A Phase 1, Placebo-Controlled Study to Determine the Safety, Tolerability, and Pharmacokinetics of Escalating Subcutaneous Doses of LJPC-401 (Synthetic Human Hepcidin) in Healthy Adults

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INTRODUCTION

• Hepcidin plays a key role in the regulation of iron homeostasis.1-4
• Patients with hemolytic anemias have decreased levels of hepcidin.1
• Increasing hepcidin levels by synthetic hepcidin injection or genetic induction has been shown to prevent iron overload.5

This phase 1, placebo-controlled, double-blind, randomized, single-center study evaluated tolerable dosing levels and safety of the synthetic human hepcidin, LJPC-401, in healthy volunteers.

OBJECTIVE

• To determine the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of escalating doses of LJPC-401 in healthy adult volunteers

METHODS

Study Design

• Study population
• Dosing cohort design
• Dose escalation protocol
• Study endpoints

RESULTS

Table 1. Baseline Demographic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>0 mg n=6</th>
<th>5 mg n=8</th>
<th>10 mg n=6</th>
<th>20 mg n=6</th>
<th>30 mg n=6</th>
<th>Placebo n=6</th>
<th>All subjects n=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y.</td>
<td>24 (24-25)</td>
<td>25 (24-26)</td>
<td>24 (24-25)</td>
<td>24 (24-25)</td>
<td>24 (24-25)</td>
<td>24 (24-24)</td>
<td>24 (24-24)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>4 (66.7)</td>
<td>4 (50.0)</td>
<td>3 (50.0)</td>
<td>3 (50.0)</td>
<td>3 (50.0)</td>
<td>6 (100.0)</td>
<td>18 (56.2)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>5 (83.3)</td>
<td>6 (100.0)</td>
<td>6 (100.0)</td>
<td>6 (100.0)</td>
<td>7 (87.5)</td>
<td>30 (93.8)</td>
<td>30 (93.8)</td>
</tr>
</tbody>
</table>

Table 2. Incidence of Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>System organ class</th>
<th>0 mg n=6</th>
<th>5 mg n=8</th>
<th>10 mg n=6</th>
<th>20 mg n=6</th>
<th>30 mg n=6</th>
<th>Placebo n=6</th>
<th>All subjects n=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEA, n (%)</td>
<td>6 (100)</td>
<td>6 (100)</td>
<td>6 (100)</td>
<td>6 (100)</td>
<td>6 (100)</td>
<td>6 (100)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Injection site reaction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Coarse skin rash</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>Rash</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<td>Hypersensitivity</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anaphylaxis</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Fat embolism</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
</tr>
</tbody>
</table>

TEA, treatment-emergent adverse event.

Safety

• The starting dose level (5 mg/60 kg) was 4-fold lower than the maximum dose at which no adverse event (AE) was observed in a sensitive animal model (male dog, 0.3 mg/kg).
• After administration of a single dose via subcutaneous injection, all subjects were evaluated from predose to 48 hours postdose to estimate the terminal half-life (1/2) of LJPC-401, and at 21 and 29 days after treatment to determine the immunogenicity of LJPC-401.
• Serum iron concentration was assessed using intensive sampling between 0 and 48 hours postdose.
• Remaining iron markers were assessed predose and at day 8 postdose

Statistical Analysis

• All subjects receiving any amount of study drug (LJPC-401) or placebo were evaluated in the safety analysis.
• Study data were summarized using descriptive statistics.
• Although no formal statistical hypothesis testing was performed, P-values were obtained from pairwise comparisons of doses from the analysis of variance using Fisher’s least significant differences.
• All PK and PD populations included all enrolled subjects who received any amount of study drug and for whom at least 1 serum concentration parameter could be determined.
• Endogenous hepcidin measured at predose was reported as LJPC-401 baseline concentration, and postdose calculations included baseline correction. Baseline-corrected serum PK parameters were obtained by noncompartmental analysis.

CONCLUSIONS

• Subcutaneous LJPC-401 at doses between 5 and 30 mg was well tolerated in healthy adults.
• LJPC-401 Cmax increased proportionally over doses of 5 to 20 mg before starting to plateau between 20 and 30 mg.
• A U<sub>0</sub> value represents the statistically significant maximum reduction in serum iron concentration from baseline estimated at 8 hours postdose following subcutaneous administration of 5 to 30 mg LJPC-401 or placebo.

REFERENCES


ACKNOWLEDGMENTS

Editorial assistance was provided by Anna Battellier and was funded by La Jolla Pharmaceutical Company, San Diego, CA, USA.

DISCLOSURES

This study was sponsored by La Jolla Pharmaceutical Company, San Diego, CA, USA.