Statistical Analysis Plan: LJ401-HH01

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

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Amendment: Version 3.0 based on Protocol Version 6.0 and 6.1 (UK), 14 December 2018
Amendment: Version 2.0 based on Protocol Version 6.0 and 6.1 (UK), 14 December 2018
Original SAP: Version 1.0 based on Protocol Version 5.0 and 5.1 (UK), 02 October 2018
Issue Date: 22 March 2019

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LIST OF ABBREVIATIONS AND SPECIALIST TERMS

The following abbreviations and specialist terms are used in this statistical analysis plan.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADaM	Analysis Data Model
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CMH	Cochran-Mantel-Haenszel
CRO	contract research organization
CSR	clinical study report
DM	data management
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
ICH	International Council on Harmonisation
IDI	Iron Disorders Institute
ITT	Intent to Treat
IXRS	Interactive Voice/Web Response System
La Jolla	La Jolla Pharmaceutical Company
LDH	lactate dehydrogenase
LLQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
PK	pharmacokinetic

Abbreviation or Specialist Term	Explanation
PP	Per Protocol
PT	preferred term
RBC	red blood cell
RDW	red cell distribution width
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	standard deviation
SDTM	Study Data Tabulation Model
SF-36v2	Short Form (36) Health Survey, Version 2
SI	Systéme International
SMC	Safety Monitoring Committee
SOC	system organ class
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse events
TIBC	total iron-binding capacity
TLFs	tables, listings, and figures
TSAT	transferrin saturation
TSH	thyroid-stimulating hormone
UIBC	unsaturated iron-binding capacity
UK	United Kingdom
USA	United States of America
USP	United States Pharmacopoeia
WHO-DD	World Health Organization Drug Dictionary
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

1. INTRODUCTION

This statistical analysis plan (SAP) outlines the statistical methods that will be used to generate the clinical study report (CSR) for Study LJ401-HH01, "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".

The second amendment to the SAP (version 3.0) was undertaken to incorporate hierarchical testing of primary and secondary endpoints as well as a clarification of the phlebotomy definition. A summary of changes incorporated in version 3.0 of the SAP is provided in the overview below.

Overview of Changes in Statistical Methods in LJ401-HH01 SAP Version 2.0 to 3.0

Hierarchical Testing of Secondary Endpoints	Hierarchical testing will be used to preserve the overall type I error across the testing of secondary endpoints (Section 7.5). Hierarchical testing will proceed as follows: 1. Given a significant treatment effect for the primary efficacy endpoint, an analysis of the first secondary endpoint (number of phlebotomies from Day 2 to End of Study) will proceed and will be tested for statistical significance. 2. Given a significant treatment effect for the primary efficacy endpoint and the first secondary efficacy endpoint, an analysis of the second secondary endpoint (change in serum ferritin) will proceed and will be tested for statistical significance. The Lan DeMets approach to the O'Brien-Fleming method for sequential designs will be applied to preserve the overall type I error rate. It is expected that a type I rate of 0.00021 will be applied for the initial interim analysis (n = 16) and adjustment for all interim analyses will be applied for the final analysis (n = 48). At the interim analysis, if hierarchical testing results in a statistically significant Lan DeMets p-value for each of the 3 endpoints, then enrollment may be halted due to overwhelming efficacy.
Number of Phlebotomies	Clarified that the number of times a patient met criteria for a phlebotomy will include the actual number of phlebotomies from Day 2 to EOS plus the number of observations of a fasting postdose TSAT >45%, but the patient refused/missed a phlebotomy, or the treating physician decided against a phlebotomy within the next 7 days. An additional sensitivity analysis of the time to first phlebotomy (following the standard of care phlebotomy on Day 1 [predose]) analyzed by logrank test was added.

Change in Ferritin	Clarified that the key secondary analyses for the change in ferritin will follow those that are specified for the primary analysis of TSAT.
Subgroup Analyses	Added HH genotype (HFE versus non-HFE) and Screening TSAT (>45% to 70% versus >70%) to univariate and multivariate analyses.

The first amendment to the SAP (version 2.0) was undertaken to incorporate the changes to the statistical analyses required following the amendment to global protocol version 6.0 and United Kingdom (UK) version 6.1 (dated 14 December 2018). A summary of changes incorporated in version 2.0 of the SAP is provided in the overview below.

Overview of Changes in Statistical Methods in LJ401-HH01 SAP Version 1.0 to 2.0

Item	Description and Rationale for Change
Efficacy Analysis Population	The Efficacy Patient Population was amended to include those patients enrolled under global protocol version 4.0/UK protocol version 4.1 or later only (Section 3.4 and Section 5.4). Prior to global protocol version 4.0/UK protocol version 4.1, a patient's need for phlebotomy was based on a TSAT assessment performed predose on the day of study drug administration and approximately 7 days after the most recent study drug administration. The amended study design (effective as of global protocol version 4.0/UK protocol version 4.1) determines a patient's need for phlebotomy based on a TSAT assessment performed 24 (± 4) hours postdose to reflect the TSAT status during treatment and not prior to study drug administration. As such, patients who enrolled prior to global protocol version 4.0/UK protocol version 4.1 will be replaced to maintain study power for the efficacy analysis (patients may be replaced for additional reasons as described in Section 3.6). Patients enrolled prior to global protocol version 4.0/UK protocol version 4.1 continue to participate in the study and will be included in other analyses including safety analyses (Section 8).
Sample Size Considerations	The revised study design will require the number of patients enrolled to be approximately 68 to 76 patients across approximately 30 sites (Section 3.4).
Interim Analysis	Clarified that the interim analysis will take place after the first 16 patients in the Efficacy Patient Population complete Week 16 or have an on-study phlebotomy prior to Week 16 after having received their initial on-study SOC phlebotomy at Week 1 (predose) (Section 4.1). Any subsequent interim analysis (eg, the first 32 patients) will similarly use this population selection definition.

It is not intended that every table, listing, or figure will be included in the CSR. It is also possible that additional analyses will be conducted after review of the data. Any analyses or summaries not specified in the SAP, but performed after review of the data, will be identified in the CSR as unplanned analyses.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objective of this study is to compare the effect of LJPC-401 versus placebo on transferrin saturation (TSAT) in adult patients with hereditary hemochromatosis.

2.1.2. Secondary Objectives

The secondary objectives of this study are to:

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

2.1.3. Exploratory Objectives

The exploratory objectives of this study are to:

- compare the effect of LJPC-401 versus placebo on serum iron parameters,
- compare the effect of LJPC-401 versus placebo on thyroid function,
- compare the effect of LJPC-401 versus placebo on liver function,
- compare the effect of LJPC-401 versus placebo on glycemic control,
- 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), and
- compare the effect of LJPC-401 versus placebo on quality of life as measured by a Quality of Life Questionnaire: Short Form (36) Health Survey, Version 2 (SF-36v2), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the modified Dreisler indices for arthritis.

2.2. Study Endpoints

2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is 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

(eg, the initial phlebotomy following the standard of care phlebotomy on Day 1 [predose]).

2.2.2. Secondary Efficacy Endpoints

The secondary endpoints to be evaluated include:

- Number of phlebotomies, from Day 2 to End of Study (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.

2.2.3. Safety and Tolerability Endpoints

The safety and tolerability endpoints to be evaluated include:

- 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.

2.2.4. 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 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 (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 parameter 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.
- 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 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.

3. STUDY DESIGN

3.1. Summary of 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 versus placebo 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 screening 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 postdose 24 (± 4) hours on 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 Iron Disorders Institute (IDI 2011) 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.

The procedures to be performed throughout the study are outlined in the Schedule of Events in the study protocol (Table 3, Section 5.6).

3.2. Treatment Assignment

Patients will be dosed once-weekly with study drug of LJPC-401 or placebo administered subcutaneously for 16 weeks.

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 of designee. To maintain the study single-blind, syringes with study drug (placebo and active drug) will be identical.

3.2.1. 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.
- For down titration, follow the safety criteria outlined in Section 3.2.2.

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.

3.2.2. Safety Criteria for Adjustment of 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 the assigned number of injections

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

1. treatment-emergent adverse events (TEAEs), including injection site reaction(s) severity grade of severe or higher
2. patient cannot or will not tolerate subcutaneous injection(s)
3. clinically significant laboratory parameters, including if TSAT is less than 10% (if this occurs, consult the Medical Monitor)

3.3. 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

3.4. Sample Size Considerations

A sample size of 48 patients has over 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 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.

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 3.6). 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.

An interim analysis of efficacy data will be conducted after the first 16 patients from the Efficacy Patient Population (defined in Section 5.4) 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 adjusted for all interim analyses 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.

3.5. Randomization, Stratification, and Blinding

This is a randomized, placebo-controlled, single-blind study. Central randomization will be performed using Interactive Voice/Web Response System (IXRS). Eligible patients will be randomized on a 1:1 schedule to LJPC-401 or placebo. Randomization will be stratified by screening TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3).

To maintain the study single-blind, syringes with study drug (placebo and active drug) will be identical.

3.6. 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 global protocol version 4.0/UK protocol version 4.1 or later will be replaced and excluded from the primary efficacy analyses. Approximately 20 to 28 patients are expected to be replaced. Patients who consent and enroll under global 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 (refer to Section 5.4 for definitions of analysis populations).

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

Note: Prior to global protocol version 4.0/UK protocol version 4.1, a patient's need for phlebotomy was based on a TSAT assessment performed predose on the day of study drug administration and approximately 7 days after the most recent study drug administration. The amended study design (effective as of global protocol version 4.0/UK protocol version 4.1) determines a patient's need for phlebotomy based on a TSAT assessment performed 24 (± 4) hours postdose to reflect the TSAT status during treatment and not prior to study drug administration. As such, patients who enrolled prior to global protocol version 4.0/UK protocol version 4.1 will be replaced to maintain study power for the efficacy analysis. Patients enrolled prior to global protocol version 4.0/UK protocol version 4.1 continue to participate in the study and will be included in other analyses including safety analyses.

4. PLANNED ANALYSES

4.1. Interim Analyses

An interim analysis of efficacy will be conducted after the first 16 patients from the Efficacy Patient Population (defined in Section 5.4) complete the Week 16 assessments or have an on-study phlebotomy after the SOC phlebotomy on Day 1 (predose) and before Week 16. The analysis will be based on hierarchical testing of the primary and secondary efficacy objectives comparing the effect of LJPC-401 versus placebo on TSAT, phlebotomy requirements, and serum ferritin in adult patients with hereditary hemochromatosis.

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 adjusted for all interim analyses 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. At the interim analysis, if hierarchical testing results in a statistically significant Lan DeMets p-value for each of the 3 endpoints, then enrollment may be halted due to overwhelming efficacy.

4.1.1. Safety Monitoring Committee

In addition to the interim analysis of efficacy data, an internal Safety Monitoring Committee (SMC) will conduct an initial safety review during the same time period of the interim efficacy analysis. Details, such as membership of the committee and timing of additional periodic safety review will be discussed in the SMC Charter.

4.2. Final Analysis

The final analyses will be performed after the SAP is finalized and the database is locked. The details of data quality assurance and database lock are provided in Section 5.1.

4.3. Changes from Planned Analyses

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 CSR.

5. GENERAL CONSIDERATIONS FOR STATISTICAL ANALYSES

5.1. Data Quality Assurance

During the conduct of the study, monitor(s) representing the Sponsor will visit the investigative sites at regular intervals. During these visits, the monitor will verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on the electronic Case Report Form (eCRF) (source data validation) and resolve outstanding data discrepancies (queries). It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported for each patient. The monitor will have access to laboratory test reports and other patient records needed to verify entries on the eCRF. After site initiation, the monitor will have access to the pharmacy inventory and dispensing records for study treatments.

Data management (DM) is planned to be performed by a contract research organization (CRO). Data entry to the eCRF and resolution of queries will be performed by the study site personnel. Queries will be generated either automatically or manually within the data management system. Each query will be attached to the corresponding data item and contain the discrepancy message. The investigator or study coordinator will resolve the queries as soon as possible by editing data on the eCRF and/or providing clarification for the discrepancy.

Sponsor personnel, including the study biostatistician, statistical programmer, medical monitor, clinical and data management team will also perform manual reviews of data on a periodic basis for data consistency across forms, logic across visits, patient completeness, and reconciliations using the most current Statistical Analysis System (SAS) programmed data listings. A Data Review Plan will formally outline and specify the review to be performed. A Data Access Plan will identify sponsor personnel or functional group access to specific data. Discrepancies identified during the manual review process will be generated by DM to be subsequently addressed by the site.

All queries generated during the course of the study, as well as any resulting data changes due to responses to queries, will be tracked within an audit trail. Resolved queries that do not result in a data change will be reviewed by DM, or the person who created the query, to accept the data as is, or generate another query for subsequent resolution. The process will be repeated until all data are deemed complete, clean, reconciled, and, if appropriate, monitored through a Database Freeze/Lock Checklist and signed-off prior to database freeze/lock.

Safety laboratory samples (complete iron studies, hematology, serum chemistry) and immunogenicity samples will be collected at the sites and analyzed at the central laboratories. If emergency or safety samples are analyzed by local labs, each laboratory's units and reference ranges will be forwarded to DM.

The protocol deviations log will be completed by the study monitors and periodically reviewed by the Sponsor. Categories (important/minor) will be assigned to the protocol deviations by the medical monitor. The monitor will enter deviations regarding study drug onto the deviation log. The log and assignments will be finalized prior to the database freeze/lock. All important deviations will be included in the final database.

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

5.2. Data Standardization

The Clinical Data Interchange Standards Consortium (CDISC) encompasses a suite of standards across the clinical space widely accepted by regulatory authorities. CDISC standards enables the drug development process to become more efficient by improving data flow and allowing a common understanding of data across the industry. The CDISC datasets, Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets, are generated to support statistical programming of the tables, listings, and figures (TLFs). An implementation guide for both CDISC models provides guidance on how to map collected data into SDTM and ADaM datasets. Where SDTM contains all the clinical data collected from the study and ADaM reconfigures the data as needed for analyses.

Datasets received from the eCRF will be converted to the most recent version of CDISC SDTM and ADaM datasets. If updates to CDISC SDTM and/or ADaM datasets are initiated mid-study, La Jolla will determine which version will be implemented.

Supplemental documents to support CDISC datasets, such as the define document (.pdf or .xml format) to describe the metadata and the reviewer's guide to give additional context of the datasets, will be generated. To ensure that SDTM and ADaM datasets meet expectations, the datasets are validated for:

- output quality through double programming per internal standard operating procedures, and
- compliance against CDISC standards per leading industry utilities such as Pinnacle21's CDISC validator.

5.3. General Considerations

Continuous (quantitative) 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. If warranted, a log transformation may be applied to laboratory data.

Statistical comparisons of differences between treatment groups may include:

- Analysis of variance (ANOVA), mixed effects repeated measures, and/or Wilcoxon rank-sum test for continuous variables

- Chi-Square, Cochran-Mantel-Haenszel (CMH), or Fisher's exact test for categorical variables
- Poisson regression model for count variables (ie, number of phlebotomies)

All statistical tests will be performed using 2-sided, 5% significance levels, 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 list of the TLFs that will be generated for this study can be found in Section 9.

5.4. Analysis Populations

Analysis populations will be defined 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 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 SOC 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 received at least 1 dose of study drug and for whom at least 1 PK parameter can be estimated

Summaries will not be reproduced for identical patient populations (eg, if all patients are treated as randomized, resulting in identical mITT Population and Safety Population analysis will not be produced for each analysis populations).

5.5. Definitions and Derived Data

An **adverse event** 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 the treatment.

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

Age will be calculated as the integer floor value in years of the difference between the date of enrollment and the date of birth.

Age = integer floor [(Date of Enrollment – Date of Birth + 1) / 365.25]

If the day of birth is missing, the first day (01) of the month will be imputed. If both the day and month of birth are missing, the first day of the year will be imputed. For more details on handling of missing data see Section 5.7.

For patients randomized, but did not receive study drug, the difference between the date of visit and date of enrollment **Study Day** will be calculated as follows:

If Date of Visit is before the Date of Enrollment, then:

Day = Date of Visit – Date of Enrollment

If the Date of Visit is on or after the Date of Enrollment, then:

Day = (Date of Visit – Date of Enrollment) + 1

For patients who received any amount of study drug, the difference between the date of visit and the date of first study drug administration in days.

If Date of Visit is before the Date of First Study Drug Administration, then:

Day = Date of Visit – Date of First Study Drug Administration

If the Date of Visit is on or after the Date of First Study Drug Administration, then:

Day = (Date of Visit – Date of First Study Drug Administration) + 1

Day 1 is the first day of study drug administration. Day −1 is the day immediately preceding the first day of study drug administration. There is no Day 0.

Study Time will be calculated as the difference between the date/time of visit and the date/time of first study drug administration or enrollment data for patients without study drug. Time will be displayed in hours and minutes in the format HH:MM. If the time of visit or the time of first study drug administration is not available, then the study time will not be calculated. There will be no imputation of collection times.

Time = Date/Time of Visit – Date/Time of First Study Drug Administration

Baseline measurement will generally be defined as:

- For patients randomized who did not receive study drug, the last measurement prior to randomization, or
- For patients who received any amount of study drug, the last measurement prior to the first study drug administration date/time (either LJPC-401 or placebo). If only the

date is available and not a time, the baseline measurement will be defined as the last measurement on or prior to the day of study drug administration.

Visit Windows: Visit date/times will be compared to nominal visits for consistency. Discrepancies may be queried to update the visits to a more appropriate visit category or to an unscheduled visit.

Change from baseline will be calculated as the difference between the value being analyzed and the value at baseline. If the value being analyzed or the value at baseline is not available, then the change from baseline value will not be calculated.

Change from Baseline = Value Being Analyzed – Value at Baseline

End of Study (EOS) is the date/time of the last study visit (per the protocol scheduled as 30 [+ 3] days after the last dose of study drug).

End of Treatment (EOT) is the date/time of the last study drug administration. The EOT visit is scheduled for Week 16.

Study drug is placebo (0.9% sodium chloride injection, USP [or equivalent]) or LJPC-401.

Treatment-emergent adverse event (TEAE) are those AEs that occur or worsen on or after the first study drug administration through EOS (30 [+3] days after last dose of study drug).
Note: if onset date is unknown, the AE is assumed to be treatment emergent.

Serious adverse event (SAE) is defined as an AE with at least 1 of the following events:

- 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 may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

Number of phlebotomies is defined as the number of phlebotomies from Day 2 to EOS.

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 within the next 7 days. 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 4 (Day 23), 8 (Day 51), 12 (Day 79), and 16 (Day 107) are known.

5.6. Definition of Subgroups

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

- Age: < 65 years versus ≥ 65 years
- Sex: male versus female
- Race: White versus non-White
- Ethnicity: Hispanic or Latino versus 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)
- Body mass index (BMI): < 30 kg/m^2; ≥ 30 kg/m^2 (BMI = weight(kg)/height$(m)^2$)
- HH Genotype: HFE versus non-HFE
- Screening TSAT: > 45% to 70% versus > 70%
- Phlebotomy frequency over the last 12 months: 0 to 3 versus > 3

Note: For the following items, baseline is considered the last blood sample collection prior to the required phlebotomy of Day 1.

- Baseline TSAT (last draw prior to required phlebotomy on Day 1): > 45% to 70% versus > 70%
- Baseline hepcidin levels (last draw prior to required phlebotomy on Day 1): < median versus ≥ median
- Baseline serum iron levels (last draw prior to required phlebotomy on Day 1): < median versus ≥ median
- Baseline serum ferritin levels (last draw prior to required phlebotomy on Day 1): < median versus ≥ median

5.7. Handling of Missing Data

Missing values will not be estimated or imputed unless otherwise specified below. 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 month, month will be imputed to January

- If missing day, day will be imputed with the first of the month

  For AEs, if the imputed date results in a date before the date of first study drug administration, then the 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 with 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.

6. POPULATION, ENROLLMENT, AND DEMOGRAPHICS

6.1. Informed Consent

A summary of the number of patients consenting under each version will be provided by analysis population. A listing will also be provided. Select analyses, excluding patients who consented prior to global protocol version 4.0/UK protocol version 4.1 and/or who did not agree to consent to later versions, may be provided.

6.2. Patient Disposition

Patient disposition will be summarized for all randomized patients by treatment group and total as follows:

- Number of patients randomized in the study
- Number of patients in each analysis population
- Treatment initiated? (yes or no)
- Last visit completed
- Did the patient complete treatment? (yes or no)
  - If no, primary reason for discontinuation of treatment
- Patient alive at EOT? (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)

6.3. Enrollment

For the ITT, Efficacy, mITT, and Safety Populations, patient enrollment (n and %) will be summarized by treatment group and total for country (Australia, France, United Kingdom, and United States of America,) and site.

6.4. Protocol Deviations

For the ITT, Efficacy, mITT, and Safety Populations, important protocol deviations will be summarized (n and %) by treatment group and total for any important protocol deviation and by deviation category (eg, Inclusion/Exclusion, Treatment Assignment or Dose Deviation, Protocol Procedure Deviation, etc.).

6.5. Randomization Stratification

For the ITT, Efficacy, mITT, and Safety Populations, summaries (n and %) of patients will be provided by treatment group and total for randomization strata (screening TSAT [> 45% to 70% versus > 70%] and phlebotomy frequency over the last 12 months [0 to 3 versus > 3]).

In addition, for the ITT, Efficacy, mITT, and Safety Populations, summaries (n and %) of patients will be provided by treatment group and total for randomization versus clinical database (screening TSAT [> 45% to 70% versus > 70%] and phlebotomy frequency over the last 12 months [0 to 3 versus > 3]).

6.6. Demographics and Baseline Characteristics

For the ITT, Efficacy, mITT, and Safety Populations, demographics and baseline characteristics will be summarized descriptively (categorical variables [n and %] and continuous variables [n, mean, SD, median, and range]) by treatment group for the following:

- Age category (< 65 years, ≥ 65 years) and age (years)
- Sex (male, female)
- 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
  - White or non-White
- Baseline weight (kg)
- Baseline height (cm)
- Baseline BMI category (< 30 kg/m^2, ≥ 30 kg/m^2) and BMI (kg/m^2)
- Baseline TSAT, where baseline is considered the last blood sample collection prior to the required phlebotomy of Day 1.
- Baseline phlebotomy frequency over the last 12 months
- Geographic region (to be determined based on enrolling countries)
- Childbearing potential (yes, no)
- Genotype (if available)

Depending on study results, demographic summaries may be repeated by another characteristic (eg, by geographic region, by total LJPC-401 dose, by mean overall LJPC-401 dose).

In addition, statistical comparisons of differences between treatment arms will be made using Wilcoxon rank-sum tests for continuous or ordinal variables, Chi-Square tests for discrete variables, and Fisher's exact tests for binary variables.

6.7. Medical History

For the Efficacy, ITT, mITT, Safety Populations, medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) most recent version 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 conditions/events and the number and percentage of patients with a condition or experiencing an event 1 or more times.

In addition, summaries for most frequent medical history may be repeated 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.

6.8. Prior and Concomitant Medications

For the Efficacy and Safety Population, prior and concomitant medications will be summarized separately. Prior medications are those with a start date within 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) classification system and PT. The coded medications will be summarized as the number of medications and the number and percentage of patients receiving medication 1 or more times. Summaries will be by treatment group, ATC, and PT in alphabetical order.

6.9. Prior and Concomitant Phlebotomy Procedures

For the ITT, Efficacy, mITT, and Safety Population, prior phlebotomy frequency (number received during the 12 months prior to randomization) and concomitant phlebotomy procedures (number received on study) will be summarized categorically ([0, 1, 2, 3, 4, etc.], n, and percent) and continuously (n, mean, SD, median, and range) by treatment group.

6.10. On Study Non-medication Therapy / Procedures

On study non-medication therapy/procedures will be reported in patient listings.

7. EFFICACY

Analysis of efficacy will be conducted on the Efficacy Population and using the randomization strata (see Section 3.5). In addition, summaries including the mITT Population will be done for efficacy endpoints besides the serum iron parameters.

If discrepancies exist in the Efficacy Population, between as treated and as randomized patients, efficacy analyses may be reproduced using data from patients as treated; however, these analyses will be considered secondary.

7.1. Test of Hypothesis

It is hypothesized that patients treated with LJPC-401 will have a different change in TSAT from baseline to the earlier of Week 16 (24 [± 4] hours postdose) or the most recent postdose fasting TSAT observed prior to the second phlebotomy (eg, the initial phlebotomy following the standard of care phlebotomy on Day 1 [predose]) than those treated with placebo.

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

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

where μ is the change in TSAT.

7.2. Primary Efficacy Analysis: Postdose TSAT

The primary efficacy endpoint will be analyzed using a general linear model with adjustment for screening 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 will be used in testing the hypothesis of treatment difference with alpha adjustments, as appropriate, for interim analyses.

The primary analysis will utilize the randomization stratification. Sensitivity analyses utilizing the clinical database stratification and an unstratified analysis will be conducted as appropriate.

7.2.1. Expanded Efficacy Population: Primary Efficacy Variable

If five or more patients enrolled after global protocol version 4.0/UK protocol version 4.1 discontinue prior to Week 16 without a second prior phlebotomy and were excluded from the Efficacy Population, two additional analyses of change in TSAT from baseline to Week 16 (24 [± 4] hours postdose) will be conducted.

- Patients discontinuing early without prior phlebotomy will be included in the analysis by use of last observation carried forward (LOCF), with the most recent TSAT observed at postdose on Weeks 3, 4, 8, and 12 used as the observation carried forward. LOCF data will be analyzed using a general linear model with adjustment for screening TSAT (> 45% to 70% and > 70%) and frequency of phlebotomy procedure over the last 12 months (0 to 3 and > 3).
- Patients will be analyzed via a mixed effects repeated measures analysis on TSAT observations at 24 [± 4] hours postdose on Weeks 3, 4, 8, 12, and 16 with patient as a random factor.

7.2.2. Univariate Subgroup Analyses: Primary Efficacy Variable

Univariate subgroup analyses utilizing the subgroups of interest defined in Section 5.6 may be analyzed for the primary efficacy endpoint as follows:

- Treatment effect analyzed within subgroup
- Subgroup effect analyzed within treatment group
- Treatment effect in the general linear model stratified by subgroup covariate
- Subgroup by treatment interaction in the general linear model

7.2.3. By-site Analyses: Primary Efficacy Variable

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 modeling will be conducted after enrollment has been completed.

7.2.4. Multivariate Analyses: Primary Efficacy Variable

In addition, multivariate analysis may be performed utilizing the subgroups of interest defined in Section 5.6. Treatment, screening TSAT randomization strata (> 45% to 70% versus > 70%), baseline phlebotomy randomization strata over the last 12 months (0 to 3 versus > 3), age category, and sex are considered as fixed factors in the model. A stepwise general linear model with covariates defined by the subgroups cutoffs will be evaluated. The values used for classification are generally designed based on a prior classification of interest or to split the population in half; if a subgroup classification results in less than 10% of the population in 1 category, the subgroup factor will be dropped from the model. A stepwise selection process will be used to determine the inclusion of each covariate in the analysis model. For the covariates, the significant level to enter the model is 0.15 and the level to stay is 0.05. Only significant parameters will be presented in the final model. Treatment by variable interaction terms may also be explored.

7.2.5. Exploratory Analysis of Week 17 TSAT

Change from baseline to Week 17 (approximately 7 days after the last dose of study drug) or the most recent postdose fasting TSAT observed prior to the second phlebotomy (eg, the initial phlebotomy following the standard of care phlebotomy on Day 1 [predose]) will be analyzed using a general linear model with adjustment for screening TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3). Additional analyses as proposed for the primary endpoint at Week 16 may be conducted for Week 17.

7.2.6. Additional Summaries of TSAT

TSAT will be summarized (n, mean, SD, median, range) and plotted (mean) by treatment group for all visits (Screening, predose, and 24 [± 4] hours postdose at Weeks 3, 4, 8, 12, 16, and a single value collected at Week 17 and at EOS.

In addition, TSAT summaries (n, mean, SD, median, range) of lowest postbaseline value, highest postbaseline value, and value at last postbaseline visit will be provided separately by treatment group.

TSAT change from baseline and percent change from baseline will be summarized in a similar manner.

7.3. Secondary Efficacy Analyses

7.3.1. Number of Phlebotomies

The key secondary analysis included number of times a patient had a phlebotomy or met criteria for a phlebotomy.

Number of phlebotomies and number of times a patient met criteria for a phlebotomy (as defined in Section 5.5) will be analyzed for the Efficacy Population as follows:

- The frequency of a phlebotomy will be analyzed using Poisson regression stratified by screening TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3) and with offset to account for time at risk. Time at risk is defined as the last date of postdose TSAT collection, phlebotomy, or study drug exposure.
- The time to the first phlebotomy (following the standard of care phlebotomy on Day 1 [predose]) will be analyzed using a logrank test stratified by screening TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3). Patients who do not have a phlebotomy will be censored at their last on-study assessment.
- The presence of any phlebotomy will be analyzed using CMH test stratified by screening TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3). Patients who do not complete Week 16 will be categorized as experiencing a phlebotomy (yes or no) based on their available data.
  - If data warrant, similar analyses may be conducted on alternative categorizations (ie, number of patients who experience at least 2 phlebotomies).

The primary analysis will utilize the randomization stratification. Sensitivity analyses utilizing the clinical database stratification and an unstratified analysis will be conducted as appropriate.

7.3.1.1. Sensitivity Analysis: Patients Not Completing Week 16

If five or more patients enrolled after global protocol version 4.0/UK protocol version 4.1 discontinue prior to Week 16 without a second prior phlebotomy and were excluded from the Efficacy Population, analyses will be conducted on the number of phlebotomies and number of times a patient met criteria for a phlebotomy as follows:

- Frequency of phlebotomy will be analyzed by Poisson regression model stratified by screening TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3). Offset will account for time at risk.

- The time to the first phlebotomy (following the standard of care phlebotomy on Day 1 [predose]) will be analyzed using a logrank test stratified by screening TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3). Patients who do not have a phlebotomy will be censored at their last on-study assessment.
- The presence of any phlebotomy will be analyzed using CMH test stratified by screening TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3).
  - If data warrant, similar analyses may be conducted on alternative categorizations (ie, number of patients who experience at least 2 phlebotomies).

7.3.1.2. Univariate Subgroup Analyses

Univariate subgroup analyses utilizing the subgroups of interest defined in Section 5.6 may be analyzed for the frequency of phlebotomy as follows:

- Treatment effect analyzed within subgroup
- Subgroup effect analyzed within treatment group
- Treatment effect in the general linear model stratified by subgroup covariate
- Subgroup by treatment interaction in the general linear model

7.3.1.3. Multivariate Analyses

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 5.6. Treatment, screening TSAT (> 45% to 70% versus > 70%), phlebotomy frequency over the last 12 months (0 to 3 versus > 3), age category, and sex are considered as fixed factors in the model. A stepwise logistic regression model with covariates defined by the subgroups cutoffs will be evaluated. The values used for classification are generally designed based on a prior classification of interest or to split the population in half; if a subgroup classification results in less than 10% of the population in 1 category, the subgroup factor will be dropped from the model. A stepwise selection process using the likelihood ratio test will be used to determine the inclusion of each covariate in the logistic regression model. For the covariates, the significant level to enter the model is 0.15 and the level to stay is 0.05. Only significant parameters will be presented in the final model. The odds ratio for the treatment effect adjusting for other prognostic factors will be reported along with 95% confidence interval. Treatment by variable interaction terms may also be explored.

7.3.2. Secondary Efficacy Analyses: Serum Ferritin

7.3.2.1. Serum Ferritin

The secondary efficacy endpoint of change from baseline in serum ferritin will be analyzed using a general linear model with adjustment for screening TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3). To account for the large

variation in baseline serum ferritin concentrations, the primary analysis will be based on the percent change from baseline.

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.

7.3.2.2. Sensitivity Analysis: Serum Ferritin

Sensitivity analyses will also be conducted for the Efficacy Population with separate analyses for predose and postdose measure and for the mITT Population for the predose measure:

- Postdose Analysis: Change from baseline to 24 (± 4) hours postdose at Weeks 3, 4, 8, 12, and 16.
- Predose Analysis: Change from baseline to predose at Weeks 3, 4, 8, 12, and 16, and at Week 17.

A mixed effects repeated measures analysis with adjustments for screening TSAT (> 45% to 70% versus > 70%), frequency of phlebotomy procedure over the last 12 months (0 to 3 versus > 3), and patient (as a random factor) will be conducted in addition to the by visit analyses.

Additional sensitivity analyses may be conducted on serum ferritin similarly to the primary analysis on serum TSAT.

7.4. Exploratory Efficacy Analyses

7.4.1. Exploratory Efficacy Analyses: Other Iron Parameters

The serum iron parameters of total serum iron, transferrin, ferritin, apoferritin, holoferritin, unsaturated iron-binding capacity (UIBC), total iron-binding capacity (TIBC), will be analyzed using a general linear model with adjustment for screening TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3). For each serum iron parameter, separate analyses will be conducted for predose and postdose measures.

7.4.1.1. Sensitivity Analyses: Other Iron Parameters

Sensitivity analyses will also be conducted for the Efficacy Population with separate analyses for predose and postdose measure and for the mITT Population for the predose measure:

- Postdose Analysis: Change from baseline to 24 (± 4) hours postdose at Weeks 3, 4, 8, 12, and 16.
- Predose Analysis: Change from baseline to predose at Weeks 3, 4, 8, 12, and 16, and at Week 17.

A mixed effects repeated measures analysis with adjustments for screening TSAT (> 45% to 70% versus > 70%), frequency of phlebotomy procedure over the last 12 months (0 to 3 versus > 3), and patient (as a random factor) will be conducted in addition to the by visit analyses.

Additional sensitivity analyses may be conducted on the other iron parameters similarly to the primary analysis on serum TSAT.

7.4.2. Exploratory Efficacy Analyses: Change in Thyroid Function

Thyroid function (triiodothyronine [T3], thyroxine [T4], thyroid-stimulating hormone [TSH], and free T4) will be analyzed as exploratory variables. For each thyroid function test, change from baseline will be calculated and the change from baseline to Week 16 will be analyzed using a general linear model with adjustment for screening TSAT (> 45% to 70% versus > 70%) and frequency of phlebotomy procedure over the last 12 months (0 to 3 versus > 3).

7.4.3. Exploratory Efficacy Analyses: Change in Liver Function

Liver function (albumin, alkaline phosphatase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin [total, indirect, and direct], lactate dehydrogenase [LDH], and total protein) will be analyzed as exploratory variables. For each liver function test, change from baseline to each postbaseline visit (Weeks 1, 4, 8, 12, 16 and 20 [follow-up]) will be calculated and the change from baseline to Week 16 will be analyzed using a general linear model with adjustment for screening TSAT (> 45% to 70% versus > 70%) and frequency of phlebotomy procedure over the last 12 months (0 to 3 versus > 3).

7.4.4. Exploratory Efficacy Analyses: Change in Glycemic Control

Hemoglobin A1c will be analyzed as exploratory variables. Change from baseline will be calculated and the change from baseline to Week 16 will be analyzed using a general linear model with adjustment for screening TSAT (> 45% to 70% versus > 70%) and frequency of phlebotomy procedure over the last 12 months (0 to 3 versus > 3).

7.4.5. Exploratory Efficacy Analyses: Change in RBC Parameters

RBC parameters (hemoglobin concentration, RBC count, and RDW) will be analyzed as exploratory variables. For each RBC test, change from baseline to each to each postbaseline visit (Weeks 1, 4, 8, 12, 16 and 20 [follow-up]) will be calculated and the change from baseline to Week 16 will be analyzed using a general linear model with adjustment for screening TSAT (> 45% to 70% versus > 70%) and phlebotomy frequency over the last 12 months (0 to 3 versus > 3).

7.4.6. Exploratory Efficacy Analyses: Change in Quality of Life

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 screening

TSAT (> 45% to 70% versus > 70%) and frequency of phlebotomy procedure over the last 12 months (0 to 3 versus > 3).

7.5. Multiplicity Adjustment

The hypothesis test of patients treated with LJPC-401 versus placebo for the primary efficacy endpoint is not affected by multiplicity. Hierarchical testing will be used to preserve the overall type I error across the testing of secondary endpoints. Hierarchical testing will proceed as follows:

1. Given a significant treatment effect for the primary efficacy endpoint, an analysis of the first secondary endpoint (number of phlebotomies from Day 2 to End of Study) will proceed and will be tested for statistical significance.
2. Given a significant treatment effect for the primary efficacy endpoint and the first secondary efficacy endpoint, an analysis of the second secondary endpoint (change in serum ferritin) will proceed and will be tested for statistical significance.

The Lan DeMets approach to the O'Brien-Fleming method for sequential designs will be applied to preserve the overall type I error rate. It is expected that a type I rate of 0.00021 will be applied for the interim analysis (n = 16) and adjustment for all interim analyses will be applied for the final analysis (n = 48). At the interim analysis, if hierarchical testing results in a statistically significant Lan DeMets p-value for each of the 3 endpoints, then enrollment may be halted due to overwhelming efficacy.

8. SAFETY AND TOLERABILITY

8.1. Adverse Events

Adverse events will be coded using the most recent version at time of database lock of MedDRA and grouped by SOC and 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.

Adverse events (AEs) 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.

Adverse events will be graded for severity using mild, moderate, severe, life-threatening, and fatal (Table 2). Relatedness, and seriousness of AEs will be summarized (see Table 4 in Section 11.2 of the protocol).

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

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 maximum relationship to study drug and maximum severity of those TEAEs.

Table 2: 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.

8.2. Deaths

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

8.3. Injection Site Reaction

Injection site reaction will be summarized by treatment group. Summaries will contain the number and percentage of patients experiencing a reaction 1 or more times, and descriptive statistics on the duration (mean, SD, median, minimum, and maximum).

8.4. Study Drug Exposure

For the Efficacy, mITT, and Safety Populations, study drug administration will be summarized by duration of exposure in weeks (n, categorized [0 to < 4, 4 to < 8, 8 to < 12, 12 to 16, 16], mean, SD, median, and range), average number of injections per week (n, mean, SD, median, and range), and total dose administered (n, mean, SD, median, and range).

In addition, mean, minimum, and maximum titrations levels (n, mean, SD, median, and range) will be summarized by week.

8.5. Clinical Laboratory Evaluations

Clinical laboratory data (serum iron parameters, hematology, serum chemistry, other clinical tests, and urinalysis) obtained from local and central 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 on the appropriate eCRF as AEs per Section 8.1.

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.

8.6. 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).

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 (LLQ).

8.7. Physical Exam

Physical exam findings will be reported in patient listings.

8.8. Vital Signs

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

8.9. Electrocardiogram

Corrected QT intervals will be calculated using the QT interval and heart rate. The QTcB value will be derived by Bazett's formula and QTcF will be derived by Frederica'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.

9. REFERENCES

Iron Disorders Institute, Phlebotomy Guidelines for Patients with Hereditary Hemochromatosis, 2011, http://www.irondisorders.org/Websites/idi/files/Content/856494/Physician%20Chart%20phlebotomy%20detail2011.pdf. Accessed 21 Nov 2017.

10. PLANNED TABLES, LISTINGS, AND FIGURES

Tables, listings, and figures (TLFs) are categorized and numbered in accordance with International Council on Harmonisation (ICH) E3 guidelines. TLFs will be generated 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).

It is not intended that every TLF will be included in the CSR. It is also possible that additional analyses will be conducted after review of the data. Any analyses or summaries not specified in the SAP, but performed after review of the data, will be identified in the CSR as posthoc.

10.1. Patient Data Tables

Tables will be summarized overall and by treatment group. In general, population, enrollment, demographic, and efficacy tables will use the Efficacy Population, safety tables will use the Safety Population, and PK tables will use the PK Population.

10.2. Tables

Population, Enrollment, and Demographic Tables

Tables summarizing population, enrollment and demographics will be indexed by analysis populations, for example 14.3.1.1.3.x: 14.1.1.3.1. Enrollment (Efficacy Population), 14.1.1.3.2. Enrollment (mITT Population), 14.1.1.3.3. Enrollment (ITT Population), 14.1.1.3.4. (Per Protocol Population), 14.1.1.3.5. Enrollment (Safety Population), and 14.1.1.3.6. Enrollment (PK Population). Tables may not be produced for all analysis populations listed above. If populations are identical, duplicate summaries will not be produced.

14.1.1.1	Patient Informed Consent by Protocol Version and Analysis Population
14.1.1.2	Disposition (Randomize Patients)
14.1.1.3.x	Enrollment
14.1.1.4.x	Important Protocol Deviations
14.1.2.1.x	Randomization versus Treated Stratification
14.1.2.2.x	Randomization Stratification
14.1.2.3.x	Demographics and Baseline Characteristics
14.1.3.1.x	Medical/Surgical History
14.1.3.2.x	Most Frequent Medical/Surgical History

Efficacy Tables

The following efficacy tables will be provided both for Efficacy Population with select tables reproduced for the mITT Population.

In addition tables summarizing efficacy using other analysis populations may be produced, if so, indexing will based on analysis population, for example 14.2.1.1.1.x: 14.2.1.1.1.1 Postdose TSAT, Change from Baseline to Week 16: Primary Efficacy Analysis (Efficacy Population), for the mITT Population (14.2.1.1.1.2), for the ITT Population (14.2.1.1.1.3), for the Per Protocol Population (14.2.1.1.1.4), for the Safety Population (14.2.1.1.1.5) and for the PK Population (14.2.1.1.3.6). If populations are identical, duplicate summaries will not be produced.

14.2.1.1.x	TSAT, Change from Baseline to Week 16: Primary Efficacy Analysis
14.2.1.2.x	Predose TSAT, Change from Baseline to Week 16
14.2.1.3.x	Predose TSAT, Change from Baseline to Week 17
14.2.2.1.x	Frequency of Phlebotomy: Secondary Efficacy Analysis, Poisson Regression
14.2.2.2.x	Time to First Post-dose Phlebotomy: Secondary Efficacy Analysis, Kaplan-Meier
14.2.2.3.x	At Least One Post-dose Phlebotomy: Secondary Efficacy Analysis, CMH
14.2.2.4.x	Number of Times a Patient Met Criteria for a Phlebotomy: Secondary Efficacy Analysis, Poisson Regression
14.2.2.5.x	Time until Patient First Met Criteria for a Phlebotomy: Secondary Efficacy Analysis, Kaplan-Meier
14.2.2.6.x	Patient Met Criteria for a Phlebotomy on at Least One Visit: Secondary Efficacy Analysis, CMH
14.2.3.1.x	Complete Iron Studies, Postdose: Serum Ferritin (ng/mL), Change from Baseline to Week 16: Secondary Efficacy Analysis
14.2.3.2.x	Complete Iron Studies, Predose: Serum Ferritin (ng/mL), Change from Baseline to Each Weekly Visit: Secondary Efficacy Analysis
14.2.3.3.x	Complete Iron Studies, Postdose: Total Serum Iron (µg/dL), Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.3.4.x	Complete Iron Studies, Predose: Total Serum Iron (µg/dL), Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.3.5.x	Complete Iron Studies Postdose: Serum Transferrin (mg/dL), Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.3.6.x	Complete Iron Studies, Predose: Serum Transferrin (mg/dL), Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.3.7.x	Complete Iron Studies Postdose: Apoferritin (mg/dL), Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.3.8.x	Complete Iron Studies, Predose: Apoferritin (mg/dL), Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis (Efficacy Population)
14.2.3.9.x	Complete Iron Studies Postdose: Holoferritin (mg/dL), Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.3.10.x	Complete Iron Studies, Predose: Holoferritin (mg/dL), Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis (Efficacy Population)
14.2.3.11.x	Complete Iron Studies, Postdose: Serum UIBC (µg/dL), Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.3.12.x	Complete Iron Studies, Predose: Serum UIBC (µg/dL), Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.3.13.x	Complete Iron Studies, Postdose: Serum TIBC (µg/dL), Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.3.14.x	Complete Iron Studies, Predose: Serum TIBC (µg/dL), Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.4.1.x	Thyroid Function: T3, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.4.2.x	Thyroid Function: T4, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.4.3.x	Thyroid Function: TSH, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.4.4.x	Thyroid Function: Free T4, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.5	Hemoglobin A1C, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.6.1.x	Liver Function: Albumin, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis

14.2.6.2.x	Liver Function: Alkaline Phosphatase, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.6.3.x	Liver Function: ALT, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.6.4.x	Liver Function: AST, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.6.5.x	Liver Function: Bilirubin, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.6.6.x	Liver Function: LDH, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.6.7.x	Liver Function: Total Protein, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.7.1.x	RBC Parameters: Hemoglobin Concentration, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.7.2.x	RBC Parameters: RBC Count, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.7.3.x	RBC Parameters: RDW, Change from Baseline to Each Weekly Visit: Exploratory Efficacy Analysis
14.2.8.1.x	Quality of Life: SF-36v2 Total Score, Change from Baseline to Week 16: Exploratory Efficacy Analysis
14.2.8.2.x	Quality of Life: SF-36v2 Subscales, Change from Baseline to Week 16: Exploratory Efficacy Analysis
14.2.8.3.x	Quality of Life: WOMAC Total Score, Change from Baseline to Week 16: Exploratory Efficacy Analysis
14.2.8.4.x	Quality of Life: WOMAC Subscales, Change from Baseline to Week 16: Exploratory Efficacy Analysis
14.2.8.5.x	Quality of Life: Modified Dreisler Indices for Arthritis, Change from Baseline to Week 16: Exploratory Efficacy Analysis
14.2.9.1.1.x	TSAT, Change from Baseline to Week 16: Univariate Analyses
14.2.9.1.2.x	TSAT, Change from Baseline to Week 16: Multivariate Analyses
14.2.9.1.3.x	Serum Ferritin, Change from Baseline to Week 16: Univariate Analyses
14.2.9.1.4.x	Serum Ferritin, Change from Baseline to Week 16: Multivariate Analyses
14.2.9.2.1.x	Frequency of Phlebotomy: Univariate Analyses
14.2.9.2.2.x	Time to First Post-dose Phlebotomy: Univariate Analyses
14.2.9.2.3.x	At Least One Post-dose Phlebotomy: Univariate Analyses
14.2.9.2.4.x	Number of Times a Patient Met Criteria for a Phlebotomy: Univariate Analyses
14.2.9.2.5.x	Time until Patient First Met Criteria for a Phlebotomy: Univariate Analyses
14.2.9.2.6.x	Patient Met Criteria for a Phlebotomy on at Least One Visit: Univariate Analyses
14.2.9.3.1.x	Frequency of Phlebotomy: Multivariate Analyses
14.2.9.3.2.x	Time to First Post-dose Phlebotomy: Multivariate Analyses
14.2.9.3.3.x	At Least One Post-dose Phlebotomy: Multivariate Analyses
14.2.9.3.4.x	Number of Times a Patient Met Criteria for a Phlebotomy: Multivariate Analyses
14.2.9.3.5.x	Time until Patient First Met Criteria for a Phlebotomy: Multivariate Analyses
14.2.9.3.6.x	Patient Met Criteria for a Phlebotomy on at Least One Visit: Multivariate Analyses
14.2.10.1	Pharmacokinetics: Hepcidin Concentration (PK Population)
14.2.10.2	Pharmacokinetics: Hepcidin Parameter Estimates (PK Population)

Safety Tables

The following safety tables will be provided both for Safety Population.

In addition, tables summarizing safety using other analysis populations may be produced, if so, indexing will based on analysis population, for example 14.3.1.1.x: 14.3.1.1.1. Study Drug Administration (Safety Population), and (14.3.1.1.2), for the Per Protocol Population. If populations are identical, duplicate summaries will not be produced.

14.3.1.1	Study Drug Administration
14.3.2.2.1.x	Summary of Treatment-Emergent Adverse Events
14.3.2.2.2.x	Treatment-Emergent Adverse Events Regardless of Relationship to Study Drug
14.3.2.2.3.x	Treatment-Emergent Adverse Events Regardless of Relationship to Study Drug by Maximum Severity: LJPC-401 Arm
14.3.2.2.4.x	Treatment-Emergent Adverse Events Regardless of Relationship to Study Drug by Maximum Severity: Placebo Arm
14.3.2.2.5.x	Treatment-Emergent Adverse Events Related to Study Drug
14.3.2.2.6.x	Treatment-Emergent Adverse Events Related to Study Drug by Maximum Severity: LJPC-401 Arm
14.3.2.2.7.x	Treatment-Emergent Adverse Events Related to Study Drug by Maximum Severity: Placebo Arm
14.3.2.2.8.x	Most Frequent Treatment-Emergent Adverse Events Regardless of Relationship to Study Drug
14.3.2.2.9.x	Most Frequent Treatment-Emergent Adverse Events Related to Study Drug
14.3.2.3.1.x	Most Frequent Treatment-Emergent Non-Serious Adverse Events Regardless of Relationship to Study Drug
14.3.2.3.2.x	Most Frequent Treatment-Emergent Non-Serious Adverse Events Related to Study Drug
14.3.2.4.1.x	Grade 3, 4 or 5 Treatment-Emergent Adverse Events Regardless of Relationship to Study Drug
14.3.2.4.2.x	Grade 3, 4 or 5 Treatment-Emergent Adverse Events Related to Study Drug
14.3.2.5.1.x	Treatment-Emergent Serious Adverse Events Regardless of Relationship to Study Drug
14.3.2.5.2.x	Treatment-Emergent Serious Adverse Events Related to Study Drug
14.3.2.5.3.x	Treatment-Emergent Adverse Events Regardless of Relationship to Study Drug Resulting in Discontinuation of Study Drug
14.3.2.5.4.x	Treatment-Emergent Adverse Events Related to Study Drug Resulting in Discontinuation of Study Drug
14.3.2.6.1.x	Fatal Treatment-Emergent Adverse Events Regardless of Relationship to Study Drug
14.3.2.6.2.x	Fatal Treatment-Emergent Adverse Events Related to Study Drug
14.3.2.7.1.x	Treatment-Emergent Adverse Events of Special Interest
14.3.2.7.2.x	Treatment-Emergent Adverse Events of Special Interest - Cardiac
14.3.2.8.1.x	Grade 3, 4 or 5 Treatment-Emergent Adverse Events of Special Interest
14.3.2.8.2.x	Grade 3, 4 or 5 Treatment-Emergent Adverse Events of Special Interest - Cardiac
14.3.2.9.1.x	Injection Site Reactions
14.3.2.10.1	Deaths
14.3.3.1.x	Summary of Hematology Value and Change from Baseline over Time for Laboratory Test (Unit)
14.3.3.2.x	Summary of Chemistry Value and Change from Baseline over Time for Laboratory Test (Unit)
14.3.3.3.x	Summary of Urinalysis Value and Change from Baseline over Time for Laboratory Test (Unit)
14.3.4	Immunogenicity (PK Population)
14.3.5.1.x	Vital Signs: Summary of Systolic Blood Pressure (mmHg) by Visit
14.3.5.2.x	Vital Signs: Summary of Diastolic Blood Pressure (mmHg) by Visit

14.3.5.3.x	Vital Signs: Summary of Respiration Rate (breaths/minute) by Visit
14.3.5.4.x	Vital Signs: Summary of Temperature (^{0}C) by Visit
14.3.5.5.x	Vital Signs: Summary of Heart Rate (beats/minute) by Visit
14.3.6.1.x	12-Lead Electrocardiogram: Summary QT Interval (msec) by Visit
14.3.6.2.x	12-Lead Electrocardiogram: Summary QTcF Interval (msec) by Visit
14.3.6.3.x	12-Lead Electrocardiogram: Summary QTcB Interval (msec) by Visit
14.3.6.4.x	12-Lead Electrocardiogram: Summary of PR Interval (msec) by Visit
14.3.6.5.x	12-Lead Electrocardiogram: Summary of QRS Interval (msec)
14.3.6.6.x	12-Lead Electrocardiogram: Summary of Heart Rate (beats/minute) by Visit
14.3.7.1.x	Prior Medications
14.3.7.2.x	Concomitant Medications
14.3.7.3.x	Prior Phlebotomies
14.3.7.4.x	Concomitant Phlebotomies
14.3.7.5.x	On-Study Procedures and Surgeries

10.3. Patient Data Listings

In general, patient data listings will be sorted by patient identification (ID) number, visit, and study day. Log data (ie, prior and concomitant medications, adverse events) will be sorted by patient ID, date, and term.

Patient IDs, displayed in the first column of all listings, will include the patient's age, sex, and treatment group.

Number	Title
16.1.6	Lot Numbers
16.1.7	IXRS Randomization
16.1.8	Patient Informed Consent
16.2.1.1	Patient Disposition
16.2.1.2	Treatment Termination
16.2.1.3	Study Termination
16.2.1.4	Unblinding of Patients
16.2.1.5	Patient Populations
16.2.2	Important Protocol Deviations
16.2.3	Enrollment and Eligibility
16.2.4.1	Demographics and Baseline Characteristics
16.2.4.2	Medical/Surgical History
16.2.4.3	Baseline Pregnancy
16.2.4.4	Prior and Concomitant Medications
16.2.4.5	Non-medication Therapy / Procedures
16.2.5.1	Study Drug Exposure: LJPC401 or Placebo Weekly Totals
16.2.5.2	Study Drug Exposure: LJPC401 or Placebo Subcutaneous Injections
16.2.6.1.1	Complete Iron Studies
16.2.6.1.2	Phlebotomy Events and Procedures
16.2.6.2	Quality of Life (SF-36vs2)
16.2.6.3	Pharmacokinetic Concentrations
16.2.7.1	Adverse Events
16.2.7.2	Serious Adverse Events
16.2.7.3	Death
16.2.7.4	Injection Site Assessment
16.2.8.1.1	Hematology
16.2.8.1.2	Hematology: Differentials
16.2.8.2.1	Serum Chemistry: Liver and Kidney Function
16.2.8.2.2	Serum Chemistry: Electrolytes
16.2.8.2.3	Serum Chemistry: Other
16.2.8.3	Screening Urinalysis
16.2.8.4	Microscopic Urinalysis
16.2.8.5	Thyroid Function
16.2.8.6	Immunogenicity
16.2.8.7	Physical Examination
16.2.8.8	Vital Signs
16.2.8.9	Pregnancy
16.2.8.10	12-Lead Electrocardiogram

10.4. Figures

Figures will be summarized by treatment group.

Number	Title
14.2.6.1.1	Mean (SE) of TSAT by Treatment and Visit (Efficacy Population)
14.2.6.1.2	Mean (SE) of Change from Baseline in TSAT by Treatment and Visit (Efficacy Population)
14.2.6.1.3	Mean (SE) of Percent Change from Baseline in TSAT by Treatment and Visit (Efficacy Population)
14.2.6.1.4	Forest Plot of Treatment Difference in TSAT, at Week 16, by Subgroups (Efficacy Population)
14.2.6.1.5	Forest Plot of Treatment Difference in Change from Baseline in TSAT, at Week 16, by Subgroups (Efficacy Population)
14.2.6.2.1	Mean (SE) of Serum Ferritin by Treatment and Visit (Efficacy Population)
14.2.6.2.2	Mean (SE) of Change from Baseline in Serum Ferritin by Treatment and Visit (Efficacy Population)
14.2.6.2.3	Mean (SE) of Percent Change from Baseline in Serum Ferritin by Treatment and Visit (Efficacy Population)
14.2.6.2.4	Forest Plot of Treatment Difference in Serum Ferritin, at Week 16, by Subgroups (Efficacy Population)
14.2.6.2.5	Forest Plot of Treatment Difference in Change from Baseline Serum Ferritin, at Week 16, by Subgroups (Efficacy Population)
14.2.6.3.1	Mean (SE) of Total Serum Iron by Treatment and Visit (Efficacy Population)
14.2.6.3.2	Mean (SE) of Change from Baseline in Total Serum Iron by Treatment and Visit (Efficacy Population)
14.2.6.3.3	Mean (SE) of Percent Change from Baseline in Total Serum Iron by Treatment and Visit (Efficacy Population)
14.2.6.4.1	Mean (SE) of Transferrin by Treatment and Visit (Efficacy Population)
14.2.6.4.2	Mean (SE) of Change from Baseline in Transferrin by Treatment and Visit (Efficacy Population)
14.2.6.4.3	Mean (SE) of Percent Change from Baseline in Transferrin by Treatment and Visit (Efficacy Population)
14.2.6.5.1	Mean (SE) of Apoferritin by Treatment and Visit (Efficacy Population)
14.2.6.5.2	Mean (SE) of Change from Baseline in Apoferritin by Treatment and Visit (Efficacy Population)
14.2.6.5.3	Mean (SE) of Percent Change from Baseline in Apoferritin by Treatment and Visit (Efficacy Population)
14.2.6.6.1	Mean (SE) of Holoferritin by Treatment and Visit (Efficacy Population)
14.2.6.6.2	Mean (SE) of Change from Baseline in Holoferritin by Treatment and Visit (Efficacy Population)
14.2.6.6.3	Mean (SE) of Percent Change from Baseline in Holoferritin by Treatment and Visit (Efficacy Population)
14.2.6.7.1	Mean (SE) of UIBC by Treatment and Visit (Efficacy Population)
14.2.6.7.2	Mean (SE) of Change from Baseline in UIBC by Treatment and Visit (Efficacy Population)
14.2.6.7.3	Mean (SE) of Percent Change from Baseline in UIBC by Treatment and Visit (Efficacy Population)
14.2.6.8.1	Mean (SE) of TIBC by Treatment and Visit (Efficacy Population)
14.2.6.8.2	Mean (SE) of Change from Baseline in TIBC by Treatment and Visit (Efficacy Population)
14.2.6.8.3	Mean (SE) of Percent Change from Baseline in TIBC by Treatment and Visit (Efficacy Population)
14.2.6.9.1	Forest Plot of Frequency of Phlebotomy Rate Ratio

14.2.6.9.2	Forest Plot of Time to First Post-dose Phlebotomy Hazard Ratio
14.2.6.9.3	Forest Plot of At Least One Post-dose Phlebotomy Odds Ratio
14.2.6.9.4	Forest Plot of Number of Times a Patient Met Criteria for a Phlebotomy Rate Ratio
14.2.6.9.5	Forest Plot of Time until Patient First Met Criteria for a Phlebotomy Hazard Ratio
14.2.6.9.6	Forest Plot of Patient Met Criteria for a Phlebotomy on at Least One Visit Odds Ratio
14.2.6.10.1	Mean Hepcidin Concentration by Visit and Treatment (No Baseline Correction, PK Population)
14.2.6.10.2	Mean Hepcidin Concentration by Visit and Treatment (Baseline Correction, PK Population)