HEPCIDIN MIMETIC PTG-300 INDUCES DOSE-RELATED AND SUSTAINED REDUCTIONS IN SERUM IRON AND TRANSFERRIN SATURATION IN HEALTHY SUBJECTS
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Hepcidin is the master regulator of systemic iron metabolism

Crielaard et al, Nature 2017
Hepcidin replacement as a potential therapy for diseases of ineffective erythropoiesis and iron overload

• In conditions of ineffective erythropoiesis, hepcidin levels are suppressed leading to increased iron absorption from the GI tract and iron export from macrophages which is toxic to developing erythrocytes.

• Agents with hepcidin activity may help correct iron distribution abnormalities with beneficial effects on erythropoiesis.

• Hepcidin mimetic has potential to treat multiple conditions:
  – Ineffective erythropoiesis, low hepcidin and iron overload, e.g. β-thalassemia, low risk MDS
  – Primary iron overload, low hepcidin, e.g. hereditary hemochromatosis
  – Exaggerated erythropoiesis, e.g. polycythemia vera
PTG-300 as a potential treatment for ineffective erythropoiesis

• PTG-300, an injectable hepcidin mimetic, is being developed as potential treatment of β-thalassemia.

• Using Protagonist’s proprietary peptide technology platform, PTG-300 has been engineered to have specific drug-like properties
  – Potency, efficacy, PK, stability, solubility, and ease of synthesis (COGS)

• Well-tolerated in nonclinical studies; expected effects of exaggerated pharmacology at high doses

• PTG-300 improved anemia and reduced liver iron in a β-thalassemia mouse model (EHA 2018, S-843).
PTG-300: Phase 1 Study in NHVs
Single ascending dose and repeat dose

Randomized, double-blind, placebo controlled Phase 1 Study in NHVs (n = 62)

Key Eligibility criteria
• Not receiving iron supplementation
• No recent transfusion or blood donation
• Normal hematology and iron parameters
• Standard diet, no iron enrichment or restriction

Endpoints
• Safety/ tolerability (AEs/ SAEs, safety labs, ECG, PE)
• PK profile
• PD: serum iron parameters
PTG-300 Induces a Dose-Dependent Reduction in Serum Iron. Maximum Mean Reduction Approximately 65%
PTG-300 Induces a Dose-Dependent Reduction in Serum Iron
Sustained Reduction >72 hrs at Doses 20 mg or Higher

Mean change in serum iron over time by single dose level

- Placebo
- 1 mg
- 3 mg
- 10 mg
- 20 mg
- 40 mg
- 80 mg

Time from study drug dose (h)

Serum Iron micromol/L
Serum Iron Inversely Correlated with PTG-300 Exposure

The line shows $\text{FeAUC} = a \times \frac{1}{\text{PTG-300AUC}} + b$ (placebo subjects omitted from fit).
PTG-300 Induces a Dose-Dependent Reduction in TSAT
Similar effects on serum iron

Transferrin Saturation (TSAT)\% by single dose level (individual subject and means)
PTG-300 Effects on Serum Iron Comparable for both Doses
Recovery to Baseline 1-2 weeks after Second Dose
Post-Treatment Iron Recovery Associated with Reticulocytosis

Cohort 7 individual subjects and means (n=5)

- **Reticulocytes**
  - Dose 1: 40 mg
  - Dose 2: 40 mg

- **Haemoglobin**
  - g/L

- **Serum Iron**
  - micromol/L

Dose 1: 40 mg  
Dose 2: 40 mg
PTG-300 PK Predictable and Well-Characterized

- Exposure increased somewhat less than proportionally with dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>10 mg (n=8)</th>
<th>20 mg (n=7)</th>
<th>40 mg (n=8)</th>
<th>80 mg (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC&lt;sub&gt;last&lt;/sub&gt;</strong> (ng.h/ml)</td>
<td>9071 (2230)</td>
<td>14860 (2668)</td>
<td>26580 (11529)</td>
<td>47100 (11496)</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;</strong> (ng/ml)</td>
<td>148 (52)</td>
<td>189 (34)</td>
<td>317 (127)</td>
<td>415 (88)</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt;</strong> (h)</td>
<td>24</td>
<td>24</td>
<td>4.5</td>
<td>2</td>
</tr>
<tr>
<td><strong>t&lt;sub&gt;1/2&lt;/sub&gt;</strong> (h)</td>
<td>26 (7)</td>
<td>35 (10)</td>
<td>45 (12)</td>
<td>52 (17)</td>
</tr>
</tbody>
</table>
PTG-300 Well-Tolerated Following Single Dose Exposure

Overall Summary of Treatment Emergent Adverse Events (single dose)

<table>
<thead>
<tr>
<th>Adverse Event Summary</th>
<th>PTG-300 1 mg (N=8)</th>
<th>PTG-300 3 mg (N=8)</th>
<th>PTG-300 10 mg (N=8)</th>
<th>PTG-300 20 mg (N=8)</th>
<th>PTG-300 40 mg (N=8)</th>
<th>PTG-300 80 mg (N=5)</th>
<th>All PTG-300 (N=45)</th>
<th>All Placebo (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>4 (50.0%)</td>
<td>5 (62.5%)</td>
<td>7 (87.5%)</td>
<td>6 (75.0%)</td>
<td>5 (62.5%)</td>
<td>4 (80.0%)</td>
<td>31 (68.9%)</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Total Events</td>
<td>4</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>6</td>
<td>9</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Total Unique Events</td>
<td>4</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>7</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Subjects with Treatment-related AEs</td>
<td>1 (12.5%)</td>
<td>2 (25.0%)</td>
<td>6 (75.0%)</td>
<td>6 (75.0%)</td>
<td>4 (50.0%)</td>
<td>4 (80.0%)</td>
<td>23 (51.1%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>SAEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>1 (12.5%)</td>
<td>1 (12.5%)</td>
<td>5 (62.5%)</td>
<td>6 (75.0%)</td>
<td>3 (37.5%)</td>
<td>3 (60.0%)</td>
<td>19 (42.2%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>-</td>
<td>2 (25.0%)</td>
<td>2 (25.0%)</td>
<td>2 (25.0%)</td>
<td>1 (12.5%)</td>
<td>2 (40.0%)</td>
<td>9 (20.0%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1 (12.5%)</td>
<td>3 (37.5%)</td>
<td>-</td>
<td>1 (12.5%)</td>
<td>2 (25.0%)</td>
<td>1 (20.0%)</td>
<td>8 (17.8%)</td>
<td>1 (9.1%)</td>
</tr>
</tbody>
</table>

- Repeat dose cohort: 4/5 subjects with injection site reactions; single events: costochondritis, headache, acne
- No clinically significant changes in safety labs, VS, ECGs
PTG-300 Phase 1 Summary

• PTG-300 demonstrated marked and sustained dose-related effects on iron distribution in healthy volunteers
  – Consistent with activities of hepcidin and pre-clinical studies of PTG-300.

• Systemic exposure increased with dose; minimal drug accumulation observed following repeat dose administration

• PTG-300 was well-tolerated following single and repeat dose injection; A transient injection site erythema was observed in some subjects
PTG-300 Phase 1 Conclusions

- This Phase 1 study establishes PD-based proof-of-concept and provides a range of doses that can be evaluated in the treatment of diseases of ineffective erythropoiesis and iron overload.

- A global phase 2 study in patients with transfusion-dependent and non-transfusion-dependent β-thalassemia is currently planned.