

[Disclosures information provided for funding and support related to the study.]

References

[References to supporting literature provided.]

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