GBT440, a Potent Anti-Sickling Hemoglobin Modifier Reduces Hemolysis, Improves Anemia and Nearly Eliminates Sickle Cells in Peripheral Blood of Patients with Sickle Cell Disease

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GBT440: Designed to Bind Hemoglobin with High Selectivity

- Reversible covalent binding to N-terminus of hemoglobin α chain → stabilizes oxy-Hb conformation
- Profile confirms properties with high selectivity for hemoglobin
  - 1:1 stoichiometry of GBT440 to Hb tetramer binding
  - Preferential partitioning into RBCs
  - Potent, dose-dependent increase in Hb-O₂ affinity
GBT440 Clinical Hypothesis: Increase in HbO2 Affinity Inhibits HbS Polymerization

GBT440 inhibits Hb polymerization \(\rightarrow\) decreases RBC damage

- Improves blood flow
- Modify course of SCD disease
- Stops hemolysis and improves anemia
GBT440-001: Study Design

- Randomized, double blind, placebo controlled study
- Population
  - Healthy subjects
  - SCD subjects
    - HbSS, 18-60 yrs, Hb 6-10 g/dL, clinically stable (no VOC or RBC transfusion within 30 days), stable HU allowed
- Dose cohorts (8 subjects/cohort; 6 active:2 placebo)
  - Single dose cohorts
    - Healthy subjects: 100, 400, 1000, 2000, 2800 mg
    - SCD subjects: one cohort 1000 mg
    - Subjects followed up to 28 days post dose
  - Multiple dose cohorts
    - Healthy subjects (15-day dosing): 300, 600 and 900 mg
    - SCD subjects (28-day dosing): 500, 700, 1000 mg
    - Subjects followed up to 60 days post initiation of dosing
- Objectives
  - Safety
  - Pharmacokinetics; pharmacodynamics (hemoglobin modification)
  - SCD subjects: hematologic parameters

Demographics, Disposition and Efficacy data: unblinded by treatment assignment
Safety data: blinded evaluation
## GBT440-001: Baseline Characteristics and Subject Disposition

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>500 mg n=10</th>
<th>700 mg n=12</th>
<th>1000 mg n=4</th>
<th>Placebo (pooled) n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female n (%)</td>
<td>2 (20)</td>
<td>8 (67)</td>
<td>2 (50)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>8 (80)</td>
<td>4 (33)</td>
<td>2 (50)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Age (years, median, range)</td>
<td>29 (19,47)</td>
<td>29 (20,56)</td>
<td>41 (36,45)</td>
<td>37 (20,53)</td>
</tr>
<tr>
<td>Weight (kg, median, range)</td>
<td>65 (53,75)</td>
<td>67 (53,83)</td>
<td>71 (68,85)</td>
<td>69 (57,88)</td>
</tr>
<tr>
<td>Hydroxyurea therapy n (%)</td>
<td>1 (10)</td>
<td>4 (33)</td>
<td>2 (50)</td>
<td>4 (45)</td>
</tr>
<tr>
<td>Baseline Hb (g/dL, median, range)</td>
<td>7.9 (7,9.7)</td>
<td>9.2 (7.5,9.8)</td>
<td>8.2 (7.5,8.4)</td>
<td>8.2 (7.2,10)</td>
</tr>
<tr>
<td>Hospitalizations due to painful crisis in prior year: n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (70)</td>
<td>5 (42)</td>
<td>4 (100)</td>
<td>4 (45)</td>
</tr>
<tr>
<td>1</td>
<td>3 (30)</td>
<td>3 (25)</td>
<td>0</td>
<td>3 (33)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>0</td>
<td>4 (33)</td>
<td>0</td>
<td>2 (22)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject Disposition</th>
<th>500 mg</th>
<th>700 mg</th>
<th>1000 mg</th>
<th>Placebo (pooled)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosed a</td>
<td>10</td>
<td>12</td>
<td>4 (ongoing)</td>
<td>9</td>
</tr>
<tr>
<td>Completed 28 day dosing</td>
<td>10</td>
<td>12</td>
<td>ongoing</td>
<td>8</td>
</tr>
<tr>
<td>Dose reduction b</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Completed 28 day follow-up</td>
<td>6</td>
<td>12</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

*a No dose discontinuations
*b One reduction from 500 mg to 200 mg due protocol specified reduction for asymptomatic Hb increase > 2 g/dL
*c One dose reduction from 700 mg to 400 mg due to abdominal cramps

Data as of 20 Nov 2015
GBT440-001: Safety Summary (blinded)

- Majority of adverse events were Grade 1 or 2 (mild-moderate) in severity
- Most common adverse event: headache
- 4 serious adverse events (all assessed not related to study drug)
  - 3 sickle cell crisis events
    - 1 unblinded (placebo treatment)
    - No sickle cell crisis have occurred during the 28-day treatment period
  - 1 event of presumed infection with hemolysis
    - Unblinded (GBT440 treatment)
- No adverse effects on liver (LFTs) or renal (creatinine) function
- No evidence of tissue hypoxia
  - No clinically significant ECG changes suggestive of ischemia
  - No resting tachycardia, hypotension or increased respiratory rate
  - No increase in erythropoietin or reticulocytes- these markers **decrease with treatment suggesting improved oxygen delivery**

*Blinded data as of 20 Nov 2015*
### GBT440-001: Common Adverse Events (blinded)

Adverse events occurring >10% of subjects

<table>
<thead>
<tr>
<th>Adverse Events (&gt;10%)</th>
<th>500 mg GBT440 or placebo (n=14)</th>
<th>700 mg GBT440 or placebo (n=16)</th>
<th>All subjects (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>12 (85.7)</td>
<td>15 (93.8)</td>
<td>27 (90.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (42.9)</td>
<td>8 (50.0)</td>
<td>14 (46.6)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2 (14.3)</td>
<td>4 (25.0)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Pain*</td>
<td>2 (14.3)</td>
<td>4 (25.0)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2 (14.3)</td>
<td>3 (18.8)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (14.3)</td>
<td>2 (12.5)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Sickle Cell Crises</td>
<td>1 (7.1)</td>
<td>3 (18.8)</td>
<td>4 (13.3)</td>
</tr>
</tbody>
</table>

Sickle cell crises were Grade 3, all other adverse events were Grade 1 or 2

*Pain events- majority assessed as sickle cell related

*Blinded data as of 20 Nov 2015*
GBT440: Dose Proportional PK

- Dose proportional increase in GBT440 exposures following single and multiple dosing
- Half-life
  - ~3 days healthy subjects
  - ~1.6 days SCD subjects
- GBT440 RBC:plasma ratio \( \rightarrow \) ~75:1

*Excludes subjects with dose reduction: 1 subject in 500 mg cohort and 1 subject in 700 mg cohort*
GBT440: Dose Proportional ‘Left Shift’ in P50

**Representative Oxygen Equilibrium Curves**

- **p50 values**
  - 12.1 mm Hg
  - 14.0 mm Hg
  - 16.7 mm Hg
  - 29.7 mm Hg
  - 31.1 mm Hg

- **p20 values**
  - 14.0 mm Hg
  - 16.7 mm Hg

- **p50 shifts to normal range**

**Key Points**

- **GBT440 results in left shift of the oxygen equilibrium curve**
  - SCD subjects are right shifted; p50 shifts to normal range (26-29 mm Hg)
- **Hemoglobin modification is proportional to dose**
  - 500 mg (n=10): ~13%
  - 700 mg (n=12): ~17%
Inhibition of Hbs Polymerization ➔ Proof of Concept Biomarkers

Data unblinded by treatment assignment
1000 mg cohort enrollment in progress
GBT440 Treatment Increases Hemoglobin and Reduces Reticulocytosis Consistent with Reduction in Hemolysis

- Rapid rise in hemoglobin followed by decline in reticulocytosis is consistent with reduction in hemolysis
- Reduction in reticulocyte counts suggests improvement of red blood cell life span
Reduction in Hemolysis Correlates with GBT440 Exposure

Higher GBT440 exposures resulted in more profound reduction in reticulocyte counts which is a measure of hemolysis and a surrogate of RBC lifespan

PK data from 500 and 700 mg dose levels; $R^2 \sim 0.56$
GBT440 Treatment Reduces Circulating Sickle Cells

Representative images from GBT440 treated subject

Day -1

Day 28 (GBT440 700 mg)

Circulating Sickle Cells (%)
(relative change from baseline, median and 25th and 75th percentile)

Percent Change in Sickle Cells (%)

--- Placebo (n=8)
--- GBT440 500 mg (n=10)
--- GBT440 700 mg (n=12)
Reduction in Unconjugated Bilirubin and LDH are Consistent with Reduced Intravascular Hemolysis

Reduction in bilirubin and LDH levels are observed as early as Day 4 and maintained throughout 28 day dosing period
Reduction in Erythropoietin is Consistent with Improved Oxygen Delivery to Tissues

- Decline in Epo levels suggest that treatment with a Hb modifier that increases the affinity of Hb for oxygen leads to improvement of oxygen delivery in SCD subjects.
- Reduction in Epo levels is sustained during the 28 day dosing period.
Reduction in soluble adhesion molecules (P-selectin, ICAM-1) may indicate decreased endothelial damage and inflammation.

Reduction in inflammation may lead to decreased risk of vaso-occlusion.

*Data currently available for subjects in 700 mg dose level*
Summary

• GBT440 was well tolerated over 28 days of dosing
  • No drug-related serious adverse events
  • No evidence of tissue hypoxia
  • Decreases in erythropoietin and reticulocyte counts are consistent with improved oxygen delivery

• Pharmacokinetic data demonstrate linear and dose-proportional properties with a half-life amenable to once daily dosing

• Pharmacodynamic data (left shift in OEC) confirm pharmacological mechanism of action of GBT440

• GBT440 increases hemoglobin, reduces reticulocytosis and improves biomarkers of hemolysis and inflammation

• Hematologic effects are correlated with GBT440 blood levels
Conclusions

• Emerging data with 28 days of dosing support the hypothesis that GBT440 inhibits polymerization of sickle hemoglobin, improves hemolytic anemia, reduces red blood cell damage, and improves oxygen delivery

• Longer term dosing will determine the optimal magnitude of hematologic effects and clinical benefit

• GBT440 offers a well-tolerated, mechanism-based and potentially disease-modifying therapy for sickle cell disease

• Additional cohorts with longer term dosing planned
Acknowledgements

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  • Professor Swee Lay Thein: King’s College Hospital (currently NIH/NHLBI)
  • Professor David Rees: King’s College Hospital

• Subjects who participated in the study
  • Healthy volunteers
  • Sickle cell patients