GMI-1070, a Pan-Selectin Inhibitor: Safety and PK in a Phase 1/2 Study in Adults with Sickle Cell Disease

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Background
• GMI-1070 is a pan-selectin antagonist which selects service binding in vivo and selective-in vivo effects.
• Selectin binding, is thought to be mediated by one or more of the selectins in the inflammatory process leading to leukocyte adhesion and recruitment to inflamed tissue, and is involved in a broad variety of disease processes that involve the selectins.
• Sickle cell disease is a rare area where selective-mediated cell adhesion and cellular aggregate formation are thought to play a role in the pathogenesis of the disease.
• GMI-1070 has been shown to prevent and interrupt vaso-occlusion in a sickle mouse model.
• The GMI-1070 pan-selectin inhibitor is well tolerated in healthy volunteers.
• Enrollment criteria included patients with sickle cell disease.
• The most common AE was headache, which occurred in 4 subjects within 24 hours of dosing, were mild or moderate (grades 1-2), and resolved within 24 hours.
• Mean hsCRP increased at 24 and 48 hours, with return to baseline at 7 days.

Objective
• To test the safety and PK of GMI-1070 in pediatric and adult sickle cell disease patients.

Methods
• In phase 1/2 study done was performed, involving adults with SCD at 3 study sites. GMI-1070 was studied at 3 different dose levels with a 1:3:3 ratio: 6 mg/kg (loading dose) and 2 mg/kg (maintenance dose)
• 15 adults were enrolled at 3 centers; 13 with HbSS, 2 with HbS-C, with 4 of these on hydroxyurea.
• Mean age 32 years (range 19-50), mean weight was 65 kg; 4 were on hydroxyurea.
• Study included 24 hours of dosing, with planned evaluation at 2 and 4 days after dosing.
• No changes in vital signs or physical exam findings.
• WBC range at peak was 4.5-28.0 K/mm3, ANC range at peak was 1.7-23.0 K/mm3.
• No significant drug-related decrease in Hb.

Results
• The most common AE was headache, which occurred in 4 subjects within 24 hours of dosing, were mild or moderate (grades 1-2), and resolved within 24 hours.
• No significant drug-related decrease in Hb.
• Mean hsCRP increased at 24 and 48 hours, with return to baseline at 7 days.
• Two subjects had marked increases in hsCRP: one associated with priapism.
• Leukocytosis, to 28.0 K/mm3 at 48 hours after drug (baseline 10.4 K/mm3), and returned to baseline.

Conclusion
• GMI-1070 is a well tolerated, and the pan-selectin inhibitor is well tolerated in healthy volunteers.
• The most common AE was headache, which occurred in 4 subjects within 24 hours of dosing, were mild or moderate (grades 1-2), and resolved within 24 hours.
• Mean hsCRP increased at 24 and 48 hours, with return to baseline at 7 days.
• Two subjects had marked increases in hsCRP: one associated with priapism.
• Leukocytosis, to 28.0 K/mm3 at 48 hours after drug (baseline 10.4 K/mm3), and returned to baseline.

Other Laboratory Findings (Mean, Range):

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<thead>
<tr>
<th>Parameter</th>
<th>Mean (mg/L)</th>
<th>Range (mg/L)</th>
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<tbody>
<tr>
<td>WBC</td>
<td>4.5-28.0</td>
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</tr>
<tr>
<td>ANC</td>
<td>1.7-23.0</td>
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Pharmacokinetics
• Greater than 99% of the drug was excreted intact in the urine.
• Observed plasma GMI-1070 concentrations and those predicted by the model showed excellent agreement.
• Even with limited sampling, the model was well fit and consistent with all subject data.
• GMI-1070 is well tolerated in healthy volunteers and those with sickle cell disease.
• The dosing of the fit healthy volunteer data indicates similar behavior of GMI-1070 in adults with sickle cell disease.
• This is consistent with liver size and corresponding PK profile.

Summary and Conclusions
GMI-1070, a pan-selectin inhibitor, was administered in two IV doses at 20 and 10 mg/kg to 15 adults with sickle cell disease. Clinical results show no changes in most clinical laboratory parameters and adverse events profile was consistent with that of healthy volunteers. Laboratory data is moderate reversible effect on white blood cell count, driven by neutrophil activity in those with sickle cell disease.

Conflict of Interest Disclosures: Lori Styles, Todd Wun, Laura DeCastro, and Marilyn Telen: Takeda sponsored the clinical trial under contract with GlycoMimetics, Inc., the Sponsor of the trial. William Kramer is a consultant to GlycoMimetics, Inc; Timothy Flanner, and Marilyn Telen are employees of GlycoMimetics, Inc.

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More information on this and related GlycoMimetics projects can be obtained at glycomimetics.com