The Pharmacokinetics (PK) of GBT440 are Similar in Adolescents and Adults with Sickle Cell Disease (SCD)

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INTRODUCTION

• Sickle cell disease (SCD) is a genetic disorder resulting in the production of mutated hemoglobin (HbS) that upon deoxygenation, polymerize and obstruct small blood vessels (RBCs) resulting in sickled RBCs, hemolysis and vaso-occlusion.
• SCD is a congenital hemoglobinopathy with disease beginning in childhood, approximately 10% of SCD prevalence is in the pediatric population.
• GBT440 is an oral, once-daily therapy that modulates hemoglobin (Hb) affinity for oxygen, thereby inhibiting polymerization in SCD (Figure 1).

Figure 1. GBT440: Designed to Bind Hemoglobin with High Selectivity

• Reversible, constant binding to H-terminus of hemoglobin α chain • stabilizes sickle Hb conformation
• Preserves functions with high selectivity for hemoglobin
• 3.5% elasticity of GBT440 to Hb to balance binding
• Protein, dose-dependent increase in Hb-O2 affinity.

METHODS

• Adult PPK Model
• Adolescents (12 to 17 years) GBT440 600 mg
• Children (≤11 years) GBT440 600 mg
• Part A – Single Oral Dose
• Adolescents (12 to 17 years) 900 mg daily for 24 weeks
• Adolescents (12 to 17 years) 1500 mg daily for 24 weeks
• Part B – Multiple Oral Doses

• Key Inclusion Criteria
CV

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>SCD (HbSS)</th>
<th>Current Hydroxyurea/Hydroxycarbamide Use</th>
<th>Part A</th>
<th>Part B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>12-17</td>
<td>&gt; 40</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Female</td>
<td>12-17</td>
<td>&gt; 40</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

• Secondary Objectives
• To support dose selection in ongoing studies evaluating safety and efficacy of GBT440 in pediatric patients
• To select doses for pediatrics (6 to 17 years) based on PK data and population PK (PPK) modeling to achieve similar exposures

RESULTS

• Safety Results
GBT440 was well tolerated following a single oral dose of GBT440 600 mg
• No serious or severe adverse events related to study drug were observed
• Two treatment-related Grade 1 adverse events (fatigue and nausea) were reported

• PK Results
• Following a single oral dose of GBT440: maximum concentrations (Cmax) in whole blood and plasma were reached at 2 and 2 hours, respectively (Table 3). GBT440 concentrations decreased in a monophasic manner, with a half-life (∼116 hours) in adults of 12 hours and plasma of 43.5 hours (Figure 4 and Table 2).

• In adolescents, higher PK plasma concentrations was observed which is consistent with high specificity for binding to hemoglobin and data observed in adults
• Based on dose-normalization and population PK of GBT440 in adolescents following a single dose of 400 mg were similar to those expected in adults (Figure 3).

• Daily doses of 900 mg and 1500 mg, which are currently being evaluated in the pivotal Phase 3 HOPE study were selected to be evaluated in adolescents in Part 3 of this study and exposures are expected to be similar to those observed in adults (Figure 4).

• Table 2. GBT440 Whole Blood and Plasma Non-compartmental PK Parameters Following a Single Oral Dose of GBT440 600 mg in Adolescents

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>GBT440 in Whole Blood</th>
<th>GBT440 in Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>24.2 (47.7%)</td>
<td>2.08 (32.5%)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>2.00</td>
<td>2.00</td>
</tr>
<tr>
<td>AUC (ng/hr/L)</td>
<td>146.1 (43.85%)</td>
<td>11.4 (9.1%)</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>32.3 (6.1)</td>
<td>43.9 ± 5.31</td>
</tr>
</tbody>
</table>

AUC = area under the time of the last quantifiable concentration; Cmax = maximum observed blood concentration; Tmax = average maximum; T1/2 = the time required for concentration to reduce by 1/2 in adults; all values reported as geometric means (percent RSE) ± median; values expressed as arithmetic means ± 95% CI.

• The PK model parameter estimates suggest that whole blood exposures are greater than 1000 ng/mL for ∼24 hours and are associated with a high specificity for hemoglobin and data observed in adults (Figure 3).

• The authors wish to thank all of the participants, families, caregivers, research nurses, study coordinators and support staff who contributed to this study.

ACKNOWLEDGEMENTS

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Figure 2. GBT440 600 mg Single Oral Dose Study Design

Part A – Single Oral Dose
• Adolescents (12 to 17 years) GBT440 600 mg
• Children (≤11 years) GBT440 600 mg

Part B – Multiple Oral Doses
• Adolescents (12 to 17 years) 900 mg daily for 24 weeks
• Adolescents (12 to 17 years) 1500 mg daily for 24 weeks

Key Inclusion Criteria

- Male or female age 6 to 17 with sickle cell disease in prior year; n (%)
- No splenic sequestration crisis in prior year; n (%)
- No history of stroke or two TCD measurements ≥200 cm/sec
- On hydroxyurea at the time of last quantifiable concentration

Table 3. PK Parameter Estimates for GBT440 in Adults and Adolescents with SCD

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>GBT440 in Whole Blood</th>
<th>GBT440 in Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/hr)</td>
<td>0.45 (13.7%)</td>
<td>0.75 (47.1%)</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>21.4 (6.5)</td>
<td>19.1 (12.7)</td>
</tr>
<tr>
<td>Ka (L/hr)</td>
<td>0.34 (6.3)</td>
<td>0.19 (38.3)</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>3.45</td>
<td>3.64</td>
</tr>
</tbody>
</table>

CL/F = apparent clearance; V/F = apparent volume of distribution; Ka = absorption rate constant, T1/2 = half-life; all values reported as geometric means (percent RSE) ± median; values expressed as arithmetic means ± 95% CI.

Table 4. Comparison of Adult (95% Simulated Prediction Interval, in blue) and Adolescent (Observed, black lines) GBT440 Whole Blood Exposures Following a Single Oral Dose of GBT440 600 mg

The external model validation shown above indicates good agreement between observed and simulated adult PK profiles following a single dose of GBT440 600 mg.

Figure 3a. Goodness of Fit Plot and Visual Predictive Check (VPC) for the Adult PK Model

• The PK model parameter estimates for GBT440 in adults with SCD was best described by a two-compartment model with first-order absorption and first-order elimination. Key model parameters are summarized in Table 2.

Figure 3b. Goodness of Fit Plot and Visual Predictive Check (VPC) for the Pediatric PK Model

• The PK model included estimates of between-subject variability on apparent clearance (CL/F) and apparent volume (V/F). A combined proportional plus additive residual error model was used.

Figure 4. GBT440 Whole Blood and Plasma Concentration-Time Profiles Following a Single Oral Dose of GBT440 600 mg in Adults

• The prediction-corrected visual predictive check (VPC) and goodness of fit diagnostic plots for the whole blood model indicate that the model describes the data adequately (Figure 3).