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

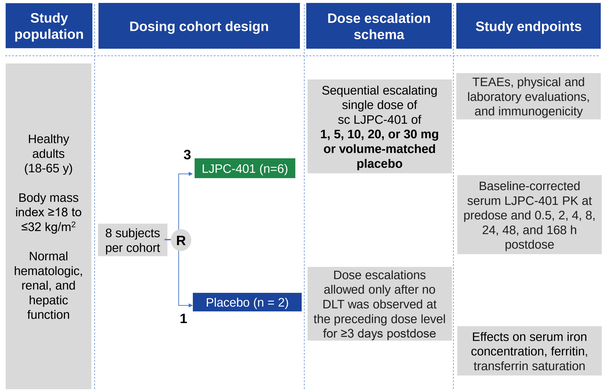
- Hepcidin plays a key role in the regulation of iron homeostasis[1-4]
- Patients with hemolytic anemias have decreased levels of hepcidin[2,3]
- Increasing hepcidin levels by synthetic hepcidin injection or genetic induction has been shown to prevent iron overload[2,5]
- This phase 1, placebo-controlled, 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



DLT, dose-limiting toxicity, sc, subcutaneous, TEAE, treatment-emergent adverse event.

- 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 ($t_{½}$) of LJPC-401, and at 7 and 21 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
- The PK and PD populations included all enrolled subjects who received any amount of study drug and for whom ≥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

RESULTS

Table 1. Baseline Demographic Data

Variable	LJPC-401 5 mg n=6	LJPC-401 10 mg n=6	LJPC-401 20 mg n=6	LJPC-401 30 mg n=6	Placebo n=8	All subjects N=32
Age, y, mean (range)	36.2 (24-63)	30.3 (20-53)	21.8 (19-26)	35.5 (24-57)	23.5 (19-29)	29.1 (19-63)
Sex, n (%) Male Female	1 (16.7) 5 (83.3)	2 (33.3) 4 (66.7)	3 (50.0) 3 (50.0)	4 (66.7) 2 (33.3)	5 (62.5) 3 (37.5)	15 (46.9) 17 (53.1)
Race, n (%) White Asian or multiracial	5 (83.3) 1 (16.7)	6 (100.0) 0	6 (100.0) 0	6 (100.0) 0	7 (87.5) 1 (12.5)	30 (93.8) 2 (6.2)

Safety

Table 2. Incidence of Treatment-Emergent Adverse Events

System organ class	LJPC-401 5 mg n=6	LJPC-401 10 mg n=6	LJPC-401 20 mg n=6	LJPC-401 30 mg n=6	All placebo N=8
Any TEAE, n (%)	6 (100)	6 (100)	6 (100)	6 (100)	2 (25)
Nausea	0	1 (16.7)	0	0	0
Injection site reaction	6 (100)	6 (100)	6 (100)	6 (100)	1 (12.5)
Catheter site phlebitis	3 (50)	0	0	0	0
Headache	0	0	0	2 (33.3)	0
Presyncope	0	0	0	0	1 (12.5)
Anxiety	1 (16.7)	0	0	0	0
Hand dermatitis	1 (16.7)	0	0	0	0

TEAE, treatment-emergent adverse event.

- All treatment-emergent adverse events (TEAEs) were mild in severity
  - No serious TEAEs, TEAEs leading to early discontinuation, or deaths were reported
- Injection site reactions did not generally require treatment, and all but one such reaction resolved before study end
- No serum samples were confirmed positive for anti–LJPC-401 antibodies, and there were no trends or changes in physical or laboratory test results with LJPC-401

Pharmacokinetics

- Mean maximum serum drug concentration (C_{max}) ranged from 54.47 to 134.17 ng/mL
- Mean time to reach C_{max} (t_{max}) was 2 hours postdose
- Mean area under the serum concentration-time curve from time 0 to 24 hours postdose (AUC_{0-24}) ranged from 562.2 to 1335.7 ng·h/mL
- The mean terminal half-life ($t_{½}$) ranged from ~3 to 11 hours

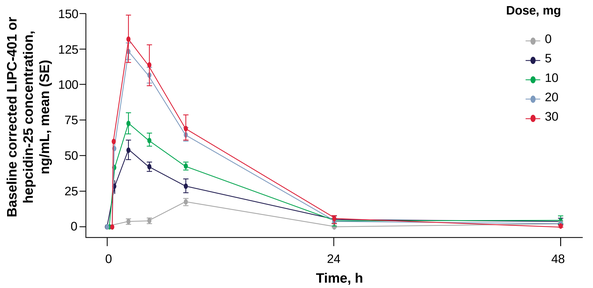
Table 3. Summary of Baseline-Corrected Serum LJPC-401 PK Parameters

PK parameters[a]	LJPC-401 5 mg n=6	LJPC-401 10 mg n=6	LJPC-401 20 mg n=6	LJPC-401 30 mg n=6
C_{max}, ng/mL	54.5 (16.7)	74.2(15.7)	123.4 (14.13)	134.2 (38.6)
t_{max}, h	2.0 (2.0-4.0)	2.0 (2.0-8.0)	2.0 (2.0-2.0)	2.0 (2.0-4.0)
AUC_{0-24}, ng·h/mL	562.2 (187.3)	717.6 (184.6)	1272.5 (175.7)	1335.7 (507.3)
AUC_{0-last}, ng·h/mL	1404.2 (971.9)	911.5 (410.0)	1831.9 (569.9)	1511.8 (586.3)
$t_{½}$, h	9.4 (1.9)[b]	11.0 (NA)[c]	3.4 (1.4)	4.4 (1.6)[d]

AUC_{0-24}, area under the serum concentration-time curve from time 0 to 24 hours postdose; AUC_{0-last}, area under the serum concentration-time curve from time 0 to the last quantifiable concentration time; C_{max}, maximum serum drug concentration; PK, pharmacokinetics; SD, standard deviation; $t_{½}$, terminal half-life; t_{max}, time to reach C_{max} following drug administration.

[a]PK parameters are all presented as mean (SD), except t_{max}, which is presented as median (minimum, maximum);; [b]n=3; [c]n=1 [d]n=4.

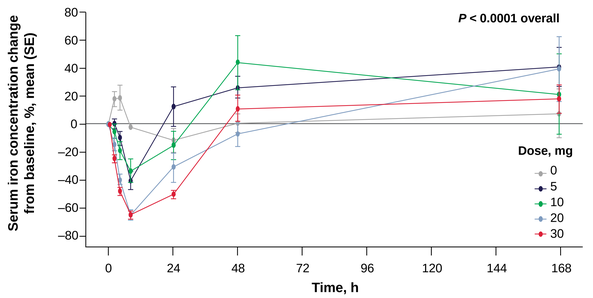
Figure 1. Mean baseline-corrected concentration vs time (0-48 hours) profiles following subcutaneous administration of 5 to 30 mg LJPC-401 (linear scale)



Concentrations of LJPC-401 (treatment group) or hepcidin-25 (placebo group) were corrected by day 1 predose (baseline) values. SE, standard error.

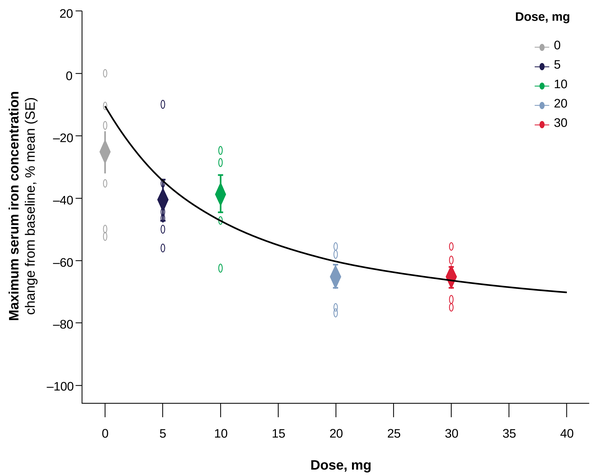
Pharmacodynamics

Figure 2. Mean percent change in serum iron concentration between baseline and day 8 following administration of 5 to 30 mg LJPC-401 or placebo



P value represents the statistically significant maximum reduction in serum iron concentration from baseline observed at 8 hours postdose for all 4 LJPC-401 dose groups combined. SE, standard error.

Figure 3. Mean percent change in serum iron concentration from baseline at 8 hours postdose following subcutaneous administration of 5 to 30 mg LJPC-401 or placebo



SE, standard error.

- The mean maximum reduction was 33% to 65% at 8 hours postdose (**Figure 3**); a larger reduction in serum iron concentrations was generally associated with an increase in dose up to 20 mg
  - There was no apparent difference in the maximum reduction of serum iron concentration between the 20- and 30-mg dose levels

CONCLUSIONS

- Subcutaneous LJPC-401 at doses between 5 and 30 mg was well tolerated in healthy adults
- LJPC-401 C_{max} and AUC_{0-24} increased proportionally over doses of 5 to 20 mg before starting to plateau between 20 and 30 mg
- All 4 tested doses of LJPC-401 showed decreased serum iron concentration at 4 and 8 hours postdose compared with baseline
  - Serum iron concentration returned to baseline levels within 48 hours
- The time course of serum iron recovery in the healthy volunteer population is considerably faster than in the iron overload population (see Oral presentation S894 taking place Saturday, June 16, from 16:45 - 17:00, Location: Room A13).

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ACKNOWLEDGMENTS

Editorial assistance was provided by Anna Battershill 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.