LJPC-401

SYNTHETIC HUMAN HEPCIDIN

LJ401-HH01

A PHASE 2, MULTI-CENTER, RANDOMIZED, PLACEBO-CONTROLLED, SINGLE-BLIND STUDY WITH LJPC-401 FOR THE TREATMENT OF IRON OVERLOAD IN ADULT PATIENTS WITH HEREDITARY HEMOCHROMATOSIS

Sponsor: La Jolla Pharmaceutical Company
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EudraCT Number: 2017-003598-33

[redacted]

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PRINCIPAL INVESTIGATOR STATEMENT OF AGREEMENT

I, the undersigned Principal Investigator, have read and understood the following protocol LJ401-HH01 version 6.0, 14 December 2018 and its appendices.

I promise to abide by the International Council on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP), the Declaration of Helsinki, and all applicable laws and regulations, and agree that, in all cases, the most restrictive regulation related to a given aspect of research involving protection of human subjects will be followed. In the event that I have a question regarding my obligations during the conduct of this protocol, I have ready access to these aforementioned regulations, as either my personal copy, or available on file from the Chairperson of the Institutional Review Board (IRB) / Ethics Committee (EC) or the Sponsor, via local authorities and,

I am authorized to enter into this commitment to conduct the study outlined in this protocol, and my signature below signifies that I agree to conduct the study as outlined herein.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

1. SYNOPSIS

Name of Sponsor/Company:

La Jolla Pharmaceutical Company (La Jolla)

Name of Investigational Product:

LJPC-401 (solution for subcutaneous [SC] injection)

Name of Drug Substance:

Synthetic human hepcidin (hepcidin-25 acetate)

Title of Study:

A Phase 2, Multicenter, Randomized, Placebo-controlled, Single-blind Study with LJPC-401 for the Treatment of Iron Overload in Adult Patients with Hereditary Hemochromatosis

Study Site(s): Approximately 30

Phase of Development: 2

Objectives:

Primary:

- To compare the effect of LJPC-401 versus placebo on transferrin saturation (TSAT) in adult patients with hereditary hemochromatosis.

Secondary:

- To compare the effect of LJPC-401 versus placebo on phlebotomy requirements.
- To establish the safety and tolerability of LJPC-401 versus placebo in adult patients with hereditary hemochromatosis.
- To compare the effect of LJPC-401 versus placebo on serum ferritin.

Exploratory:

- To compare the effect of LJPC-401 versus placebo on serum iron parameters.
- To compare the effect of LJPC-401 versus placebo on thyroid function.
- To compare the effect of LJPC-401 versus placebo on liver function.
- To compare the effect of LJPC-401 versus placebo on glycemic control.
- To compare the effect of LJPC-401 versus placebo on red blood cell (RBC) parameters including hemoglobin concentration, RBC count, and red cell distribution width (RDW).
- To compare the effect of LJPC-401 versus placebo on quality of life as measured by Quality of Life Questionnaires, Short Form (36) Health Survey, Version 2 (SF-36v2), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and modified Dreisler indices for arthritis.

Endpoints:

Primary efficacy endpoint:

- Change in TSAT, defined as follows:
  - For patients with 1 phlebotomy (the standard of care therapeutic phlebotomy on Day 1 [predose]), change in TSAT from baseline to Week 16 (24 [± 4] hours postdose).
  - For patients undergoing 2 or more phlebotomies, change in TSAT from baseline to the most recent postdose fasting TSAT observed prior to the second phlebotomy.

Secondary efficacy endpoints:

- Number of phlebotomies from Day 2 to End of Study (EOS)/30 (+ 3) days after the last dose of study drug.
- Change in serum ferritin, defined as follows:
  - For patients with 1 phlebotomy (the standard of care therapeutic phlebotomy on Day 1 [predose]), change in serum ferritin from baseline to Week 16 (24 [± 4] hours postdose).
  - For patients undergoing 2 or more phlebotomies, change in serum ferritin from baseline to the most recent postdose serum ferritin observed prior to the second phlebotomy.

Safety and tolerability endpoints:

- Adverse events (AEs) from consent to EOS.
- Changes in clinical laboratory evaluations including serum iron parameters from baseline to EOS.
- Changes in vital signs, electrocardiograms (ECGs), use of concomitant medications, and physical examinations from baseline to EOS.
- Immunogenicity (anti-drug antibody)/pharmacokinetics (PK) from baseline to EOS.

Exploratory endpoints:

- Change in serum iron parameters, defined as follows:
  - For patients with 1 phlebotomy (the standard of care therapeutic phlebotomy on Day 1 [predose]), change in serum iron parameters from baseline to Week 16 (24 [± 4] hours postdose).
  - For patients undergoing 2 or more phlebotomies, change in serum iron parameters from baseline to the most recent postdose serum iron parameters observed prior to the second phlebotomy.
  - For patients with 1 phlebotomy (the standard of care therapeutic phlebotomy on Day 1 [predose]), change in serum iron parameters from baseline to Week 17 (approximately 7 days after the last dose of study drug).

- For patients undergoing 2 or more phlebotomies, change in serum iron parameters from baseline to the most recent predose serum iron parameters observed prior to the second phlebotomy.

- Change in thyroid function from baseline to Week 16.
- Change in liver function from baseline to Week 16.
- Change in hemoglobin A1c from baseline to Week 16.
- Change in RBC parameters including hemoglobin concentration, RBC count, and RDW as defined as follows:
  - For patients with 1 phlebotomy (the standard of care therapeutic phlebotomy on Day 1 [predose]), change in RBC parameters from baseline to Week 16 (24 [± 4] hours postdose).
  - For patients undergoing 2 or more phlebotomies, change in RBC parameters from baseline to the most recent postdose RBC parameters observed prior to the second phlebotomy.
- Change in Quality of Life Questionnaires, SF-36v2, WOMAC, and modified Dreisler indices for arthritis, from baseline to Week 16.

Study Design: This study is a multicenter, randomized, placebo-controlled, single-blind study. The primary objective of the study is to evaluate the effect of LJPC-401 on TSAT in adults with hereditary hemochromatosis.

Eligible patients will be randomized 1:1 to LJPC-401 or placebo. Randomization will be stratified by baseline TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3).

All randomized patients will receive a standard of care therapeutic phlebotomy (500 cc or appropriate for weight) on Day 1 (predose). Thereafter, phlebotomy decisions by the Investigator will be based on the patient's fasting TSAT results collected 24 (± 4) hours postdose at Week 4 (Day 23); Week 8 (Day 51); Week 12 (Day 79); and Week 16 (Day 107); and based on the 2011 Iron Disorders Institute (IDI) phlebotomy guidelines for patients with hereditary hemochromatosis. If a phlebotomy is indicated based on the TSAT criteria of the IDI phlebotomy guidelines, the patient should receive phlebotomy treatment predose, on or before the following visit.

The primary efficacy analysis will take place after all patients have completed the Week 16 assessments (or have withdrawn from the study early).

Number of patients (planned): Approximately 68 to 76 patients

Inclusion Criteria:

1. Patients with a clinical diagnosis of hereditary hemochromatosis.
2. Patients who are prescribed therapeutic phlebotomy for the treatment of hereditary hemochromatosis.
3. Patients ≥ 18 years of age.
4. Patients with a serum ferritin level ≥ 100 ng/mL.
5. Patients with a TSAT level > 45%.
6. Female patients must be of nonchildbearing potential or using a highly effective method of contraception during participation in the study and for 30 days after the last dose of study drug. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate when used consistently and correctly. Refer to Section 10.1.6.5.1 for the list of highly effective methods of contraception that can be used in this study.
7. Female patients of child bearing potential must have a negative serum pregnancy test at Screening (within 30 days prior to the first dose of study drug), and a negative urine pregnancy test on Day 1 (ie, prior to initial dosing of study drug).
8. Male patients must be surgically sterile (vasectomy) or using a highly effective method of contraception during participation in the study and for 30 days after the last dose of study drug. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate when used consistently and correctly. Refer to Section 10.1.6.5.1 for the list of highly effective methods of contraception that can be used in this study.
9. Patient must be willing and able to provide written informed consent.

Exclusion Criteria:

1. Patients receiving iron chelation therapy within 7 days prior to the first dose of study drug.
2. Patients recently diagnosed, who have initiated phlebotomy treatments less than 3 months prior to the first dose of study drug.
3. Patients with a concomitant disease, disability or condition, including laboratory abnormality and ECG findings, which may interfere with the conduct of the study, or which would, in the opinion of the Investigator, pose an unacceptable risk to the patient in this study, including, but not limited to, clinically significant arrhythmias, alcohol dependency or abuse, drug dependency or abuse, or psychiatric disease. Patients with depression are eligible if receiving a stable dose of medication for at least 90 days prior to the first dose of study drug.
4. Pregnant or lactating women.
5. Patients taking an immunosuppressive agent that has not been approved by La Jolla for use (excluding topical over-the-counter steroids, inhaled steroid medications, and nonsteroidal anti-inflammatory drugs). Refer to Section 7.1 for the list of prohibited medications and procedures.
6. Patients participating in an unapproved investigational drug or investigational therapeutic device study within 30 days prior to study drug dosing, ie, there must be at least 30 days in between the last dose on a prior study and the first dose administration on this trial.
7. Patients who are unwilling or unable to comply with the study protocol requirements.
8. Patients with type 1 diabetes or type 2 diabetes with hemoglobin Alc greater than 8% within 2 months prior to randomization.
9. Patients with uncontrolled active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection.
10. Patients with Child Pugh class C cirrhosis or liver failure.
11. Patients with severe congestive heart failure (New York Heart Association [NYHA] = Class 4).
12. Patients who have advanced renal failure with an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m^2.
13. Patients with a history of allergic reaction to hepcidin or excipients.
14. Patients who have planned surgery (excluding dental surgery or simple dermatologic procedures) during participation in this study.

Investigational Product/Dosage Formulation:

LJPC-401 (synthetic human hepcidin) solution for SC injection

Dose Regimen and Route of Administration:

Patients will be dosed once-weekly with LJPC-401 or placebo (0.9% sodium chloride) administered SC for 16 weeks. LJPC-401 dose will start at 5 mg at Week 1, and the dose will increase to 10 mg at Weeks 2 and 3. The patient's fasting TSAT at Week 3 (Day 16), collected 24 (± 4) hours postdose, will determine the Week 4 dose. At Week 4, if the patient's fasting TSAT is > 45 %, then the LJPC-401 dose will increase to 20 mg. If the fasting TSAT remains ≤ 45% then the dose will remain at 10 mg. The patient's fasting TSAT results at Week 8 (Day 51) and Week 12 (Day 79), collected 24 (± 4) hours postdose, will be used to determine if a dose adjustment is needed at Weeks 9 and 13. Refer to Section 5.4 for dose adjustments information.

For those patients randomized to placebo, a syringe of 0.9% sodium chloride injection will be prepared by the study pharmacist or designee. To maintain the study single-blind, syringes with study drug (placebo and active drug) will be identical.

Duration of treatment: 16 Weeks

Statistical Methods:

A sample size of 48 patients has 80% power to detect a 15% difference in the change in TSAT between the placebo arm and the LJPC-401 arm, assuming a common standard deviation of 18% and a 2-sided type I error of 0.05.

Patients who do not enroll under global protocol version 4.0/United Kingdom (UK) protocol version 4.1 or later or discontinue the study early prior to dosing will be replaced. Patients who receive study drug and discontinue prior to Week 16 may be replaced. Approximately 20 to 28 patients are expected to be replaced. The plan is to enroll and randomize approximately 68 to 76 patients (1:1 to LJPC-401 or placebo) to ensure that at least 48 patients are included in the primary efficacy analysis.

The primary efficacy analysis and secondary efficacy analyses will include the Efficacy Patient Population which is defined as all patients enrolled under global protocol version 4.0/UK protocol version 4.1 or later who received study drug, and who completed the Week 16 assessments or had an on-study phlebotomy after the standard of care therapeutic phlebotomy on Day 1 (predose) and before Week 16.

All enrolled patients, regardless of protocol version, who receive at least 1 dose of study drug will be included in the safety analyses.

Central randomization will be used with stratification by baseline TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3).

Data will be summarized by treatment group, study visit, and, if appropriate, study interval using summary statistics for continuous variables and number and percentage for categorical values. Statistical comparisons of differences between treatment arms will be made using Wilcoxon rank-sum tests, mixed effects repeated measures, and/or analysis of variance (ANOVA) for continuous or ordinal variables, Chi-Square or Cochran-Mantel-Haenszel tests for categorical variables, Fisher's exact tests for binary variables, and Poisson regression model for count data (eg, number of phlebotomies).

Subgroups that are considered of interest include age, sex, race, ethnicity, country, geographic region, body mass index, baseline TSAT, phlebotomy frequency over the last 12 months, baseline hepcidin level, baseline serum iron level, and baseline serum ferritin level.

The change in TSAT, serum iron panel, thyroid function, liver function, glycemic control, RBC parameters, and quality of life questionnaire scores from baseline to Week 16 (and Week 16 24 (± 4) hours postdose for serum iron parameters), and the change in serum iron parameters from baseline to Week 17, will be evaluated, where appropriate, using the appropriate statistical methods listed above with adjustment for baseline TSAT and phlebotomy frequency over the last 12 months.

Number of phlebotomies and the number of times a patient met criteria for a phlebotomy will be analyzed. Whether a patient meets the criteria for a phlebotomy (yes or no) will be assessed after the results of each fasting TSAT recorded at postdose 24 (± 4) hours on Week 4 (Day 23); Week 8 (Day 51); Week 12 (Day 79); and Week 16 (Day 107) are known. The patient should receive phlebotomy treatment predose, on or before the following visit. The presence of any phlebotomy will be analyzed by a Cochran-Mantel-Haenszel test with adjustment for baseline TSAT and phlebotomy frequency over the last 12 months. The frequency of a phlebotomy will be analyzed by Poisson regression model with baseline TSAT and phlebotomy frequency over the last 12 months included in the model.

Sensitivity analyses of TSAT, serum ferritin, and number of phlebotomies will be conducted. Details will be provided in the statistical analysis plan.

Safety data including analyses of AEs, clinical laboratory data, ECG, vital signs, and immunogenicity findings will be summarized by descriptive statistics within and across treatment arms. Severity, relatedness, and seriousness of AEs will be summarized. Physical examination data will be provided in the listings.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CRA	Clinical Research Associate
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HAMP	hepcidin antimicrobial peptide
HED	human equivalent dose
HEENT	head, eyes, ears, nose, throat
HFE	human factors engineering
HFE2	human factors engineering type 2
HIV	human immunodeficiency virus
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDI	Iron Disorders Institute
IEC / EC	International Ethics Committee / Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat
IXRS	Interactive Voice/Web Response System

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
IUD	intrauterine device
IUS	intrauterine system
La Jolla	La Jolla Pharmaceutical Company
LDH	lactate dehydrogenase
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
MOE	Margins of exposure
NIH	National Institutes of Health
NTBI	nontransferrin bound iron
NYHA	New York Heart Association
PD	pharmacodynamic
PK	pharmacokinetic
PP	Per Protocol Population
PT	preferred term
RBC	red blood cell
RDW	red cell distribution width
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SF-36v2	Short Form (36) Health Survey, Version 2
SI	Systéme International
SLC40A1	solute carrier family 40 member 1
SOC	system organ class
T3	Triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TFR	transferrin receptor 2 (TFR2)
TIBC	total iron binding capacity
TSAT	transferrin saturation
TSH	thyroid-stimulating hormone

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
UIBC	unsaturated iron binding capacity
UK	United Kingdom
USP	United States Pharmacopeia
USPI	United States Prescribing Information
WHO-DD	World Health Organization Drug Dictionary
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

3. INTRODUCTION

Hereditary hemochromatosis is an autosomal recessive disorder that causes excessive amounts of iron to be absorbed and stored in the body. It is the most common hereditary disorder observed in Caucasians (Bacon 2011) and occurs most often in people of northern European descent, particularly those with Nordic or Celtic ancestry.

Mutations in several genes, including high iron (also known as human factors engineering [HFE] protein), HFE2, hepcidin antimicrobial peptide (HAMP), solute carrier family 40 member 1 (SLC40A1), and transferrin receptor 2 (TFR2), can cause hereditary hemochromatosis (National Institutes of Health [NIH] 2017). Approximately 80% of hereditary hemochromatosis cases are caused by HFE mutations, and the remaining 20% of cases are designated as non-HFE hemochromatosis (de Lima Santos 2010). Classical hereditary hemochromatosis presents with fasting transferrin saturation (TSAT) > 45% and elevated serum ferritin > 300 ng/mL in males or > 200 ng/mL in females, with positive HFE genetic testing of the C282Y homozygote or C282Y/H63D compound heterozygote (Iron Disorders Institute 2011). Although homozygosity for the C282Y mutation is present in approximately 1 per 220 to 250 people with northern European ancestry, less than 10% of these individuals will develop severe iron overload accompanied by organ damage and clinical manifestations of hemochromatosis.

Hepcidin controls iron homeostasis by dictating how iron is absorbed, used, and stored in the body. Hepcidin regulates entry of iron into circulation through inhibition of ferroportin, which controls iron export out of cells in the gut and liver as well as circulating erythrophagocytic macrophages. In patients with hereditary hemochromatosis, low plasma hepcidin levels cause ferroportin to direct iron into circulation (ie, a reduction in hepcidin correlates with an increase in circulating iron). Since humans lack the ability to excrete excess iron, it progressively accumulates in the plasma and organs. In healthy humans, total body iron content is approximately 40 to 50 mg/kg body weight, with most of the iron (30 mg/kg) contained in circulating red blood cells (RBCs) such as hemoglobin; 5 to 6 mg/kg is present in tissues in a variety of heme compounds, enzymes with iron-sulfur complexes, and other iron-dependent enzymes; 5 to 12 mg/kg is stored as ferritin and hemosiderin in the liver, bone marrow, spleen, and muscle; and a small fraction (3 mg/kg) circulates in the plasma. Increases in tissue levels of iron ≥ 20 mg/kg are associated with symptomatic iron overload (Gordeuk 1987, Munoz 2009), with potential damage to the liver, heart, and endocrine glands, and even death (Hoffbrand 2012).

The primary treatment for hereditary hemochromatosis is phlebotomy (Bacon 2011). Approximately 90% to 100% of patients will achieve iron depletion with this treatment (Hicken 2003), although 2 to 3 years of weekly or biweekly phlebotomy may be required to adequately reduce iron stores in patients with total body iron > 30 g (Bacon 2011). Thereafter, phlebotomy can be stopped and the patient assessed for maintenance therapy. The frequency of maintenance therapy varies by individual patients, with some requiring monthly phlebotomy and others requiring phlebotomy only once or twice a year. Some patients develop intolerance to phlebotomy, and patient compliance with maintenance phlebotomy has been shown to decline over time.

Other treatments that may be used in cases of severe iron overload or in patients intolerant of phlebotomy include erythrocytapheresis, deferoxamine chelation, or deferasirox chelation (Adams 2010). These treatments are associated with the risk of significant side effects, such as

transfusion reactions following erythrocytapheresis, agranulocytosis, increased serum creatinine, adult respiratory distress syndrome, renal failure, hepatic failure, and gastric hemorrhage following chelation therapy (Deferiprone United States Prescribing Information [USPI] 2011; Deferoxamine Mesylate USPI 2011; Deferasirox USPI 2015).

The bioactive form of hepcidin is a peptide of 25 amino acids that derives from a precursor (pre-prohepcidin) of 84 amino acids that undergoes 2 enzymatic cleavages. LJPC-401 is a synthetic version of the naturally occurring human peptide hepcidin-25. Preliminary nonclinical and clinical studies show that administration of LJPC-401 has a favorable safety profile, and the iron lowering effects of a single subcutaneous (SC) injection last up to 1 week (LJ401-TPP01).

Subcutaneous LJPC-401 is being developed for the treatment of acute and chronic iron excess in patients with hereditary hemochromatosis or attributed to frequent blood transfusions required to treat diseases such as beta thalassemia and sickle cell disease. LJPC-401 has been evaluated in 2 completed Phase 1 clinical trials. Phase 1 Study LJ401-TPP01 was an open-label, single-dose, dose-escalation study in adult patients at risk for iron overload disorders. Phase 1 Study LJ401-NHV01 was a randomized, placebo-controlled, single dose-escalation study in healthy adults. Phase 1 Study LJ401-NHV02 was a randomized, double-blind, placebo-controlled, single and multiple dose-escalation study that has completed dosing and is undergoing data analysis and reporting. The most frequently reported treatment-emergent adverse events (TEAEs) in LJ401-TPP01 and LJ401-NHV01 were injection site reactions, catheter site phlebitis, headache, nausea, alanine aminotransferase (ALT) increased, and decreased appetite. These studies, primarily focused on safety/tolerability and pharmacodynamics (PD), are further described in Section 3.3.

The purpose of this Phase 2, multicenter, randomized, placebo-controlled, single-blind study is to determine the effects of LJPC-401 (synthetic human hepcidin) on TSAT in adult patients with hereditary hemochromatosis.

Two formulations of LJPC-401 have been developed. The original formulation was used in early nonclinical studies and 2 Phase 1 clinical studies (LJ401-NHV01, LJ401-TPP01). Modifications to the drug product were made to improve purity and increase stability. The improved formulation has been used in nonclinical studies and clinical studies (completed Phase 1 Study LJ401-NHV02 and ongoing Phase 2 Studies LJ401-BT01 and LJ401-HH01). Further information about the drug product formulation development is described in the Investigator's Brochure. Ongoing and future clinical studies will be conducted using various concentrations of the improved formulation. Comparability of the LJPC-401 formulations is detailed in Section 2.1.3 in Section 3.2.P.2 (Pharmaceutical Development), Investigational Medicinal Product Dossier Section 2.1.P.2 Subsection 2.1.2, and Report [redacted].

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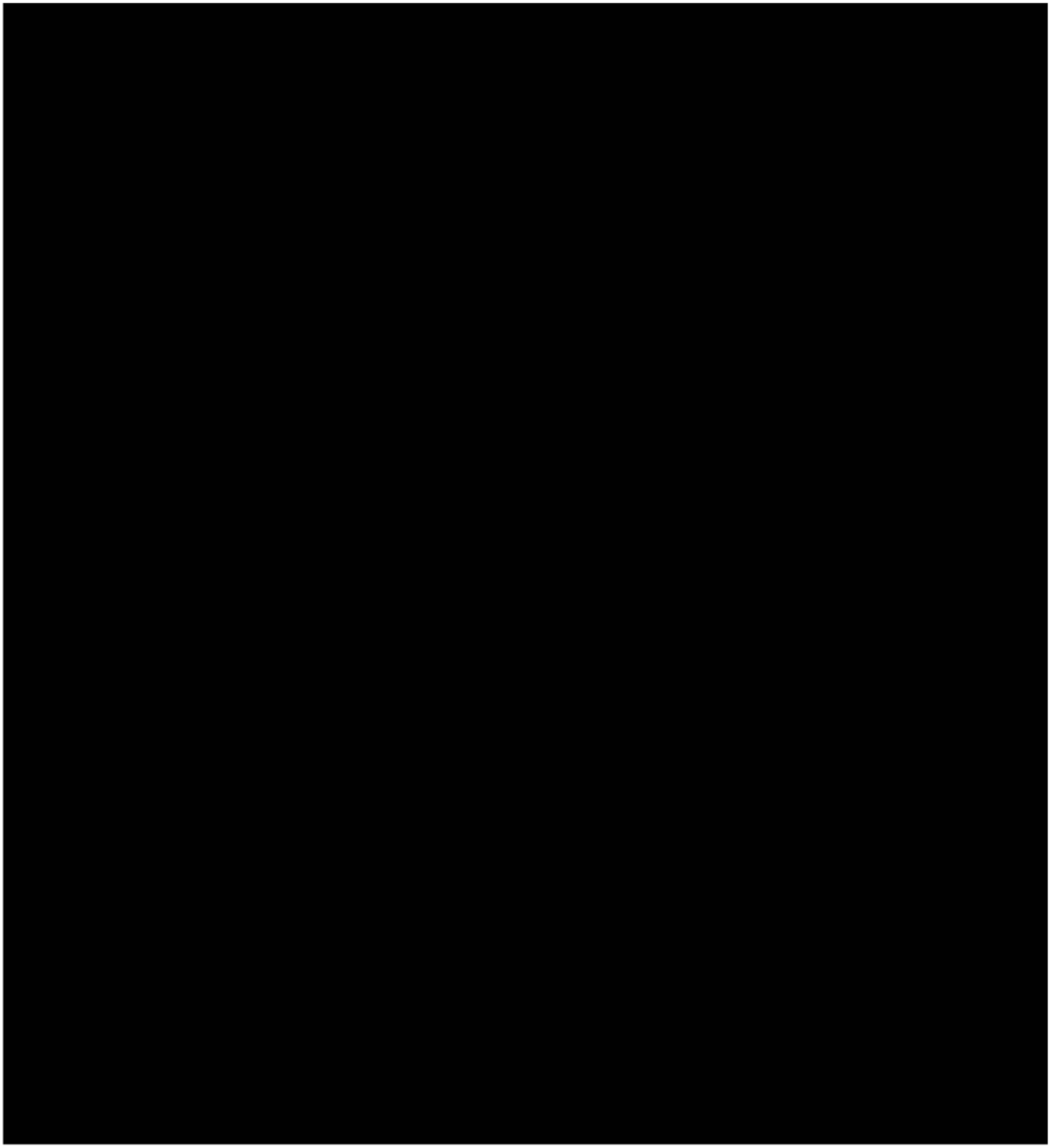

3.3. Summary of LJPC-401 Clinical Studies

3.3.1. LJ401-TPP01

LJ401-TPP01 was a Phase 1, multiple-center, open-label, dose-escalation study to determine the safety, tolerability, pharmacokinetics (PK), serum iron kinetics, and immunogenicity of escalating single doses of LJPC-401 in 18 patients at risk for iron overload disorders (ie, refractory or hemolytic anemia or hemochromatosis). The study enrolled patients in 6 cohorts comprised of 5 doses (1 mg, 5 mg, 10 mg, 20 mg, 30 mg). A sixth planned dose of 40 mg was not administered after a perceived PD effect was noted at the 20-mg dose. Patients received 1 or two 1-mL SC injections to achieve the desired dose level. LJPC-401 concentration ranged from 1 to 15 mg/mL.

A decrease in serum iron levels compared to baseline was generally observed in all 5 dose groups. Mean maximum percentage reductions per dose group occurred at 8 hours postdose and were up to 58% in the 20-mg dose group. A significant dose response was present with greater decrease in serum iron in a dose related manner from 1 to 20 mg. The serum iron reduction was sustained up to Day 8/End of Study (EOS) (hour 168) in most patients. Decreases in ferritin, total iron binding capacity (TIBC), transferrin, and TSAT levels were also observed from baseline (predose) to Day 8/EOS.

Sixteen of the 18 patients (88.9%) reported TEAEs. All TEAEs were considered mild (Grade 1) or moderate (Grade 2) in severity, and none led to early discontinuation or death. One serious AE (SAE; sickle cell crisis) occurred during the study; the Investigator deemed the event as not related to study drug.

Across all dose groups, the most frequently occurring AEs by preferred term (PT) were injection site reactions (12 patients [66.7%]), nausea (2 patients [11.1%]), ALT increased (2 patients [11.1%]), decreased appetite (2 patients [11.1%]) and hypoesthesia (2 patients [11.1%]). The frequency of injection site reactions in each dose group was 0 in 3 (0%) in the 1-mg group, 3 out of 3 (100%) in the 5-mg group, 0 in 3 (0%) in the 10-mg group, 6 out of 6 (100%) in the 20-mg group, and 3 out of 3 (100%) in the 30-mg group. All injection site reactions were mild in severity and resolved by the end of the study (Day 22). The mean and median duration of injection site reactions were as follows: 5 mg (1.0 and 1.0 days), 20 mg (2.0 and 1.0 days), and 30 mg (14.8 and 4.0 days).

All samples were confirmed negative for anti-drug antibodies to LJPC-401.

3.3.2. LJ401-NHV01

The Phase 1 clinical trial LJ401-NHV01 was a randomized, double-blind, placebo-controlled, single-center study to determine the safety, tolerability, PK, serum iron kinetics, and immunogenicity of escalating single doses of LJPC-401 in 32 healthy adult subjects. The study enrolled subjects in 4 dose groups of 8 subjects per cohort, with 6 subjects assigned to LJPC-401 and 2 subjects assigned to placebo in each cohort. The starting dose was 5 mg of LJPC-401 or placebo; subsequent dose groups received 10 mg, 20 mg, and 30 mg, respectively. Subjects received between one and three 1-mL SC injections to deliver the desired dose level. LJPC-401 concentration was either 5 mg/mL or 10 mg/mL. For data analysis purposes, placebo subjects for all cohort groups were pooled.

A decrease in serum iron levels compared to baseline was observed in all 4 dose groups, with mean maximum reduction of 33% to 65% at 8-hours post dose. Serum iron levels returned to baseline before 48 hours. A significant dose response was observed, with larger reductions in serum iron generally associated with increases in dose up to 20 mg. There was no apparent difference in the maximum reduction between the 20 and 30 mg dose levels. Ferritin, TIBC, transferrin, and TSAT were increased from baseline at Day 8 for all treatment groups. There was no trend associated with an increase in LJPC-401 dose and the amount of increase in any of these iron parameters. Unsaturated iron binding capacity (UIBC) levels showed no trends in changes from baseline at Day 8.

TEAEs were reported by all 24 subjects (100%) in the LJPC-401 dose groups and 2 of 8 subjects (25%) in the placebo group. All TEAEs were considered mild (Grade 1) in severity, and none were deemed serious or led to early discontinuation or death. The number of TEAEs was similar among all dose groups. Across all dose groups, the most frequently reported AEs were injection site reactions (24 subjects [100%] LJPC-401 and 1 subject [12.5%] placebo), catheter site phlebitis (3 subjects [12.5%] LJPC-401), headache (2 subjects [8.3%] LJPC-401), presyncope (1 subject [12.5%] placebo), and anxiety, nausea, and hand dermatitis (1 subject [4.2%] LJPC-401 each). All injection site reactions were mild in severity, and all but 1 resolved before the end of the study. The mean and median duration of injection site reactions in the 5 dose groups were as follows: placebo (1.0, 1.0 days), 5 mg (1.0, 1.0 days), 10 mg (5.6, 8.0 days), 20 mg (13.3, 15.5 days), and 30 mg (11.7, 8.0 days).

All samples were confirmed negative for anti-drug antibodies to LJPC-401.

3.3.3. LJ401-NHV02

The Phase 1 clinical trial LJ401-NHV02 is a randomized, double-blind, placebo-controlled, single and multiple dose escalation study to assess the safety and tolerability of LJPC-401 in healthy adult subjects.

The study enrolled 21 subjects total. In the single dose arm of the study, 10 subjects received LJPC-401 and 3 subjects received placebo. In the multiple dose arm of the study, 6 subjects received LJPC-401 and 2 subjects received placebo 4 times over a 2-week period. Results demonstrated that LJPC-401 was well tolerated at all administered doses (4 mg, 10 mg and 20 mg). There were no dose-limiting toxicities at any dose. Consistent with both completed Phase 1 studies, the most common adverse event (AE) was injection site reaction. Both severity and duration of these skin reactions were similar in this study in both the single and multiple dosing cohorts compared to the previous formulation used in studies LJ401-TPP01 and LJ401-NHV01.

3.4. Clinical Rationale for the LJ401-HH01 Study

Patients with hereditary hemochromatosis absorb too much iron from their diet (NIH 2017). Human iron elimination is limited and unable to compensate for an abnormal state of iron absorption. This excess iron can eventually damage tissues and organs, particularly the skin, heart, liver, pancreas, and joints. The primary treatment for hereditary hemochromatosis is phlebotomy. Typically, phlebotomy is initially performed at weekly or twice-weekly intervals until desired iron levels are attained, and then performed less often (2 to 4 times per year) on an indefinite basis (Counsyl 2017). Phlebotomy is inconvenient and tedious, and patient compliance decreases over time (Hicken 2003). Hicken et al (2003) reported that 53% (75/142 patients) of patients became noncompliant at some time during maintenance therapy, less than 50% of patients complied with maintenance therapy by the end of their sixth year after achieving iron depletion, and that average compliance with maintenance therapy decreased 6.8% annually. Other treatments for iron overload, including erythrocytapheresis and chelation therapy have significant and undesirable side effects.

The iron-regulating effects of hepcidin, which is reduced in patients with hereditary hemochromatosis, make it a potentially beneficial therapeutic for the treatment of hereditary hemochromatosis. LJPC-401, a synthetic equivalent of the endogenous circulating peptide hepcidin-25, is expected to reduce iron overload in this patient population. The safety profile to date indicates that the product is well tolerated, with injection site reaction being the most frequently reported AE. In addition, the once-weekly single-dose administration, is expected to be less burdensome than standard phlebotomy with a large bore needle.

3.4.1. Rationale for the Study Design for Study LJ401-HH01

This study was designed to evaluate the efficacy of LJPC-401 for the treatment of hereditary hemochromatosis by showing a significant and clinically meaningful change in TSAT levels. TSAT was chosen as an appropriate endpoint for assessing the clinical efficacy of LJPC-401 since it considers both the iron level and the TIBC (AACC 2015). Nontransferrin bound iron (NTBI), the toxic form of iron, has been correlated with cardiac disease (Piga 2013), and TSAT correlates with both cardiac disease and levels of NTBI.

The study will employ a randomized, placebo-controlled, single-blind design. Randomization will be used to minimize bias in the assignment of patients to treatment groups by increasing the

likelihood that known and unknown patient attributes (eg, demographic and baseline characteristics) are evenly balanced, thereby enhancing the validity of statistical comparisons across treatment groups (LJPC-401 versus placebo). Investigators will not be blinded to treatment arm or TSAT results so they can adjust study drug per the dose adjustment criteria if needed.

Randomization will occur in a 1:1 ratio and will be stratified by baseline TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3), since adequately treated patients have a better prognosis than those treated inadequately (Duchini 2017).

A treatment period of 16 weeks was considered adequate to evaluate the efficacy of LJPC-401 and serve as the basis for the design of a Phase 3 study. The decision to include 1 phlebotomy at Day 1 (predose) was made in consideration of the likely elevations in TSAT and ferritin in the study population at baseline.

The dose range that will be used in this study (Section 5.3) has been evaluated in 3 Phase 1 clinical trials. The 5-mg starting dose was selected for this study based on data from previous studies in patients and healthy volunteers (Section 3.3) and has been previously tested in patients with iron overload (Section 3.3.1). The reduction in TSAT in these patients at 5 mg was approximately 27%, which occurred at 8 to 12 hours and returned to baseline by 72 to 96 hours. LJPC-401 5 mg was well tolerated and provided a minimal efficacy of reduction in TSAT. As such, the first dose is likely to be both safe and sub-therapeutic with an allowance for adjustment. The maximum dose of 20 mg was chosen for this study based on the results of patient Study LJ401-TTP01 that showed a larger dose-response/reduction in serum iron was generally associated with increasing dose up to 20 mg. LJPC-401 has been evaluated at doses as high as 30 mg (healthy volunteer LJ401-NHV01); however, in Study LJ401-TTP01, it was observed that patients with hemochromatosis had a lower mean serum iron level at baseline compared with patients with hemoglobinopathies. This is consistent with the higher mean endogenous hepcidin concentration observed in patients with hemochromatosis. As such, LJPC-401 20 mg is considered the appropriate maximum dose for the patient population in this study. Both the maximum dose (20 mg) and dose-escalation plan were well-tolerated and efficacious in both Phase 1 studies.

A 30-day follow-up visit was chosen based on regulatory guidance for assessing and monitoring safety, including potential immunogenic effect, in patients who have discontinued or completed clinical studies of investigational agents with prompt action and relatively short elimination half-lives (Food and Drug Administration [FDA], 2010).

3.4.2. Rationale for Using Iron Disorders Institute Phlebotomy Guidelines

This study will use the 2011 Iron Disorders Institute (IDI) phlebotomy guidelines as the basis for defining the criteria for phlebotomy. The IDI is partnered with the United States Centers for Disease Control and Prevention, the National Institutes of Health, and multiple patient advocacy groups for people with iron disorders. Iron Disorders Institute provides clinical support, services, and educational information. The IDI Medical and Scientific Advisory Board is comprised of experts in iron metabolism and iron balance. The materials published by IDI contain reference ranges, diagnosis algorithms, diagnostic aids, therapeutic approaches, and genetic and diet information. This content has been peer-reviewed and approved by members of the IDI Medical and Scientific Advisory Board.

In addition, use of the TSAT criteria of the IDI phlebotomy guidelines will ensure that patients are prescribed phlebotomy in a consistent manner across both groups and improves patient safety as the recommendations are endorsed by medical and scientific experts.

4. TRIAL OBJECTIVES AND PURPOSE

To evaluate the effect of once-weekly dosing of LJPC-401 for 16 weeks on the following parameters in adult patients with hereditary hemochromatosis.

4.1. Primary Objective

To compare the effect of LJPC-401 versus placebo on transferrin saturation (TSAT) in adult patients with hereditary hemochromatosis.

4.2. Secondary Objectives

- To compare the effect of LJPC-401 versus placebo on phlebotomy requirements.
- To establish the safety and tolerability of LJPC-401 versus placebo in adult patients with hereditary hemochromatosis.
- To compare the effect of LJPC-401 versus placebo on serum ferritin.

4.3. Exploratory Objectives

- To compare the effect of LJPC-401 versus placebo on serum iron parameters.
- To compare the effect of LJPC-401 versus placebo on thyroid function.
- To compare the effect of LJPC-401 versus placebo on liver function.
- To compare the effect of LJPC-401 versus placebo on glycemic control.
- To compare the effect of LJPC-401 versus placebo on red blood cell (RBC) parameters including hemoglobin concentration, RBC count, and red cell distribution width (RDW).
- To compare the effect of LJPC-401 versus placebo on quality of life as measured by Quality of Life Questionnaires: 36-Item Short Form (SF-36v2), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the modified Dreisler indices for arthritis.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

This study is a multicenter, randomized, placebo-controlled, single-blind study. The primary objective of the study is to evaluate the effect of LJPC-401 on TSAT in adults with hereditary hemochromatosis.

Eligible patients will be randomized on a 1:1 schedule and blinded to study treatment, LJPC-401 or placebo. Randomization will be stratified by baseline TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3).

All randomized patients will receive standard of care therapeutic phlebotomy (500 cc or appropriate for weight) on Day 1 (predose). Thereafter, phlebotomy decisions by the Investigator will be based on the patient's fasting TSAT results collected at Week 4 (Day 23); Week 8 (Day 51); Week 12 (Day 79); and Week 16 (Day 107); and based on the TSAT criteria of the IDI phlebotomy guidelines for patients with hereditary hemochromatosis. If a phlebotomy is indicated, based on the TSAT criteria of the IDI guidelines, the patient should receive phlebotomy treatment predose, on or before the following visit.

Investigators are not blinded to treatment arm or TSAT results so they can adjust study drug per the dose adjustment criteria if needed.

The primary efficacy analysis will take place after all on-study patients have completed the Week 16 assessments (or have withdrawn from the study early).

5.2. Number of Patients

Approximately 68 to 76 patients are planned to be enrolled and randomized across approximately 30 sites to ensure that at least 48 patients complete the Week 16 assessments and are included in the primary efficacy analysis (Section 12.2). All patients must meet the eligibility criteria outlined in Section 6. One rescreening for eligibility will be allowed for each patient. As inclusion criteria are laboratory parameters that are dynamic in this population, additional rescreens may be allowed upon approval from the Medical Monitor. If rescreened, the patient will keep the previously assigned screening number.

5.3. Treatment Assignment

Patients will be dosed once-weekly with LJPC-401 or placebo administered SC for 16 weeks. LJPC-401 dose will start at 5 mg at Week 1 and increase to 10 mg at Week 2. Refer to Section 5.4 for dose adjustments outside of these fixed doses. For those patients randomized to placebo, a syringe of 0.9% sodium chloride injection, United States Pharmacopoeia (USP; or equivalent) will be prepared by the study pharmacist or designee. To maintain the study single-blind, syringes with study drug (placebo and active drug) will be identical. Refer to the study specific Pharmacy Manual for detailed guidance.

5.4. Dose Adjustment Criteria

Dosing Adjustments:

- Week 1: 5 mg LJPC-401 or placebo
- Week 2: 10 mg LJPC-401 or placebo
- Week 3: 10 mg LJPC-401 or placebo

Week 3: Fasting TSAT (postdose 24 [± 4] hours), ie, 20 to 28 hours, determines the Week 4 dose:

  - If the TSAT is > 45%, dose increased to 20 mg LJPC-401 or placebo
  - If the TSAT is ≤ 45%, dose remains at 10 mg LJPC-401 or placebo
- Week 4: LJPC-401 (or placebo) dose as indicated by Week 3 fasting TSAT (10 to 20 mg LJPC-401 or placebo)
- At Weeks 9 and 13 (after Weeks 8 and 12 fasting TSAT results are available):
  - Maintain or increase dose to 20 mg if TSAT is > 45%
  - Maintain dose (10 or 20 mg) if TSAT remains ≤ 45%, and no dose reduction is required for toxicity (refer to Section 5.4.1)
- For down titration, follow the safety criteria outlined in Section 5.4.1.

Important Guidelines:

1. The last central laboratory fasting TSAT result at Week 3 (Day 16), Week 8 (Day 51), and Week 12 (Day 79) will be used to determine if a dose adjustment is needed at Weeks 4, 9, and 13. TSAT for dose adjustments must be collected 24 (± 4) hours postdose.
2. If fasting TSAT level is greater than 45% collected at postdose 24 (± 4) hours on Week 4 (Day 23); Week 8 (Day 51); Week 12 (Day 79); and Week 16 (Day 107), a phlebotomy (500 cc or appropriate for weight) is indicated predose, on or before the following visit.
3. Round TSAT with decimal values using the standard rounding rule.

The pharmacist, or designee, will prepare the study drug (LJPC-401 or placebo) to ensure the patient will remain blinded. Refer to the study specific Pharmacy Manual for detailed guidance.

5.4.1. Safety Criteria for Adjustment or Stopping Doses

For each individual patient, the safety criteria used to adjust (reduce) dosing include 1 or more of the following:

1. injection site reaction(s) severity grade of severe
2. patient cannot or will not tolerate assigned injections (refer to Section 5.4 for dose adjustment directions)

For each individual patient, the safety criteria used to stop doses include 1 or more of the following:

1. TEAEs, including injection site reaction(s) severity grade of severe or higher
2. patient cannot or will not tolerate SC injection(s)

3. clinically significant laboratory parameters, including if TSAT is less than 10% (if this occurs, consult the Medical Monitor)

5.5. Criteria for Study Termination

This study may be prematurely terminated if in the opinion of La Jolla, there is sufficient reasonable cause. Written notification documenting the reason for study termination would be provided to the Investigators by La Jolla. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enroll study patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient and/or unevaluable data
- Plans to modify, suspend, or discontinue development of the study drug

5.6. Schedule of Assessments

The procedures and timing of the assessments scheduled for this study are displayed in Table 3. Efficacy and safety assessments are described in Section 9 and Section 10, respectively. Refer to Section 10.1.6 lists of protocol-specified laboratory analytes.

Table 3: Schedule of Assessments

Procedures	Screening	Timing of Assessments																
	Within 90 Days of Week 1/Day 1	Week/Day ± 2-day window Weeks 2 through 17																
	Week	1	2	3		4		5, 6, 7	8		9, 10, 11	12		13, 14, 15	16 /EWD[1]		17	20/EOS[2] (Follow-up)
	Day	1	8	15	16 ± 4 hr	22	23 ± 4 hr	29, 36, 43	50	51 ± 4 hr	57, 64, 71	78	79 ± 4 hr	85, 92, 99	106	107 ± 4 hr	113	134
Informed Consent	X																	
Confirm Eligibility[3]	X	X																
Randomization[4]		X																
Medical History	X																	
Physical Exam[5]	X														X			X
Vital Signs[6]	X	X	X	X		X		X	X		X	X		X	X			X
Prior/Concomitant Medication[7]	X	X	X	X		X		X	X		X	X		X	X			X
Adverse Events[8]	X	X	X	X		X		X	X		X	X		X	X			X
LJPC-401 or Placebo Dosing[9]		X	X	X		X		X	X		X	X		X	X			
12-Lead ECG[10]	X																	X
Phlebotomy		X[11]				Weeks 4 to 16[11]												
Laboratory:																		
Hematology	X	X				X			X			X			X	X		X
Chemistry Panel	X	X				X			X			X			X			X
Thyroid Panel		X													X			

Table 3: Schedule of Assessments (Continued)

Procedures	Screening	Timing of Assessments																
	Within 90 Days of Week 1/Day 1	Week/Day ± 2-day window Weeks 2 through 17																
	Week	1	2	3		4		5, 6, 7	8		9, 10, 11	12		13, 14, 15	16 /EWD[1]		17	20/EOS[2] (Follow-up)
	Day	1	8	15	16 ± 4 hr	22	23 ± 4 hr	29, 36, 43	50	51 ± 4 hr	57, 64, 71	78	79 ± 4 hr	85, 92, 99	106	107 ± 4 hr	113	134
Hemoglobin A1c		X													X			
Complete Iron Study	X[12]	X[13]		X[13]	X[13]	X[13]	X[13]		X[13]	X[13]		X[13]	X[13]		X[13]	X[13]	X[14]	X
Urinalysis	X														X			X
Serum Pregnancy[15]	X																	
Urine Pregnancy[16]		X																X
Immunogenicity/ PK[17]	X[18]	X[19]	X			X			X			X			X[19]			X
Quality of Life:																		
Questionnaires		X[20]													X[20]			

Abbreviations: AE=adverse event; ECG=electrocardiogram; EOS=End of Study; EWD=Early Withdrawal; PK=pharmacokinetics; SAE=serious adverse event; Questionnaires=(SF-36v2) Short Form Health Survey, Version 2, WOMAC, and modified Dreisler indices for arthritis; TSAT=transferrin saturation.

General Instructions:

All assessments must be performed prior to dosing unless otherwise specified.

Patients are not to eat any food or drink any beverages, except water, for at least 6 hours prior to collecting blood for laboratory tests including iron studies (Immunogenicity/PK and pregnancy test samples are not required to be fasting).

From Weeks 2 through 17 there is a ± 2-day window for visits; once the visit occurs, the patient should return to the regular interval schedule.

Assessments:

1. For patients who withdraw early, all Week 16 procedures plus a 12-lead ECG and urine pregnancy test (females of child-bearing potential only) will be performed, to the extent possible, for the Early Withdrawal Visit.
2. The EOS follow-up visit will occur 30 days (+ 3 days; approximately Week 20) after the last dose of study drug.
3. Confirm inclusion/exclusion criteria at Screening and on Week 1/Day 1 (predose). Screening laboratory results must be received and reviewed for eligibility prior to dosing.
4. Randomization must occur after inclusion/exclusion criteria are confirmed.
5. Height will be performed at Screening only; weight will be performed at Screening and Week 16.
6. Vitals will include blood pressure, heart rate, respiration rate, and body temperature. Blood pressure will be assessed after the patient has been resting in the sitting position for at least 5 minutes.
7. Record all medications taken and any procedures performed, beginning 14 days prior to Screening. Starting Week 2, record all new or changes to concomitant medications through the follow-up visit that will occur 30 days (+ 3 days) after the last dose of study drug.
8. Record any AEs and SAEs starting at consent. Report any SAEs per Section 11.3.2.
9. Patients will be dosed once-weekly. Refer to Section 5.4 for dose adjustment criteria.
10. 12-lead ECGs will be collected in triplicate (≥ 1 minute apart). The Screening ECG must be performed within 30 days prior to the first dose of study drug. Abnormalities noted at Screening should be included in the medical history. Additional ECGs will be collected if clinically indicated (ie, palpitations, lightheadedness). If a patient withdraws from the study early, a 12-lead ECG will be performed as part of the Early Withdrawal procedures (if possible).
11. All randomized patients will receive a standard of care therapeutic phlebotomy (500 cc or appropriate for weight) on Day 1 (predose). Thereafter, phlebotomy decisions by the Investigator will be based on the patient's fasting TSAT results collected postdose at Weeks 4 (Day 23); Week 8 (Day 51); Week 12 (Day 79); and Week 16 (Day 107); and based on the TSAT criteria of the IDI guidelines for patients with hereditary hemochromatosis. If a phlebotomy is indicated, based on the TSAT criteria of the IDI guidelines, the patient should receive phlebotomy treatment predose, on or before the following visit. If therapeutic

phlebotomy is performed the same day as dosing, the order should be: laboratory samples; phlebotomy; LJPC-401 or placebo dose.

12. If the fasting Screening ferritin and TSAT levels do not meet entry criteria, the patient's regularly scheduled phlebotomy may be deferred, and fasting and complete iron studies repeated every 30 days for up to 90 days until entry criteria are met.
13. Blood for fasting complete iron studies must be collected predose and again 24 (± 4) hours after dosing at the same time of day each visit whenever possible. TSAT at Weeks 3, 8, and 12 (24 [± 4] hours postdose) will determine the LJPC-401 dose for subsequent study visits (Weeks 4, 9, and 13). Refer to Section 5.4 for dose information and dose adjustments. Additional blood samples will be collected for scientific research, including PK analyses and analyses of apoferritin and holoferritin.
14. Collect blood for complete iron studies.
15. Serum pregnancy test (female patients of childbearing potential only – Screening) must be performed within 30 days prior to the first dose of study drug (fasting is not required).
16. Urine pregnancy test (ie, dipstick) will be performed for females of childbearing potential on Week 1/Day 1 predose and Week 20 or Early Withdrawal (if possible).
17. Blood for immunogenicity/PK testing to be collected (fasting is not required) at Screening and predose at: Week 1 (with a window of −30 minutes before dosing), Week 2, Week 4, Week 8, Week 12, Week 16; and EOS/30 days (+ 3 days) after the last dose of study drug (approximately Week 20). Additional immunogenicity testing may be performed as described in Section 10.1.6.7.
18. Two blood samples (2 tubes) need to be collected for the immunogenicity/PK analysis at Screening; these samples may be collected at the same visit.
19. Collect additional blood samples (fasting is not required) for immunogenicity/PK analysis postdose 1 hour or later at Weeks 1 and 16.
20. Quality of Life Questionnaires, (SF-36v2), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and modified Dreisler indices for arthritis, should be completed prior to phlebotomy.

6. SELECTION AND WITHDRAWAL OF PATIENTS

Each patient must meet all the following inclusion criteria and none of the exclusion criteria in order to be enrolled in the study.

6.1. Patient Inclusion Criteria

1. Patients with a clinical diagnosis of hereditary hemochromatosis.
2. Patients who are prescribed therapeutic phlebotomy for the treatment of hereditary hemochromatosis.
3. Patients ≥ 18 years of age.
4. Patients with a serum ferritin level ≥ 100 ng/mL.
5. Patients with a TSAT level > 45%.
6. Female patients must be of nonchildbearing potential or using a highly effective method of contraception during participation in the study and for 30 days after the last dose of study drug. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate when used consistently and correctly. Refer to Section 10.1.6.5.1 for the list of highly effective methods of contraception that can be used in this study.
7. Female patients of child bearing potential must have a negative serum pregnancy test during Screening (within 30 days prior to the first dose of study drug), and a negative urine pregnancy test at Day 1 (ie, prior to initial dosing of study drug).
8. Male patients must be surgically sterile (vasectomy) or using a highly effective method of contraception during participation in the study and for 30 days after the last dose of study drug. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate when used consistently and correctly. Refer to Section 10.1.6.5.1 for the list of highly effective methods of contraception that can be used in this study.
9. Patient must be willing and able to provide written informed consent.

6.2. Patient Exclusion Criteria

1. Patients receiving iron chelation therapy within 7 days prior to the first dose of study drug.
2. Patients initiating phlebotomy treatments less than 3 months prior to the first dose of study drug.
3. Patients with a concomitant disease, disability or condition, including laboratory abnormality and ECG findings, which may interfere with the conduct of the study, or which would, in the opinion of the Investigator, pose an unacceptable risk to the patient in this study, including, but not limited to, clinically significant arrhythmias, alcohol dependency or abuse, drug dependency or abuse, or psychiatric disease. Patients with

depression are eligible if receiving a stable dose of medication for at least 90 days prior to the first dose of study drug.

4. Pregnant or lactating women.
5. Patients taking an immunosuppressive agent that has not been approved for use by La Jolla (excluding topical over-the-counter steroids, inhaled steroid medications, and nonsteroidal anti-inflammatory drugs). Refer to Section 7.1 for the list of prohibited medications and procedures.
6. Patients participating in an unapproved investigational drug or investigational therapeutic device study within 30 days prior to study drug dosing, ie, there must be at least 30 days in between the last dose on a prior study and the first dose administration on this trial.
7. Patients who are unwilling or unable to comply with the study protocol requirements.
8. Patients with type 1 diabetes or type 2 diabetes with hemoglobin Alc greater than 8% within 2 months prior to randomization.
9. Patients with uncontrolled active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection.
10. Patients with Child Pugh class C cirrhosis or liver failure.
11. Patients with severe congestive heart failure (NYHA = Class 4).
12. Patients who have advanced renal failure with an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m^2.
13. Patients with a history of allergic reaction to hepcidin or excipients.
14. Patients who have planned surgery (excluding dental surgery or simple dermatologic procedures) during participation in this study.

6.3. Patient Withdrawal Criteria

Patients will be informed that they have the right to withdraw from the study at any time and for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw patients from the study for any of the following reasons:

1. Clinically significant intercurrent illness
2. Occurrence of an unacceptable AE. AEs of concern must be discussed with La Jolla's Medical Monitor for possible adjustments in dosing schedule (delay, skip, or rechallenge).
3. At patient's request
4. Important protocol deviation / violation
5. Non-compliance
6. Administrative reason
7. Failure to return for follow-up

8. General or specific changes in the patient's condition unacceptable for further participation based upon the judgment of the Investigator

Patients that may withdraw prior to Week 16 should be discussed with the Medical Monitor. At the time of withdrawal, all efforts should be made to perform procedures equivalent to Week 16 plus a 12-lead ECG and urine pregnancy test (Table 3), to the extent possible. Patients should be encouraged to complete EOS follow-up procedures 30 days (+ 3 days) after the last dose of LJPC-401. The reason(s) for a patient's withdrawal from the study must be recorded on the appropriate electronic Case Report Form (eCRF).

7. TREATMENT OF PATIENTS

For description of study drug, see Section 8.

	Investigational Product
Product Name:	LJPC-401 (synthetic human hepcidin)
Dosage Form:	Solution for Injection
Unit Dose:	5 or 10 mg/mL
Route of Administration:	Subcutaneous
Physical Description:	LJPC-401 for SC administration is a clear colorless solution, with essentially no visible particles, supplied in clear glass vials, with a rubber stopper, aluminum over-seal, and plastic flip-off cap.

7.1. Concomitant Medications and Procedures

All medications and other therapies that are administered starting from 14 days prior to Screening and during the study, including the start and stop date(s), dose and amount administered, and indication, must be recorded in the eCRFs and in the source documents. No other experimental therapy is permitted. Concomitant medications for other medical conditions are permitted as clinically indicated, subject to specific requirements outlined in this protocol.

Prohibited medications and therapies:

- Any investigational agent other than LJPC-401
- Any immunosuppressive agent that has not been approved for use by La Jolla (excluding topical over-the-counter steroids, inhaled steroid medications, and nonsteroidal anti-inflammatory drugs)
- Vitamin C supplements
- Surgery for any reason (excluding dental surgery or simple dermatologic procedures)

When an immediate deviation from the protocol is required to eliminate an immediate hazard(s) to a patient, the Investigator will contact the study Medical Monitor, if circumstances permit, to discuss the planned course of action. Any important deviations from the protocol must be fully documented on the appropriate eCRF and in the source documentation.

7.2. Treatment Compliance

Study drug will be administered to eligible patients under the supervision of the Investigator or identified Sub-Investigator(s). Upon completion of appropriate training, the Investigator may delegate study drug administration to a trained home care nurse/research staff. The pharmacist or designee will maintain records of study drug receipt, preparation, and dispensing, including the total drug administered. The placebo lot number (from vial of sodium chloride for injection)

and the quantity of placebo solution administered to the placebo patient will be maintained in the pharmacy records. Any discrepancy between the assigned dose and dose administered, as well as the reason for the discrepancy, must be recorded in the source documents.

7.3. Randomization and Single-Blind

This is a randomized, placebo-controlled, single-blind study. Investigators are not blinded to treatment arm or TSAT results so they can adjust study drug per the dose adjustment criteria if needed. The study patients will not be informed of the treatment being administered (to maintain the single-blind). A study pharmacist or designee at the clinical site will obtain the appropriate randomization code from the Interactive Voice/Web Response System (IXRS) system in order to dispense study drug to each patient. The lot number will be recorded within the IXRS system. Refer to the study specific Pharmacy Manual for detailed guidance.

LJPC-401 will be supplied in vials as open-label stock. Labeling will fulfill all requirements specified by governing regulations.

7.4. Study Procedures

The timing and frequency of assessments and the details provided in Table 3 should be the primary source. From Weeks 2 through 17 there is a ± 2-day window for visits; once the visit occurs, the patient should return to the regular interval schedule. All assessments must be performed prior to dosing, unless otherwise specified. If therapeutic phlebotomy is performed the same day as dosing, the procedure order should be: laboratory samples, then phlebotomy, then study drug (LJPC-401 or placebo) dose.

Patients are not to eat any food or drink any beverages, except water, for at least 6 hours prior to collecting blood for laboratory tests including iron studies (Immunogenicity/PK and pregnancy test samples are not required to be fasting).

Blood for complete iron studies must be collected predose and again 24 (± 4) hours after dosing. Refer to Section 5.4 for specifics on dosing and dose adjustments. Blood for immunogenicity must follow the specified collection times outlined in Table 3 is per the following sections.

7.4.1. Screening (Within 90 days of Week 1/Day 1)

The following assessments will be performed as reflected in Table 3: Screening (within 90 days of Week 1/Day 1)

- Obtain informed consent
- Obtain the patient's complete medical history, including the demographic information, hereditary hemochromatosis diagnosis and genotype (if available), surgical history and therapeutic phlebotomy history
- Record medications and procedures, beginning 14 days prior to Screening
- Perform a physical examination and measurement of height and weight
- Obtain vital signs after the patient has been resting in the sitting position for at least 5 minutes
- Perform 12-lead ECG (in triplicate and ≥ 1 min apart) within 30 days prior to the first dose of study drug
- Collect blood predose for:
  - complete iron studies (including an additional sample for apoferritin and holoferritin); if ferritin and TSAT levels do not meet entry criteria, the patient's regularly scheduled phlebotomy may be deferred, and fasting and complete iron studies repeated every 30 days for up to 90 days until entry criteria are met
  - hematology
  - serum chemistry
  - serum pregnancy test within 30 days prior to the first dose of study drug for females of childbearing potential only (fasting is not required)
  - immunogenicity/PK testing (collect 2 blood samples [2 tubes], fasting is not required)
- Collect urine for urinalysis
- Assess inclusion/exclusion criteria and patient eligibility
- Assess and record AEs and SAEs, starting at consent

7.4.2. Week 1 (Day 1)

The following assessments will be performed as reflected in Table 3: Week 1/Day 1

- Confirm inclusion/exclusion criteria and patient eligibility prior to randomization
- Assess and record AEs and SAEs
- Record new or changes to concomitant medications/procedures
- Obtain vital signs after the patient has been resting in the sitting position for at least 5 minutes
- Collect blood predose for:
  - complete iron studies, including an additional sample for apoferritin and holoferritin
  - hematology
  - serum chemistry
  - thyroid function testing
  - hemoglobin A1c testing
  - immunogenicity/PK testing (with a window of -30 minutes before dosing, fasting is not required)
- Collect urine from females of childbearing potential only (ie, dipstick) prior to study drug administration
- Administer Quality of Life Questionnaires (SF-36v2), WOMAC, and modified Dreisler indices for arthritis) prior to phlebotomy
- Standard of care therapeutic phlebotomy (500 cc or appropriate for weight). Phlebotomy should be performed after laboratory samples are collected and before study drug dose (ie, order is laboratory samples, phlebotomy, LJPC-401 or placebo dose).
- Complete randomization procedures
- Administer single-blinded study drug (LJPC-401 or placebo)
  - Patients will not be informed of the treatment being administered (to maintain the single-blind).
- Collect postdose blood for immunogenicity/PK (1 hour or later, fasting is not required)

7.4.3. Week 2 (Day 8)

The following assessments will be performed as reflected in Table 3: Week 2/Day 8

- Assess and record AEs and SAEs
- Record new or changes to concomitant medications/procedures

- Obtain vital signs after the patient has been resting in the sitting position for at least 5 minutes
- Collect blood for immunogenicity/PK testing (fasting is not required)
- Administer single-blinded study drug (LJPC-401 or placebo)
  - Patients will not be informed of the treatment being administered (to maintain the single-blind).

7.4.4. Week 3 (Day 15 and Day 16)

The following assessments will be performed as reflected in Table 3: Week 3/Day 15 and Day 16

- Assess and record AEs and SAEs
- Record new or changes to concomitant medications/procedures
- Obtain vital signs after the patient has been resting in the sitting position for at least 5 minutes
- Collect blood for complete iron studies, including an additional sample for apoferritin and holoferritin
- Administer single-blinded study drug (LJPC-401 or placebo)
  - Patients will not be informed of the treatment being administered (to maintain the single-blind).
- **Week 3 (Day 16)**: Collect blood 24 (± 4) hours postdose for complete iron studies for TSAT to determine the LJPC-401 dose for Week 4. Refer to dose adjustment criteria and guidelines in Section 5.4.)

7.4.5. Week 4 (Day 22)

The following assessments will be performed as reflected in Table 3: Week 4/Day 22

- Assess and record AEs and SAEs
- Record new or changes to concomitant medications/procedures
- Obtain vital signs after the patient has been resting in the sitting position for at least 5 minutes
- Collect blood predose for:
  - complete iron studies, including an additional sample for apoferritin and holoferritin
  - hematology
  - serum chemistry
  - immunogenicity/PK testing (fasting is not required)
- Administer single-blinded study drug (LJPC-401 or placebo)

  - Patients will not be informed of the treatment being administered (to maintain the single-blind).

- **Week 4 (Day 23)**: Collect blood 24 (± 4) hours postdose for complete iron studies for TSAT to determine the if the patient requires a phlebotomy. If the TSAT result from Week 4, Day 23 is > 45%, the patient must be contacted so he/she can receive a phlebotomy (based on the TSAT criteria of the IDI guidelines).
  - If indicated, phlebotomy must be completed on or before Week 5. If therapeutic phlebotomy is performed the same day as dosing, the order should be: laboratory samples; phlebotomy; LJPC-401 or placebo dose.

7.4.6. Weeks 5, 6, and 7 (Days 29, 36, and 43)

The following assessments will be performed as reflected in Table 3: Weeks 5, 6, and 7/Days 29, 36, and 43

- Assess and record AEs and SAEs
- Record new or changes to concomitant medications/procedures
- Obtain vital signs after the patient has been resting in the sitting position for at least 5 minutes
- Administer single-blinded study drug (LJPC-401 or placebo)
  - Patients will not be informed of the treatment being administered (to maintain the single-blind).

7.4.7. Week 8 (Day 50 and Day 51)

The following assessments will be performed as reflected in Table 3: Week 8/Day 50 and Day 51

- Assess and record AEs and SAEs
- Record new or changes to concomitant medications/procedures
- Obtain vital signs after the patient has been resting in the sitting position for at least 5 minutes
- Collect blood predose for:
  - complete iron studies, including an additional sample for apoferritin and holoferritin
  - hematology
  - serum chemistry
  - immunogenicity/PK testing (fasting is not required)
- Administer single-blinded study drug (LJPC-401 or placebo)
  - Patients will not be informed of the treatment being administered (to maintain the single-blind).

- **Week 8 (Day 51)**: Collect blood 24 (± 4) hours postdose for complete iron studies for TSAT to determine if the patient requires a phlebotomy. If the TSAT result from Week 8, Day 51 is > 45%, the patient must be contacted so he/she can receive a phlebotomy (based on the TSAT criteria of the IDI guidelines).
- If indicated, phlebotomy must be completed on or before Week 9. If therapeutic phlebotomy is performed the same day as dosing, the order should be: laboratory samples; phlebotomy; LJPC-401 or placebo dose.

7.4.8. Weeks 9, 10, and 11 (Days 57, 64, and 71)

The following assessments will be performed as reflected in Table 3: Weeks 9, 10, and 11/Days 57, 64, and 71

- Assess and record AEs and SAEs
- Record new or changes to concomitant medications/procedures
- Obtain vital signs after the patient has been resting in the sitting position for at least 5 minutes
- Administer single-blinded study drug (LJPC-401 or placebo refer to dose adjustment Section 5.4.)
  - Patients will not be informed of the treatment being administered (to maintain the single-blind).

7.4.9. Week 12 (Day 78 and Day 79)

The following assessments will be performed as reflected in Table 3: Week 12/Day 78 and Day 79

- Assess and record AEs and SAEs
- Record new or changes to concomitant medications/procedures
- Obtain vital signs after the patient has been resting in the sitting position for at least 5 minutes
- Collect blood predose for:
  - complete iron studies, including an additional sample for apoferritin and holoferritin
  - hematology
  - serum chemistry
  - immunogenicity/PK testing (fasting is not required)
- Administer single-blinded study drug (LJPC-401 or placebo)
  - Patients will not be informed of the treatment being administered (to maintain the single-blind).

- **Week 12 (Day 79)**: Collect blood 24 (± 4) hours postdose for complete iron studies for TSAT to determine if the patient requires a phlebotomy. If the TSAT result from Week 12, Day 79 is > 45%, the patient must be contacted so he/she can receive a phlebotomy (based on the TSAT criteria of the IDI guidelines).
- If indicated, phlebotomy must be completed on or before Week 13. If therapeutic phlebotomy is performed the same day as dosing, the order should be: laboratory samples; phlebotomy; LJPC-401 or placebo dose.

7.4.10. Weeks 13, 14, and 15 (Days 85, 92, and 99)

The following assessments will be performed as reflected in Table 3: Weeks 13, 14, and 15/Days 85, 92, and 99

- Assess and record AEs and SAEs
- Record new or changes to concomitant medications/procedures
- Obtain vital signs after the patient has been resting in the sitting position for at least 5 minutes
- Administer single-blinded study drug (LJPC-401 or placebo; refer to dose adjustment Section 5.4.)
  - Patients will not be informed of the treatment being administered (to maintain the single-blind).

7.4.11. Week 16 (Day 106 and Day 107)

The following assessments will be performed as reflected in Table 3: Week 16/Day 106 and Day 107

- Assess and record AEs and SAEs
- Record new or changes to concomitant medications/procedures
- Obtain vital signs after the patient has been resting in the sitting position for at least 5 minutes
- Perform a physical examination (including weight)
- Collect blood predose for:
  - complete iron studies, including an additional sample for apoferritin and holoferritin
  - hematology
  - serum chemistry
  - thyroid function testing
  - hemoglobin A1c testing
  - immunogenicity/PK testing (fasting is not required)

- Collect urine for urinalysis
- Administer Quality of Life Questionnaires (SF-36v2), WOMAC, and modified Dreisler indices for arthritis) prior to phlebotomy
- Administer single-blinded study drug (LJPC-401 or placebo)
  - Patients will not be informed of the treatment being administered (to maintain the single-blind).
  - Collect postdose blood for immunogenicity/PK (1 hour or later, fasting is not required)
- **Week 16 (Day 107)**: Collect blood 24 (± 4) hours postdose for hematology and complete iron studies for TSAT to determine if the patient requires a phlebotomy. If the TSAT result from Week 16, Day 107 is > 45%, the patient must be contacted so he/she can receive a phlebotomy (based on the TSAT criteria of the IDI guidelines).
- If indicated, phlebotomy must be completed on or before Week 17 (Day 113). If therapeutic phlebotomy is performed the same day as the Week 17, fasting iron studies should be collected before phlebotomy.

7.4.12. Week 17 (Day 113)

- Collect blood for fasting iron studies (trough sample, approximately 7 days after last dose).

7.4.13. Follow-up (30 days [+ 3 days] from last dose of study drug)

The following assessments will be performed as reflected in Table 3: Approximately Week 20 (30 days [+ 3 days] after the last dose of study drug)

- Assess and record AEs and SAEs
- Record new or changes to concomitant medications/procedures
- Obtain vital signs after the patient has been resting in the sitting position for at least 5 minutes
- Perform a physical examination
- Perform 12-lead ECG (in triplicate and ≥ 1 min apart)
- Collect blood for:
  - complete iron studies, including an additional sample for apoferritin and holoferritin
  - hematology
  - serum chemistry
  - immunogenicity/PK testing (fasting is not required)

- Collect urine for:
  - urinalysis
  - pregnancy test, for females of childbearing potential only (ie, dipstick test)

7.4.14. Early Withdrawal

The following procedures are to be collected, to the extent possible, for patients who withdraw early. Procedures include all Week 16 procedures plus a 12-lead ECG and urine pregnancy testing (females of child-bearing potential only).

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1. Study Drug

LJPC-401 for SC administration is a clear colorless solution, with essentially no visible particles, supplied in clear glass vials, with a rubber stopper and aluminum over-seal with a plastic flip-off cap. Product concentration is 5 or 10 mg/mL. The extractable fill volume is 1.0 mL. Refer to the product label and/or the Pharmacy Manual for dose preparation instructions.

8.2. Study Drug Packaging and Labeling

LJPC-401 will be supplied in vials as open-label stock. Labeling will fulfill all requirements specified by participating governing regulations.

A volume-matched placebo (0.9% sodium chloride injection, USP [or equivalent]) will be provided by the study sites from their own stock.

Refer to the study specific Pharmacy Manual for detailed guidance.

8.3. Study Drug Storage

Vials containing LJPC-401 should be stored refrigerated at 5°C ± 3° (2°C to 8°C) in a secure area with limited access. La Jolla has tested product stability and shown the product to be stable within that temperature range for the anticipated duration of use.

Refer to the study specific Pharmacy Manual for detailed guidance.

8.4. Study Drug Preparation

Prior to administration, vials of LJPC-401 should be stored at room temperature for a minimum of 30 minutes following removal from the refrigerator. Study drug can be stored at room temperature for up to 24 hours prior to dosing.

A pharmacist or designee will prepare the study drug using safe practices for medical injections. For those patients randomized to placebo, a volume-matched syringe of 0.9% sodium chloride injection, USP (or equivalent) will be prepared by the pharmacist or designee and labeled as such that those syringes containing drug product and those containing placebo appear identical (to maintain the study single-blind).

Refer to the study specific Pharmacy Manual for detailed guidance.

8.5. Study Drug Administration

Vials are for single-use administration and will be given via SC injection. Study drug will only be administered to eligible patients under the supervision of the Investigator or identified Sub-Investigator(s). Upon completion of appropriate training, the Investigator may delegate study drug administration to a trained home care nurse/research staff.

Refer to the study specific Pharmacy Manual for detailed guidance.

8.6. Study Drug Accountability

All used (empty or partially empty) and unused study drug vials must be saved for the Study Monitor for reconciliation prior to destruction or initiating a return of study drug. Destruction of study drug may only be performed if La Jolla has agreed to on-site destruction of used vials.

Refer to the study specific Pharmacy Manual for detailed guidance.

8.7. Study Drug Handling and Disposal

All unused study drug and other study materials must be returned to La Jolla or its designee and/or destroyed at the study site (if approved by La Jolla) after reconciliation has been completed by the Study Monitor, or unless otherwise directed by La Jolla. All unused material containing LJPC-401 will be treated and disposed of as hazardous waste in accordance with governing regulations.

Refer to the study specific Pharmacy Manual for detailed guidance.

9. ASSESSMENT OF EFFICACY

9.1. Complete Iron Studies

Blood samples for analysis of iron study parameters include:

- Total Serum Iron
- Ferritin
- Transferrin
- TIBC
- UIBC
- TSAT

Complete iron studies will be assessed at times specified in Table 3. Patients are not to eat any food or drink any beverages, except water, for at least 6 hours prior to collecting blood for complete iron studies. Additional blood samples will be collected for scientific research, including PK analyses and analyses of apoferritin and holoferritin.

9.2. Phlebotomy

All randomized patients will receive a standard of care therapeutic phlebotomy (500 cc or appropriate for weight) on Day 1 (predose). Thereafter, phlebotomy decisions by the Investigator will be based on the patient's fasting TSAT results collected postdose 24 (± 4) hours at Week 4 (Day 23); Week 8 (Day 51); Week 12 (Day 79); and Week 16 (Day 107). If the resulting TSAT is > 45% a phlebotomy is indicated. If a phlebotomy is indicated, the patient should receive phlebotomy treatment predose, on or before the following visit.

If therapeutic phlebotomy is performed the same day as dosing, the order should be: laboratory samples; phlebotomy; LJPC-401 or placebo dose.

Number of phlebotomies and the number of times a patient met criteria for a phlebotomy will be evaluated (Section 12.8.4.2).

10. ASSESSMENT OF SAFETY

Assessments will be performed at times specified in Table 3.

10.1. Safety Parameters

Safety assessments will include monitoring of all AEs, regular monitoring of laboratory parameters including hematology, serum chemistry and iron panel, ECGs, concomitant medications, physical examinations, vital signs, and testing for immunogenicity.

10.1.1. Demographics

Demographic information will be collected at Screening, to include age, sex, childbearing potential, race, ethnicity, and geographic region (where allowed, per local regulations). Refer to Section 12.8.1 for the full list of characteristics that will be collected.

10.1.2. Medical History

A complete review of the patient's medical history should include the patient's hereditary hemochromatosis diagnosis and genotype (if available), concurrent medical conditions, surgical and medical procedures, and therapeutic phlebotomy history.

Prior and concomitant medications will be recorded through the follow-up visit. This recording should include any medication taken, including oral contraceptives, and medical procedure(s) performed from 14 days prior to Screening to the follow-up visit (30 days [+ 3 days] after the last dose of study drug).

10.1.3. Vital Signs

Vital signs, including heart rate, respiratory rate, body temperature, and blood pressure, as outlined in Table 3, will be measured after the patient has been resting in a sitting position for at least 5 minutes.

Vital signs may be performed by an Investigator, Sub-Investigator, or Investigator-designated nurse, physician's assistant, or any staff member appropriately trained and included on the delegation of authority log as able to conduct these assessments.

10.1.4. Physical Examination

A complete physical examination (including evaluation of general appearance/mental status, HEENT [head, eyes, ears, nose, throat] and the following body systems: dermatologic, cardiovascular, respiratory, gastrointestinal, and neurologic) will be performed at specified times, outlined in Table 3.

These physical exams will include disease related symptoms assessment and measurement of weight at Screening and Week 16. Height will be measured at Screening only.

10.1.5. Electrocardiogram

12-lead ECGs will be measured in triplicate (≥ 1 minute apart) after the patient has been resting for at least 5 minutes in a supine position. Additional ECGs will be collected if clinically indicated (eg, patients with palpitations, lightheadedness).

Abnormalities noted at Screening should be included in the medical history. If observed as abnormal and clinically significant thereafter it should be noted as an AE.

10.1.6. Laboratory Assessments

Samples will be collected at times specified in Table 3. Appendix 1 provides a summary list of the laboratory parameters in this study. All samples will be sent to the central laboratory unless in the case of a safety or emergent event, or otherwise instructed by the Sponsor. Unscheduled laboratory kits should be used for all repeat laboratory tests whenever possible.

Patients are not to eat any food or drink any beverages, except water, for at least 6 hours prior to collecting blood for laboratory tests (immunogenicity/PK and pregnancy test samples are not required to be fasting).

If therapeutic phlebotomy is performed the same day as dosing, the order should be: laboratory samples; phlebotomy; LJPC-401 or placebo dose.

10.1.6.1. Hematology

Blood samples for analysis of the hematologic parameters include:

- Hematocrit
- Hemoglobin
- RBC count, including reticulocyte count, RDW, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume
- Platelet count
- White blood cell count and differential including percent and absolute: neutrophils, lymphocytes, monocytes, eosinophils, and basophils

10.1.6.2. Clinical Chemistries

Blood samples for analysis of clinical chemistry parameters include:

- Serum creatinine
- Uric acid
- Calcium
- Magnesium
- Alkaline phosphatase
- Lactate dehydrogenase (LDH)
- Blood urea nitrogen
- Phosphate
- Chloride
- Bicarbonate
- ALT (serum glutamic-pyruvic transaminase)
- Albumin
- Sodium
- Potassium
- Glucose
- Aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase)
- Bilirubin (total, direct, and indirect)
- Total protein

10.1.6.3. Thyroid Function

Blood samples for analysis of thyroid function parameters include:

- Thyroid-stimulating hormone (TSH)
- Thyroxine (T4)
- Triiodothyronine (T3)
- Free T4

10.1.6.4. Glycemic Control

Blood samples for analysis of hemoglobin A1c will be collected to assess glycemic control.

10.1.6.5. Pregnancy Screen

A serum pregnancy test will be performed for women of childbearing potential during Screening within 30 days prior to the first dose of study drug. Fasting is not required.

A urine pregnancy test (ie, dipstick) will be performed for women of childbearing potential at Week 1/Day 1 predose and Week 20 or Early Withdrawal (if possible).

Refer to Section 11.5 for pregnancy reporting and follow-up procedures.

10.1.6.5.1. Contraception

The effects of the study drug, LJPC-401, or procedures performed during this study may pose some unknown risks to the reproductive system, developing fetus or during breastfeeding. Since the effects of the investigational drug on the female and male reproductive systems are still unknown, it is very important that patients in this study use a highly effective method of contraception during participation in this study and for 30 days after the last dose of study drug, and not become pregnant or father a child during this study and for 30 days after the last dose of study drug.

Women who are pregnant or breastfeeding may not participate in this study. Highly effective methods of contraception are required during participation in this study, and for 30 days after the last dose of study drug, for both male and female patients and/or for their partners, unless he or she is surgically sterile or of nonchildbearing potential (ie, postmenopausal, defined as 12 consecutive months with no menses without an alternate medical cause). Highly effective methods of contraception are defined as those that result in a low failure rate when used consistently and correctly, alone or in combination. Note, the effects of LJPC-401 on the effectiveness of hormonal contraception are currently unknown.

The following are considered highly effective methods of contraception:

- Surgical sterility (vasectomy, bilateral tubal ligation, or hysterectomy)
- Intrauterine device (IUD)
- Hormonal intrauterine system (IUS), implants, or injections
- Consistent use of an approved oral contraceptive pill (combined progestin/estrogen pill or progestin-only pill)

- Combined intravaginal or transdermal method

Abstinence can be used as a method of contraception. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides or condoms only, and lactational amenorrhea method are not acceptable methods of contraception.

Oral, implantable, or injectable contraceptives are only considered effective if used properly and begun at least 30 days prior to the Screening visit.

10.1.6.6. Urinalysis

Urine samples for routine urinalysis parameters include:

- Specific gravity
- pH
- Blood
- Bilirubin
- Protein
- Ketones
- Glucose
- Nitrite

Any parameter with abnormal urinalysis results will be further characterized through urine microscopy.

10.1.6.7. Immunogenicity

Blood samples will be collected to assess immunogenic effect. Pharmacokinetics will be assessed concomitantly to determine if there is a relationship between drug concentration and immunogenicity (if anti-drug antibodies or neutralizing antibodies develop). In addition, the sparse concentration data of LJPC-401 that will be collected may be used in combination with data collected from other studies to support future composite PK/PD modeling and analysis that will be not be reported in this study.

If a patient develops antibodies to LJPC-401, treatment will be discontinued, and the patient will be monitored until antibody levels return to baseline. In patients that seroconvert, antibody levels will be monitored until they return to baseline and characterized for titer, binding to endogenous counterparts, and neutralizing capacity. For safety, patients may be asked to return to the clinic for collection of additional immunogenicity samples to confirm whether antibody levels have returned to baseline.

10.2. Quality of Life Questionnaires

Quality-of-Life Questionnaires (SF-36v2), WOMAC, and the modified Dreisler indices for arthritis will be administered to patients (in local language) to complete during study visits. Evaluations will be performed at times specified in Table 3.

11. ADVERSE AND SERIOUS ADVERSE EVENTS

11.1. Definition of Adverse Events

11.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. For recording purposes, pregnancy is a medical condition and is not considered an AE (see the Pregnancy and Follow-up Section 11.5 below).

Patients should be questioned in a general way, without leading the subject or asking about the occurrence of any specific symptom.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a gastric ulcer, it would not be appropriate to record the AE by describing the symptoms "stomach pain, or indigestion, or appetite loss, etc." The AE medical term of "gastric ulcer" should be recorded as the AE.

11.1.2. Serious Adverse Event

An SAE (experience or reaction) is an AE that results in 1 or more of the following:

- Results in death - An AE that caused or contributed to a fatal outcome.
- Is life-threatening - Refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction. It does not refer to an event/reaction which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Important medical events when based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent1 of the outcomes listed in this definition.

11.2. Relationship to Investigational Product and Severity

The Investigator will document her/his opinion of the relationship of the AE to treatment with the investigational product using the criteria outlined in Table 4. An AE for which there is a "reasonable possibility" that the investigational product caused the AE means there is evidence to suggest a causal relationship between the investigational product and the AE.

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable," the event will be considered to be related to the investigational product.

Table 4: Relationship of Adverse Events to Investigational Product

Relationship	Description
Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the investigational product, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge); or an event that could also be explained by concurrent disease or other drugs or chemicals where information on investigational product withdrawal may be lacking or unclear. Re-challenge or de-challenge information is not required to fulfill this definition.
Not Related	A clinical event, including laboratory test abnormality, with sufficient evidence to accept that there is no causal relationship to investigational product administration (eg, no temporal relationship to investigational product administration, because the investigational product was administered after onset of event; investigation shows that the drug was not administered; proof of other cause; etc.); or an event with a temporal relationship to investigational product administration, which makes a causal relationship improbable, and other drugs, chemicals or underlying disease provide plausible explanations.

AEs must be graded for severity (mild, moderate, severe, life-threatening, and fatal) as defined in Table 5, and must be entered on the AE page of the eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious." The assessment of severity is made regardless of investigational product relationship or of the seriousness of the AE.

Table 5: Severity of Adverse Events

Grade	Clinical Description of Severity
Mild	An experience that is transient or mild and requires no medical treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.
Moderate	No or minimal medical intervention/therapy required. Mild to moderate limitation in activity – some assistance may be needed. Includes laboratory test alterations indicating injury, but without long-term risk.
Severe	An experience that requires medical intervention/therapy, hospitalization possible. Marked limitation in activity, some assistance usually required.
Life-threatening	Life-threatening consequences; urgent intervention indicated.
Fatal	Death related to AE

11.3. Reporting of Adverse Events and Serious Adverse Events

11.3.1. Reporting of Adverse Events

AE data will be collected at consent until the patient fully completes her/his study participation.

All AEs, whether believed by the Investigator to be related or unrelated to the investigational product, must be documented in the patient's medical records, in accordance with the Investigator's normal clinical practice and on the AE eCRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product.

11.3.2. Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to La Jolla. Immediate reporting implies within 24 hours of becoming aware of the occurrence of an SAE.

SAE data will be collected starting at consent until the patient fully completes her/his study participation.

All SAEs that occur within 30 days following the cessation of investigational product, regardless of the causal relationship to the investigational product, must be reported to La Jolla by following the instructions provided in this section. Redacted medical record source documentation will be requested for all SAEs and emergency room visits.

The method for reporting a SAE is by completing the AE/SAE eCRF and sending a Serious Adverse Event Report Form. The Serious Adverse Event Report Form, and if applicable, a copy of redacted source documents (such as hospital discharge summary, medical records, etc.) related to the SAE will be sent to:

- E-mail to: safety@ljpc.com
- Or fax to: +1-858-263-1593

The Investigator will assess whether the event is causally related to the investigational product. La Jolla will also assess whether the event is causally related to the investigational product, in addition to assessing the overall safety profile of the investigational product.

La Jolla will notify the appropriate regulatory authorities in accordance with country regulations.

Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to La Jolla in the same manner as described above for the initial SAE report.

If an Investigator becomes aware of an SAE that may be attributable to the investigational product after the study is completed, La Jolla should be notified as soon as possible via email, phone, or fax at:

- E-mail to: safety@ljpc.com
- Phone (see title page for phone numbers)
- Or fax to: +1-858-263-1593

11.4. Follow-up of AEs and SAEs

All AEs must be followed during the course of the study until the AE resolves, is no longer of clinical concern, has stabilized or is otherwise explained, or the patient is lost to follow-up.

AEs ongoing at the final follow-up visit that are deemed to be "related" to the investigational product or of other clinical significance, must be followed for as long as necessary to adequately evaluate the safety of the patient or until the event stabilizes, resolves, or is no longer of clinical concern. If resolved, a resolution date for the AE should be documented in the eCRF. The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator.

11.5. Pregnancy and Follow-up

Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, or if a male patient makes his partner pregnant while he is enrolled in the clinical study, then the Investigator must be informed immediately. La Jolla must be notified within 24 hours of the Investigator's learning of the pregnancy by completing and sending the Pregnancy Report Form to safety@ljpc.com (or alternatively, fax to +1 (858) 263-1593).

Completing the Pregnancy Report Form is not a substitute for reporting an AE/SAE when an AE/SAE has occurred. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures described in Sections 11.3.1 and 11.3.2 must also be followed.

Female patients: The female patient must discontinue treatment with investigational product if she becomes pregnant. The progress of the pregnancy will be followed by the Investigator until the outcome of the pregnancy is known. If the pregnancy results in the birth of a child, the patient and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and La Jolla.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known. If the pregnancy results in the birth of a child, additional follow-up outcome information may be requested for the mother and neonate. Follow-up will only be performed to the extent permitted by applicable regulations and privacy considerations.

Refer to Section 10.1.6.5.1 for contraception guidance and information.

12. STATISTICS

12.1. Statistical Hypothesis

It is hypothesized that those treated with LJPC-401 will have a different change in TSAT from baseline to Week 16 postdose 24 (± 4) hours than those treated with placebo.

Null Hypothesis: $\mu_{active} = \mu_{placebo}$

Alternative Hypothesis: $\mu_{active} \neq \mu_{placebo}$

where μ is the mean change in TSAT from baseline to Week 16 postdose 24 (± 4) hours.

12.2. Sample Size and Power Considerations

A sample size of 48 patients has 80% power to detect a 15% difference in the change in TSAT between the placebo arm and the LJPC-401 arm, assuming a common standard deviation (SD) of 18% and a 2-sided type I error of 0.05. The primary efficacy analysis and secondary efficacy analyses will include the Efficacy Patient Population defined in Section 12.7 (ie, all patients enrolled under global protocol version 4.0/United Kingdom (UK) protocol version 4.1 or later who received study drug, and who completed the Week 16 assessments or had an on-study phlebotomy after the standard of care therapeutic phlebotomy on Day 1 [predose] and before Week 16). Patients who do not enroll under global protocol version 4.0/UK protocol version 4.1 or later or discontinue the study early prior to dosing will be replaced (patients may be replaced for additional reasons as described in Section 12.4). The plan is to enroll and randomize approximately 68 to 76 patients (1:1 to LJPC-401 or placebo) to ensure that at least 48 patients are included in the primary efficacy analysis.

Refer to Section 12.5 for planned analyses.

12.3. Stratification and Randomization

Central randomization will be performed using IXRS. Eligible patients will be randomized on a 1:1 schedule to LJPC-401 or placebo. Randomization will be stratified by baseline TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3).

12.4. Replacement of Patients

Patients who are randomized but terminate prior to dosing will be replaced and excluded from the safety and efficacy analyses. Patients who have received study drug and terminate the study early may be replaced by decision of the Investigator and La Jolla. Patients who do not enroll under protocol version 4.0/UK protocol version 4.1 or later will be replaced and excluded from efficacy analyses. Approximately 20 to 28 patients are expected to be replaced. Patients who consent and enroll under protocol version 4.0/UK protocol version 4.1 or later will be included in efficacy analyses. All enrolled patients, regardless of protocol version, who receive at least 1 dose of study drug will be included in safety analyses.

Patient enrollment numbers are unique and will not be re-assigned. Patients will not be permitted re-randomization after the initial randomization for any reason. Patients will not be permitted to re-enroll after withdrawing from the study for any reason.

12.5. Planned Analyses

An interim analysis of efficacy data will be conducted after the first 16 patients from the Efficacy Patient Population (defined in Section 12.7) complete the Week 16 assessments or have an on-study phlebotomy after the standard of care therapeutic phlebotomy on Day 1 (predose) and before Week 16. The Lan Demets approach to the O'Brien-Fleming method for sequential designs will be applied to preserve the overall type I error rate resulting in type I rates of values of 0.00021 at the interim analysis (n = 16) and 0.0499 at the final analysis (n = 48). Any subsequent interim analyses will similarly include adjustment using the Lan Demets approach to the O'Brien-Fleming method for sequential designs.

The final analyses will be performed after the statistical analysis plan (SAP) is finalized and the database is locked. The details of data quality assurance and database lock are provided in SAP.

In addition to the interim analysis of efficacy data, an internal Safety Monitoring Committee will conduct an initial safety review simultaneously with the interim efficacy analysis; additional safety reviews will be conducted thereafter. Details, such as membership of the committee, will be discussed in the Safety Monitoring Committee Charter.

Modifications to the planned statistical analyses should be minimized. However, the data obtained from the study may indicate that the planned analyses are inappropriate or that additional analyses need to be performed due to factors such as the distribution of the data or the presence of important covariates. Any deviations from the planned statistical analyses will be reported in the clinical study report.

12.6. Analysis Parameters

12.6.1. Endpoints

12.6.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is change in TSAT, defined as follows:

- For patients with 1 phlebotomy (the standard of care therapeutic phlebotomy on Day 1 [predose]), change in TSAT from baseline to Week 16 (24 [± 4] hours postdose).
- For patients undergoing 2 or more phlebotomies, change in TSAT from baseline to the most recent postdose fasting TSAT observed prior to the second phlebotomy.

12.6.1.2. Secondary Efficacy Endpoints

The secondary endpoints to be evaluated include:

- Number of phlebotomies from Day 2 to EOS.
- Change in serum ferritin, defined as follows:
  - For patients with 1 phlebotomy (the standard of care therapeutic phlebotomy on Day 1 [predose]), change in serum ferritin from baseline to Week 16 (24 ± 4] hours postdose).

- For patients undergoing 2 or more phlebotomies, change in serum ferritin from baseline to the most recent postdose serum ferritin observed prior to the second phlebotomy.

12.6.1.3. Safety and Tolerability Endpoints

The safety and tolerability endpoints to be evaluated include:

- Adverse Events from consent to EOS.
- Changes in clinical laboratory evaluations including serum iron parameters from baseline to EOS.
- Changes in vital signs, electrocardiograms (ECGs), use of concomitant medications, and physical examinations from baseline to EOS.
- Immunogenicity (anti-drug antibody)/PK baseline to EOS.

12.6.1.4. Exploratory Endpoints

The exploratory endpoints to be evaluated include:

- Change in serum iron parameters, defined as follows:
  - For patients with 1 phlebotomy (the standard of care therapeutic phlebotomy on Day 1 [predose]), change in serum iron parameters from baseline to Week 16 (24 [± 4] hours postdose).
  - For patients undergoing 2 or more phlebotomies, change in serum iron parameters from baseline to the most recent postdose serum iron parameters observed prior to the second phlebotomy.
  - For patients with 1 phlebotomy (the standard of care therapeutic phlebotomy on Day 1 [predose]), change in serum iron parameters from baseline to Week 17 (approximately 7 days after the last dose of study drug).
  - For patients undergoing 2 or more phlebotomies, change in serum iron parameters from baseline to the most recent predose serum iron parameters observed prior to the second phlebotomy.
- Change in thyroid function from baseline to Week 16.
- Change in liver function from baseline to Week 16.
- Change in hemoglobin A1c from baseline to Week 16.
- Change in RBC parameters including hemoglobin concentration, RBC count, and RDW defined as follows:
  - For patients with 1 phlebotomy (the standard of care therapeutic phlebotomy on Day 1 [predose]), change in RBC parameters from baseline to Week 16 (24 [± 4] hours postdose).

  - For patients undergoing 2 or more phlebotomies, change in RBC parameters from baseline to the most recent postdose RBC parameters observed prior to the second phlebotomy.

- Change in Quality of Life Questionnaires, (SF-36v2), WOMAC, and modified Dreisler indices for arthritis, from baseline to Week 16.

12.6.2. Definition of Subgroups

The following subgroups are considered of interest to comparatively explore the treatment effect:

- Age category: < 65 years versus ≥ 65 years
- Sex: male versus female
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Country: United States of America, Australia, United Kingdom, and France (may be collapsed prior to data freeze)
- Geographic regions: (to be determined based on enrolling countries)
- Race: White versus non-White
- Body mass index (BMI): < 30 kg/m^2; ≥ 30 kg/m^2 (BMI = weight(kg)/height(m)^2)
- Phlebotomy frequency over the last 12 months: 0 to 3 versus > 3
- Baseline TSAT: $> 45\%$ to 70% versus $> 70\%$
- Baseline hepcidin levels: $<$ median versus $\geq$ median
- Baseline serum iron levels: $<$ median versus $\geq$ median
- Baseline serum ferritin levels: $<$ median versus $\geq$ median

Baseline is considered the last blood sample collection prior to the required phlebotomy of Day 1.

12.7. Analysis Population

Analysis populations are as follows:

- Intent to Treat (ITT) Population: all randomized patients, as randomized.
- Modified Intent to Treat (mITT) Population: enrolled patients, as randomized, who received at least 1 dose of study drug.
- Efficacy Population: enrolled patients under global protocol version 4.0/UK protocol version 4.1 or later, as randomized, who received study drug, and who completed 4 months (Week 16) on study or who had at least 1 phlebotomy after the standard of care therapeutic phlebotomy on Day 1 (predose) and before Week 16.
- Per Protocol Population (PP): Efficacy patients, without any important protocol deviations.

- Safety Population: enrolled patients, as treated, who received at least 1 dose of study drug.
- PK Population: enrolled patients, as treated, who receive at least 1 dose of study drug and for whom at least 1 PK parameter can be estimated.

12.8. Statistical Methods

Continuous variables will be summarized using descriptive statistics, including the number of observations, mean, SD, minimum, median, and maximum values. Other descriptive statistics such as lower quartile, upper quartile, geometric mean, and geometric SD may be calculated if appropriate. Categorical (qualitative) variables will be summarized by the number of observations and percentages. Unless otherwise stated, the calculation of proportions will be based on the sample size of the population of interest.

Data will be summarized by treatment group, study visit, and if appropriate, study interval. Statistical comparisons of differences between treatment arms will be made using Wilcoxon rank-sum tests, mixed effects repeated measures, and/or analysis of variance (ANOVA) for continuous or ordinal variables, Chi-Square or Cochran-Mantel-Haenszel tests for categorical variables, Fisher's exact tests for binary variables, and Poisson regression model for count data (eg, number of phlebotomies).

All statistical tests will be done at the 2-sided, 5% significance level, unless otherwise specified. The assumptions underlying the statistical tests applied will be evaluated for appropriateness (ie, sample distribution, paired or correlated data, equality of variances). Confidence intervals will be done at 95%, unless otherwise specified.

All analyses will be performed using SAS, Version 9.4 or later (SAS Institute, Cary, NC). Graphic displays may be produced using SAS, S-Plus or R, Version 3.1.1 or later (R Foundation for Statistical Computing, Vienna, Austria).

A complete description of statistical considerations will be provided in a separate SAP.

12.8.1. Patient Disposition, Demographic, and Background Characteristics

Patient disposition will be summarized by treatment group as follows:

- Number of patients enrolled in the study
- Number of patients in each analysis population
- Treatment initiated? (yes or no)
- Last visit completed
- Last study day completed
- Did the patient complete treatment? (yes or no)
  - If no, primary reason for discontinuation of treatment
- Patient alive at End of Treatment? (yes or no)
- Was Day 30 follow-up conducted? (yes or no)

- Did the patient complete the study? (yes or no)
  - If no, primary reason for study discontinuation
- Patient alive at EOS visit? (yes or no)

Demographics and baseline characteristics will be summarized descriptively by treatment group as follows:

- Age category (< 65 years, ≥ 65 years) and age (years)
- Sex (male, female)
- Childbearing potential (yes, no)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other; and White or Non-White)
- Geographic region of origin (to be determined based on enrolling countries)
- Genotype (if available)
- Baseline height (cm)
- Baseline weight (kg)
- Baseline BMI category (< 30 kg/m^2, ≥ 30 kg/m^2) and BMI (kg/m^2)
- Baseline TSAT
- Baseline phlebotomy frequency over the last 12 months

Refer to the SAP for demographic summary statistical methods.

12.8.2. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA) most recent version and grouped by system organ class (SOC) and PT. The coded terms will be summarized by treatment group, SOC, and PT in alphabetical order as the number of conditions/events and the number and percentage of patients with a condition or experiencing an event 1 or more times.

In addition, summaries of medical history may be repeated for most frequent medical history where "most frequent" is defined as a medical event occurring in > X% of the sample in either treatment arm, where X% will be determined from the data.

12.8.3. Prior and Concomitant Medications and Procedures

Prior and concomitant medications will be summarized separately. Prior medications are those with a start date beginning 14 days prior to Screening. Concomitant medications are medications that are taken any time while on study (on or after first study drug administration).

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) most recent version and grouped by Anatomical Therapeutic Chemical (ATC) and PT. The coded medications will be summarized by treatment group, ATC, and PT in

alphabetical order as the number of medications and the number and percentage of patients receiving medication 1 or more times.

Prior phlebotomy procedures (number received during the 12 months prior to randomization) and concomitant phlebotomy procedures (number received on study) will be summarized by treatment group using descriptive statistics.

12.8.4. Efficacy Analyses

12.8.4.1. Primary Endpoint Analyses (Postdose TSAT)

The primary endpoint will be analyzed using a general linear model with adjustment for baseline TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3). A 2-tailed alpha of 0.05 (1-sided alpha of 0.025) will be used in testing the hypothesis of treatment difference with adjustments, as appropriate, for interim analyses.

In addition, TSAT will be summarized by treatment group and visit, and by lowest postbaseline value, highest postbaseline value, and last postbaseline visit. The change from baseline and percent change from baseline will be summarized in a similar manner.

TSAT and change from baseline in TSAT will be plotted by treatment and visit on a linear scale.

12.8.4.1.1. Sensitivity Analysis of Primary Efficacy Analysis

The presence of a site effect and site by treatment interaction will be examined using a general linear model with adjustment for site and site by treatment interaction. Alpha of 0.15 will be used for testing of site effects. Selection of sites for the modelling will be conducted after enrollment has been completed.

Subgroup analyses will be conducted using a general linear model with adjustments for treatment, subgroup, and subgroups by treatment interaction.

Multivariate analysis may be performed utilizing the subgroups of interest defined in Section 12.6.2. Detail will be provided in the statistical analysis plan.

A sensitivity analysis of TSAT will be conducted on the mITT Population. Detail will be provided in the statistical analysis plan.

Exploratory analyses of predose TSAT will be performed using the parameters described above.

12.8.4.2. Secondary Efficacy Endpoint Analyses

Change in serum ferritin from baseline to each weekly postdose visit and each weekly predose visit will be analyzed using a general linear model with adjustment for baseline TSAT (> 45% to 70% versus > 70%) and frequency of phlebotomy procedure over the last 12 months (0 to 3 versus > 3). A sensitivity analysis of change serum ferritin from baseline to each weekly postdose visit and each weekly predose visit will be conducted on the mITT Population. Patients not completing Week 16 or Week 17 for the postdose and predose analyses will be included in the analysis mixed effects repeated measures analysis with adjustments for baseline TSAT (> 45% to 70% versus > 70%) and frequency of phlebotomy procedure (0 to 3 versus > 3).

Phlebotomy criteria will be based on TSAT criteria of the IDI guidelines. Criteria for receiving a phlebotomy will be assessed after the results of each fasting TSAT assessment at postdose (24 [± 4] hours) on Weeks 4 (Day 23), 8 (Day 51), 12 (Day 79), and 16 (Day 107) are known.

Number of phlebotomies is defined as:

a. number of phlebotomies from Day 2 to EOS, or
b. number of phlebotomies from Day 2 to EOS + 1 (if, through the Week 16 assessment, no phlebotomy has been administered since the last observed fasting TSAT and the last observed fasting TSAT is > 45%).

Number of times a patient met criteria for a phlebotomy is defined as number of times from Day 2 to EOS that 1 of the following conditions is met:

a. Patient received a phlebotomy.
b. Patient had a fasting TSAT > 45%, but the patient refused/missed a phlebotomy, or the treating physician decided against a phlebotomy. Whether a patient meets the criteria for a phlebotomy (yes or no) will be assessed after the results of each fasting TSAT recorded at postdose 24 (± 4) hours on Weeks (Day 23), 8 (Day 51), 12 (79), and 16 (Day 107) are known.

The presence of any phlebotomy will be analyzed by a Cochran-Mantel-Haenszel test with adjustment for baseline TSAT and phlebotomy frequency over the last 12 months. The frequency of phlebotomies will be analyzed by Poisson regression model with baseline TSAT and phlebotomy frequency over the last 12 months and will offset to account for time at risk.

Sensitivity analyses of the number of phlebotomies will be conducted as follows:

- Using the mITT Population, an analysis including patients not completing Week 16 will be conducted on the frequency of times a patient met criteria for a phlebotomy. For these data, the Poisson regression model and Cochran-Mantel-Haenszel test as defined above will be repeated. To account for time at risk, the offset parameter will be used in the Poisson regression model. For the Cochran-Mantel-Haenszel test, patients who do not complete Week 16 will be categorized as experiencing a phlebotomy (yes or no) based on their available data.
- Impact of subgroups of interest (including site) will be analyzed by Poisson regression with terms for treatment subgroup and treatment by subgroup interaction.
- A multivariate logistic regression will be performed on patients receiving at least 1 phlebotomy (yes or no) utilizing the subgroups of interest defined in Section 12.6.2. Detail will be provided in the SAP.

The number of times a patient met criteria for phlebotomy will be analyzed is a similar manner as described above.

12.8.4.3. Exploratory Endpoint Analyses

Serum iron parameters (serum iron, transferrin, ferritin, apoferritin, holoferritin, UIBC, TIBC) will be analyzed by each postdose visit and each predose visit using a general linear model with adjustment for baseline TSAT (> 45% to 70% versus > 70%) and frequency of phlebotomy

procedure over the last 12 months (0 to 3 versus > 3). Sensitivity analysis will be conducted on the mITT population.

Thyroid function (T3, T4, TSH, and free T4), liver function (albumin, alkaline phosphatase, ALT, AST, bilirubin [total, direct, and indirect], LDH, and total protein), glycemic control, and RBC parameters (hemoglobin concentration, RBC count, and RDW) will be analyzed using a general linear model with adjustment for baseline TSAT (%) (> 45% to 70% versus > 70%) and frequency of phlebotomy procedure over the last 12 months (0 to 3 versus > 3). If warranted, a log transformation may be applied to data.

Total SF-36v2, WOMAC, and modified Dreisler indices for arthritis scores will be calculated according to the authors' instructions. The total score as well as the 8 subscales will be analyzed as exploratory variables. For the total score of each subscale, change from baseline to Week 16 will be calculated and then analyzed using a general linear model with adjustment for baseline TSAT (%) (> 45% to 70% versus > 70%) and frequency of phlebotomy procedure (0 to 3 versus > 3).

12.8.5. Safety Analysis

12.8.5.1. Adverse Events

TEAEs are those AEs that occur or worsen on or after the first study drug administration through EOS, 30 (+ 3 days) days after last dose of study drug.

TEAEs will be coded using the most recent version of MedDRA and grouped by system organ class (SOC) and preferred term (PT). The coded terms will be summarized by treatment group, SOC, and PT in alphabetical order as the number of events and the number and percentage of patients experiencing an event 1 or more times.

TEAEs will be graded for severity using mild, moderate, severe, life-threatening, and fatal (Table 5). Severity, relatedness, and seriousness of AEs will be summarized. AEs leading to discontinuation of study drug and AEs leading to death will be summarized if applicable. If the relationship to study drug is missing, the TEAE will be classified as related. In the case of more than 1 occurrence of a TEAE for a given patient, by-patient analyses will include the maximum relationship to study drug and the maximum severity of those TEAEs.

Adverse events of special interest may be defined by La Jolla to support the characterization of the safety profile of LJPC-401 across SOCs and/or PTs. These events may be defined during the ongoing clinical development of LJPC-401.

12.8.5.1.1. Deaths

Deaths will be summarized by treatment arm and cause of death. A listing of fatal AEs will be provided and summarized by SOC and PT. Deaths due to AE considered related to study drug will be discussed.

12.8.5.1.2. Injection Site Reaction

Injection site reaction will be summarized by treatment group and visit. Summaries will contain the number and percentage of patients experiencing a reaction 1 or more times.

12.8.5.2. Study Drug Exposure

The total dose administered, the total number of injections per week, and the average number of injections per week will be summarized by treatment group.

12.8.5.3. Clinical Laboratory Data

Clinical laboratory data (hematology, serum chemistry, other clinical tests, and urinalysis) obtained from local laboratories will be converted to Systéme International (SI) units and/or United States conventional units. Laboratory results will be classified as low, normal, and high dependent on the reference ranges of the local laboratory. Clinically significant laboratory abnormalities that result in treatment modification and/or require intervention will be recorded as AEs per Section 11.1.

Laboratory results will be summarized by treatment group and visit, lowest postbaseline grade, highest postbaseline grade, and last postbaseline visit. The change from baseline and percent change from baseline will also be summarized. Shifts from the baseline value to each visit, lowest postbaseline grade, highest postbaseline grade, and last postbaseline visit may be displayed.

12.8.5.4. Immunogenicity/Pharmacokinetics

Immunogenicity/PK will be summarized by visit and timepoint (eg, Week 1 and Week 16 require predose blood sample collection and an additional blood sample collection postdose 1 hour or later). Fasting is not required for immunogenicity/PK blood collections.

Immunogenicity (antibody titer, based on screening cut point) will be summarized by treatment group and visit. At each assessment, potentially positive results (based on the screening assay) will be followed by subsequent confirmatory assays, where the titer will be assigned.

The relationship between drug concentration and immunogenicity (if anti-drug antibodies or neutralizing antibodies develop) will be assessed.

A value of zero will be substituted for all drug concentrations below the lower limit of quantification.

12.8.5.5. Physical Exam

Physical exam findings will be reported in patient listings.

12.8.5.6. Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and body temperature) will be summarized by treatment group and visit. The change from baseline will also be summarized.

12.8.5.7. Electrocardiogram

Corrected QT intervals will be calculated using the QT interval and heart rate. QTcB will be derived by Bazett's formula and QTcF will be derived by Fridericia's formula as follows:

$QTcB = QT / (60/HR)^{1/2}$

$QTcF = QT / (60/HR)^{1/3}$

QTcB and QTcF values will be classified as follows:

- ≤ 450 msec
- > 450 msec to ≤ 480 msec
- > 480 msec to ≤ 500 msec
- > 500 msec

QTcB and QTcF change from baseline will be classified as follows:

- ≤ 30 msec
- > 30 msec to ≤ 60 msec
- > 60 msec

Electrocardiogram (heart rate, PR interval, QRS interval, QT interval, QTcB interval, and QTcF interval) will be summarized by treatment group and visit. The change from baseline will also be summarized.

12.8.6. Missing Values and Criteria for Data Exclusions

Missing values will not be estimated unless specified in the SAP. All data will be included in safety analysis.

Incomplete dates from medical history, AE, and concomitant medication logs will be imputed to calculate the study day and durations as follows:

- Start/Onset Date: If missing day and/or month, the day will be replaced with the 1st of the month and the month will be replaced with January. For AEs, if the imputed date results in a date before the date of first study drug administration, then the date of first study drug administration will be used, unless month is known and is prior to the dosing month, in which case the imputed date will be used.
- End/Resolution Date: If missing day and/or month, the day will be replaced by the last day of the month and the month will be replaced with December. If the imputed date results in a date later than the date of death, then the date of death will be used.

In patient data listings, incomplete dates will be displayed as entered on the eCRF without any imputations. Study days will be derived with imputation and displayed in the data listings.

12.8.7. Quality of Life Analysis

Standardized SF-36v2 scores will be calculated according to the authors' instructions.

Each of the 8 scales is directly transformed into a 0 to 100 scale on the assumption that each question carries equal weight. The lower the score the more disability. The higher the score the less disability. Analyses will be described in a separate SAP.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring, Audits, and Inspections

Site visits will be conducted by an authorized La Jolla representative, who will inspect study data, patient's medical records, and eCRFs according to Good Clinical Practice (GCP) and FDA and International Council on Harmonisation (ICH) guidelines. In addition to monitoring by La Jolla or its designees, the study may be audited by representatives of the FDA or other regulatory authorities, who will also be allowed access to study documents. The Investigator should immediately notify La Jolla's Clinical Operations department of any proposed or scheduled audits by regulatory authorities.

The Investigator will permit authorized representatives of La Jolla and national or local health authorities to inspect facilities and records relevant to this study.

The Investigator must obtain Institutional Review Board (IRB) / International Ethics Committee (IEC) approval for the investigation. Initial IRB or IEC approval, and all materials approved by the IRB or IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

La Jolla or its designee will instruct the study site regarding the conduct of the study and data capture procedures on eCRFs. Logic and consistency checks will be performed on all data entered into the eCRF or ultimately transferred into a database to ensure accuracy and completeness.

Training sessions, regular monitoring of the study at the study site by the La Jolla or designated personnel (eg, Clinical Research Associate [CRA]), instruction manuals, data verification, cross checking, and data audits will be performed to ensure quality of all study data. Investigators' meetings and/or onsite study initiations will be performed to prepare Investigators and other study site personnel for appropriate conduct of the study and collection of study data.

It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported for each patient. Source documentation supporting the data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

The Investigator, or designated representative, should complete data entry as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries should be completed immediately after the final examination. An explanation should be given for all missing data. The Investigator must sign and date the Investigator's Statement that will be supplied to endorse the recorded data.

All requests to unlock the database after database lock will be assessed by La Jolla and will follow La Jolla database unlocking standard operating procedures.

To ensure compliance with GCP and all applicable regulatory requirements, La Jolla may conduct a quality assurance audit.

15. IRB (INSTITUTIONAL REVIEW BOARD) / ETHICS

15.1. IRB / Ethics Review

The final study protocol, including the final version of the informed consent form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to La Jolla before he or she can present informed consent and begin screening activities for any patient on the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study, if applicable. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. La Jolla will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

15.2. Protocol Compliance

The Investigator will conduct the trial in compliance with the protocol provided by La Jolla. Modifications to the protocol may not be made without agreement of both the Investigator and La Jolla. Changes to the protocol will require a written IRB or IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB or IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB or IEC.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact La Jolla and/or the Medical Monitor, if circumstances permit, to discuss the planned course of action. Any important departures from the protocol must be fully documented on the appropriate eCRF and in the source documentation and reported to the IRB or IEC per institutional and/or local requirements.

The protocol deviations log will be completed by the study monitors and periodically reviewed by the Sponsor, and categories will be assigned to the protocol deviations. The log and assignments will be finalized prior to the database freeze/lock. All important deviations will be included in the final database.

15.3. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and La Jolla (or its designees) applicable policies and standard operating procedures.

15.4. Written Informed Consent

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent form must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed informed consent form. A copy of the signed informed consent form must be given to the patient.

15.5. Patient Confidentiality

In order to maintain patient privacy, data capture tools, investigational product accountability records, study reports, and communications will identify the patient only by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from La Jolla or its designee and regulatory authority(ies) access to the patient's original medical records, including medical history, laboratory studies, and medication administrations, for verification of data gathered and to audit the data collection process. This information will be accessed for the duration of the research study, including the follow-up period, for the purpose of data reconciliation. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.5.1. General Data Protection Regulation for Clinical Studies Conducted in the European Economic Area

The processing of personal data in this study is subject to the General Data Protection Regulation (GDPR) and only applies to studies conducted in the European Economic Area. The GDPR requires that certain information be provided to the study subject/patient in the ICF.

For purposes of this study, Sponsor will be the "data controller" under the GDPR. The contract research organization that is assisting with the study is Sponsor's "data processor". Other organizations involved in processing personal data on Sponsor's behalf for purposes of the study, such as contract laboratories that analyse blood samples, are also Sponsor's data processors.

Each study subject's/patient's personal data will be handled for purposes of the study and subsequent research uses by Sponsor and third parties as described in the ICF.

Sponsor is responsible for compliance with data controller obligations under the GDPR and other applicable laws in connection with the data collected by or on behalf of Sponsor for purposes of the study. Sponsor can be contacted regarding data protection matters at La Jolla Pharmaceutical Company, Attn: Head of Privacy, 4550 Towne Centre Court, San Diego, California, 92121, or by e-mail at privacy@ljpc.com.

Subject to certain limitations of the GDPR and other applicable data protection laws, study subjects/patients will have the right to access and correct their personal data, and to request its deletion or restriction or object to its processing, but these rights may be limited under the

GDPR's provisions relating to scientific research and data processing that is conducted in the public interest, or other grounds.

The laws governing clinical studies require consent from study participants (and for minors, to obtain a parent or guardian's consent to the child's participation in the study). However, the laws governing data protection, including the GDPR, provide legal bases besides consent for the processing of certain personal data. For purposes of applicable data protection laws, Sponsor's lawful basis for processing the personal data of its study subjects/patients is that the processing is necessary for scientific research purposes, subject to Article 89 of the GDPR. Processing that is directly required for carrying out the study is done on the basis of necessity of ensuring high standards of quality and safety of health care and of medicinal products.

Among its other obligations, Sponsor intends to transfer personal data outside of the European Economic Area and will ensure there is a lawful basis for transfer of data outside of the European Economic Area.

16. RECORDKEEPING

16.1. Inspection of Records

La Jolla and designees of La Jolla will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow La Jolla representatives to inspect the drug storage area, LJPC-401 inventory, drug accountability records, patient charts and study source documents, and other records relative to the study conduct.

16.2. Retention of Records

The Investigator will coordinate with the study site to ensure retention of all documentations relating to the study for a period of 2 years after marketing application approval, or if not approved, 2 years following the notification to FDA of the discontinuance of the test article for investigation. If it becomes necessary for La Jolla or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

17. PUBLICATION POLICY

All information regarding LJPC-401 supplied by La Jolla to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for any other purposes without written consent from La Jolla. It is understood that there is an obligation to provide La Jolla with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of La Jolla's LJPC-401 program and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, shareholders, or consultants as required.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal.

La Jolla is committed to the highest scientific and ethical standards for publications. The data for all publications will be reported in an objective, accurate, scientifically-balanced, and complete manner (eg, manuscripts, review articles, abstracts, posters, and/or oral presentations that contain data from La Jolla sponsored studies, have La Jolla authors, or for which La Jolla provides writing and/or editorial assistance).

La Jolla's principles for authorship of publications are consistent with criteria developed by the International Committee of Medical Journal Editors (ICMJE; www.icmje.org).

The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be submitted/presented; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

La Jolla prohibits the practices of guest authorship, ghost writing, or plagiarism on publications. Guest authoring is the practice in which the names of individuals who contributed little to no content on the publication appear on the byline. Ghost writing is the practice in which individuals who wrote the publication are neither acknowledged nor listed on the byline.

18. REFERENCES

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18.2. Study Reports

18.2.1. Clinical

LJ401-TPP01, A Phase 1, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Escalating Subcutaneous Doses of LJPC-401 in Patients at Risk for Iron Overload

LJ401-NHV01, A Phase 1, Placebo-Controlled Study to Determine the Safety, Tolerability and Pharmacokinetics of Escalating Subcutaneous Doses of LJPC-401 in Healthy Adult Volunteers

LJ401-NHV02, A Phase 1, Randomized, Double-Blind, Two-Arm, Placebo-Controlled, Single and Multiple Dose Escalation Study to Assess the Safety and Tolerability of LJPC-401 in Healthy Adults

18.2.2. Nonclinical

[redacted]

APPENDIX 1. SUMMARY OF LABORATORY PARAMETERS

Summary of Laboratory Parameters

Disease-specific	Hematology	Chemistry	Urinalysis	Subset/Special
• Total serum iron[b] • Serum transferrin • Serum ferritin[b] • UIBC[b] • TIBC[b] • Transferrin saturation[b] • Apoferritin • Holoferritin	• Hematocrit[b] • Hemoglobin[b] • Platelet count[b] • White blood cell count[b, c] • Red blood cell count[b, d]	• Serum creatinine[b] • Uric acid[b] • Alkaline phosphatase[b] • Blood urea nitrogen[b] • Albumin • Bilirubin (total, direct, and indirect)[b] • Phosphate[b] • Bicarbonate[b] • Lactate dehydrogenase • Glucose[b] • Calcium[b] • Magnesium[b] • Chloride[b] • Sodium[b] • Potassium[b] • Alanine aminotransferase (SGPT)[b] • Aspartate aminotransferase (SGOT)[b] • Total protein	• Specific gravity • Bilirubin • Glucose • pH • Protein • Nitrite • Blood • Ketones	• Pregnancy[a] • Pharmacokinetics • Thyroid-stimulating hormone • Hemoglobin Alc • Thyroxine (T4 and free T4) • Triiodothyronine (free T3) • Immunogenicity[b, e]

SGOT=serum glutamic- oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; TIBC=total iron binding capacity; UIBC=unsaturated iron binding capacity.

[a] Serum and urine.

[b] Laboratory parameters that must be collected to monitor patient safety.

[c] White blood cell count and differential including percent and absolute: neutrophils, lymphocytes, monocytes, eosinophils, and basophils

[d] Red blood cell count, including reticulocyte count, red cell distribution width, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration.

[e] LJPC-401 anti-drug antibody.