A Phase 1, Open-Label Study to Determine the Safety, Tolerability, and Pharmacokinetics of Escalating Doses of LJPC-401 (Synthetic Human Hepcidin) in Patients with Iron Overload

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Iron overload is a significant complication in patients with hereditary hemolytic anemias and hereditary hemochromatosis 1-3.

- Can cause damage to the liver, heart, and endocrine glands and may result in death.
- Reduced serum hepcidin levels characterize iron overload.

Endogenous hepcidin regulates dietary iron absorption and tissue distribution 4,5.

- Iron efflux to the bloodstream is restrained by hepcidin.
- As a result, recycled iron remains in macrophages, and dietary iron absorption is inhibited.

• In animal models, increasing hepcidin levels by synthetic hepcidin injection or genetic induction has been shown to improve iron overload\textsuperscript{1}
  – A moderate increase in expression of hepcidin in $\beta$-thalassemic mice limited iron overload and improved anemia\textsuperscript{2}
  – Supply of exogenous hepcidin or increased expression of hepcidin ameliorated hemochromatosis and $\beta$-thalassemia in mice\textsuperscript{3,4}

• These observations suggest that increasing hepcidin levels may help treat the abnormal iron absorption in individuals with $\beta$-thalassemia and related disorders

LJPC-401, a synthetic human hepcidin, is being developed as a therapeutic intervention for iron overload.

Tested in 3 clinical studies to date:
- 2 single-dose studies
  - NHV01 in healthy volunteers (poster presentation PF470)
  - TPP01 in patients at risk for iron overload
- 1 multidose study
  - NHV02 in healthy volunteers
**Eligible patients were adults with 1 of the following:**
- Transfusion-dependent anemia and hemochromatosis
- Iron chelation therapy in the past 6 months
- Serum ferritin level >1000 μg/L, or hemochromatosis*

*Patients with hemochromatosis that required phlebotomy at least once every 2 months or had received iron chelation therapy in the past 6 months.

ECG, electrocardiogram; SC, subcutaneous; TEAE, treatment-emergent adverse event.
# Study Assessments

## Safety assessments
- TEAEs
- Physical examinations
- Laboratory evaluations
- Immunogenicity
- Visits/sampling on day 1 predose, day 8, and day 22

## PK assessments
- Parameters of baseline-corrected serum LJPC-401 obtained by noncompartmental analysis
- Blood samples collected at predose and 0.5, 2, 4, 8, 24, 48, and 168 hours postdose

## PD assessments
- Effects on
  - Serum iron level
  - Transferrin level
  - Transferrin saturation
  - Ferritin level
- Samples collected at screening, day 1 predose, 24, 48, and 168 hours postdose

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PD, pharmacodynamics; PK, pharmacokinetics; TEAE, treatment-emergent adverse event.
# Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter, n (%)</th>
<th>1 mg (n = 3)</th>
<th>5 mg (n = 3)</th>
<th>10 mg (n = 3)</th>
<th>20 mg (n = 6)</th>
<th>30 mg (n = 3)</th>
<th>Total (N = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>3 (100)</td>
<td>1 (33.3)</td>
<td>3 (100)</td>
<td>6 (100)</td>
<td>3 (100)</td>
<td>16 (88.9)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>0</td>
<td>2 (66.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2 (66.7)</td>
<td>0</td>
<td>3 (100)</td>
<td>2 (33.3)</td>
<td>1 (33.3)</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td>Female</td>
<td>1 (33.3)</td>
<td>3 (100)</td>
<td>0</td>
<td>4 (66.7)</td>
<td>2 (66.7)</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td><strong>Iron overload disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemochromatosis</strong></td>
<td>1 (33.3)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>3 (50.0)</td>
<td>1 (33.3)</td>
<td>11 (61.1)</td>
</tr>
<tr>
<td>BL serum ferritin, mean (SD), 248 (592) ng/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Sickle cell disease</strong></td>
<td>2 (66.7)</td>
<td>0</td>
<td>0</td>
<td>1 (16.7)</td>
<td>1 (33.3)</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>BL serum ferritin, mean (SD), 10151 (7375) ng/mL</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TD β-Thalassemia</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (33.3)</td>
<td>1 (33.3)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>BL serum ferritin, mean (SD), 1599.7 (2040) ng/mL</td>
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</tr>
</tbody>
</table>

BL, baseline; SD, standard deviation.
Summary of Safety

- No severe (grade ≥3) TEAEs, TEAEs leading to discontinuation, or deaths.
- Individual patient clinical labs reviewed by the study investigator suggested no clinically significant shifts.
Immunogenicity Assay and Results

**Positive Control/Assay Format**

- Sample or serum spiked with anti-LJPC surrogate antibody
- Streptavidin ( conjugated to SulfoTag ( )
- Species-specific anti-Ig conjugated to biotin ( )
- Hepcidin
- LJPC-401 coat

**Detection Control**

- Human IgG at 100 ng/mL
- Species-specific anti-Ig conjugated to biotin ( )

In 3 clinical trials, which included analysis of a total of 227 samples, all samples were confirmed negative for antibody to LJPC-401.

Signal from positive control demonstrates the assay is properly detecting Ab to hepcidin

Signal generated by the detection control verifies the assay is capable of detecting at least 100 ng/mL of Ab
Mean Baseline-Corrected Serum LJPC-401

- Dose-dependent increase in exposure (except 30 mg)
- Peak concentrations occurred at 2-4 h
- Half-life ~6-13 h

SE, standard error.
Mean Serum Iron Concentration at 8 Hours Postdose

Mean Serum Iron Change from Baseline (SD), %

Dose Response
\( P=0.0478 \)

Note: For analyses excluding the 30-mg dose group, a dose-dependent, statistically significant reduction in serum iron level was observed (\( P=0.008 \) for dose response; not adjusted for multiple comparisons).

SD, standard deviation.
Percent Changes in Iron Parameters in Individual Subjects (20- and 30-mg Dose Groups)

*One outlier patient in the 30-mg group had an exchange transfusion 2 days prior to study entry that may have altered iron homeostasis.

SD, standard deviation; TSAT%, transferrin saturation.
Mean Serum Iron Concentration at 8 Hours Postdose
Post Hoc Analysis, Excluding 1 Subject Outlier

Dose Response

P=0.0102

Mean Serum Iron Change From Baseline (SD), %

LJPC-401 dosing cohorts

1 mg (n=3) 5 mg (n=3) 10 mg (n=3) 20 mg (n=6) 30 mg (n=2)

SD, standard deviation.
Sustained Iron-Lowering Effect With Comparable PK Exposures Between Healthy Subjects and Patients

- PK exposures (AUC and $C_{\text{max}}$) are generally comparable between healthy subjects and patients
- Longer and sustained iron-lowering effect observed in patients returning toward baseline after 1 week
- PD effect likely due to difference in iron hemostasis and regulation between the 2 populations

AUC, Area under the curve; $C_{\text{max}}$, maximum drug concentration.
Improved Hepcidin Production

- Human hepcidin is difficult to manufacture, with challenges around stability and aggregate formation.
- The original methods for synthesis of hepcidin resulted in ~15% higher molecular weight hepcidin aggregate that was prone to further aggregation under in-use conditions.
- The updated proprietary process for producing hepcidin results in <1% aggregate that is stable under in-use conditions.

HPLC Trace

Red: Original process
Black: Improved process

High-order aggregate

HPLC, high-performance liquid chromatography.
A new improved formulation increased subcutaneous bioavailability (AUC and $C_{\text{max}}$) up to 3-fold.
Improved Formulation—Enhanced Iron-Lowering Effect

Enhanced bioavailability resulted in greater iron reduction at the same dose.
Conclusions

- LJPC-401 was well tolerated at doses between 1 mg and 30 mg, with the maximum iron-lowering effect observed at 20 mg

- LJPC-401 showed significant decreases in serum iron levels compared with baseline, which were sustained in most patients for up to 8 days

- In comparison to healthy adults, in whom LJPC-401 caused a decrease in serum iron levels that returned to baseline levels within 48 hours, the iron-lowering effect in iron overload patients was more sustained

1. Yaeger D et al. Presented at the 23rd Congress of the European Hematology Association; June 14-17, 2018; Stockholm, Sweden; poster PF470.
Conclusions (cont’d)

- New formulation has improved PK exposure and PD effect with no corresponding increase of injection site reaction severity or duration

- Additional studies are ongoing to further explore the iron-regulating effects of LJPC-401 in patients with iron-overload disorders

1. Pivotal study in patients with transfusion-dependent beta thalassemia (HELIOS)
   - 100 patient, 12 mo., parallel group study, evaluating the effects of LJPC-401 on myocardial iron

2. Phase 2 study in patients with hereditary hemochromatosis (HERCULES Study)
   - 60 patient, 4 mo., single-blind, placebo-controlled study evaluating the effects of LJPC-401 on TSAT and phlebotomy requirements