



Clinical trial results:

A Phase 2, Multi-center, Randomized, Placebo Controlled, Double-Blind Study with LJPC-401 for the Treatment of Iron Overload in Adult Patients with Hereditary Hemochromatosis

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2017-003598-33 |
| Trial protocol | GB FR |
| Global end of trial date | 22 November 2019 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 11 January 2022 |
| First version publication date | 11 January 2022 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | LJ401-HH01 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03395704 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | La Jolla Pharmaceutical Company |
| Sponsor organisation address | 4747 Executive Drive, Suite 240, San Diego, United States, 92121 |
| Public contact | Regulatory Affairs, La Jolla Pharmaceutical Company, 001 8314211450, lajollaregulatoryaffairs@ljpc.com |
| Scientific contact | Regulatory Affairs, La Jolla Pharmaceutical Company, 001 8314211450, lajollaregulatoryaffairs@ljpc.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 October 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 22 November 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 November 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of weekly dosing of LJPC-401 for 12 weeks on Transferrin saturation (TSAT) in adult patients with hereditary hemochromatosis

Protection of trial subjects:

This study was conducted in accordance with the ethical principles founded in the Declaration of Helsinki and in compliance with the protocol, the International Council on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirements.

The study was conducted in accordance with the ICH E6 GCP for obtaining informed consent. Each patient provided written informed consent after the study was fully explained and before any study-specific procedures (including screening procedures) were performed.

Background therapy:

All enrolled patients were allowed to receive standard of care therapy (phlebotomy) per protocol-specified guidelines.

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 05 January 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Australia: 23 |
| Country: Number of subjects enrolled | United States: 35 |
| Worldwide total number of subjects | 70 |
| EEA total number of subjects | 3 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 | 0 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 44 |
| From 65 to 84 years | 26 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled on 08 May 2018 and the last patient completed the study on 28 Oct 2019. The study enrolled patients in Australia, the United Kingdom, France and the United States.

Pre-assignment

Screening details:

Patients were screened to ensure they were clinically diagnosed with hereditary hemochromatosis for which therapeutic phlebotomy was prescribed. Patients were to be more than 18 years old with a serum ferritin level greater than or equal to 100 mg/mL and a TSAT level greater than 45%.

Period 1

| | |
|------------------------------|----------------------------|
| Period 1 title | Treatment (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

Blinding implementation details:

Investigators and unblinded pharmacists at the sites had access to treatment allocation information.

Investigators at sites had access to TSAT results.

Patients were blinded. The study pharmacist was to prepare either LJPC-401 or placebo in identical syringes to maintain the blind.

The sponsor and Safety Monitoring Committee had access to unblinded data for interim analyses and safety monitoring.

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | LJPC-401 |

Arm description:

Interventional arm - patients received LJPC-401

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | synthetic human hepcidin |
| Investigational medicinal product code | LJPC-401 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Study drug was administered QW. Dosing was as follows:

- Week 1: 5 mg LJPC-401 or volume-matched placebo
 - Week 2: 10 mg LJPC-401 or volume matched placebo
 - Week 3: 10 mg LJPC-401 or volume-matched placebo
 - Week 3: Fasting TSAT (postdose 24 (+/-4) hours) determined the Week 4 dose
- If the TSAT was > 45%, then the dose at Week 4 increased to 20 mg LJPC-401 or volume-matched placebo.

If the TSAT was < or = 45%, then dose at Week 4 maintained at 10 mg LJPC-401 or volume-matched placebo.

- At Weeks 9 and 13 (after Weeks 8 and 12 fasting TSAT results were available):

- Maintained or increased dose to 20 mg if TSAT was > 45%
- Maintained dose (10 or 20 mg) if TSAT remained < or = 45%, and no dose reduction was required for toxicity.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Volume-matched 0.9% sodium chloride for injection

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|-------------------------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | 0.9% sodium chloride injection, USP |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular and intravenous use |

Dosage and administration details:

Placebo was the volume-matched equivalent of the LJPC-401 dosing regimen.

| Number of subjects in period 1^[1] | LJPC-401 | Placebo |
|---|----------|---------|
| Started | 34 | 35 |
| Completed | 30 | 33 |
| Not completed | 4 | 2 |
| Consent withdrawn by subject | 2 | 1 |
| Adverse event, non-fatal | 2 | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One patient was enrolled in the study, but did not initiate study treatment. Therefore, they are counted in the worldwide enrollment numbers, but are not included in Period 1 of the study.

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | LJPC-401 |
|-----------------------|----------|

Reporting group description:

Interventional arm - patients received LJPC-401

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Volume-matched 0.9% sodium chloride for injection

| Reporting group values | LJPC-401 | Placebo | Total |
|--|----------|---------|-------|
| Number of subjects | 34 | 35 | 69 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 23 | 20 | 43 |
| From 65-84 years | 11 | 15 | 26 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| least squares mean | 55 | 60 | |
| standard deviation | ± 13.83 | ± 12.43 | - |
| Gender categorical Units: Subjects | | | |
| Female | 9 | 18 | 27 |
| Male | 25 | 17 | 42 |
| Hereditary Hemochromatosis Genotype Units: Subjects | | | |
| HFE | 1 | 2 | 3 |
| Not Available | 5 | 5 | 10 |
| Other | 28 | 28 | 56 |

End points

End points reporting groups

| | |
|---|----------|
| Reporting group title | LJPC-401 |
| Reporting group description: | |
| Interventional arm - patients received LJPC-401 | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Volume-matched 0.9% sodium chloride for injection | |

Primary: Post-dose TSAT

| | |
|------------------------|----------------|
| End point title | Post-dose TSAT |
| End point description: | |
| | |
| End point type | Primary |
| End point timeframe: | |
| Baseline to Week 16 | |

| End point values | LJPC-401 | Placebo | | |
|---|----------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 28 | | |
| Units: percent | | | | |
| least squares mean (standard deviation) | -32.8 (\pm 20.53) | -2.5 (\pm 18.50) | | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Week 16 TSAT Change from Baseline |
| Comparison groups | Placebo v LJPC-401 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | General Linear Model |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From consent through End of Study.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | LJPC-401 |
|-----------------------|----------|

Reporting group description:

Interventional arm - patients received LJPC-401

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo was locally-sourced 0.9% sodium chloride injection, USP (or equivalent).

| Serious adverse events | LJPC-401 | Placebo | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 2 / 35 (5.71%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 35 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 35 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriospasm coronary | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 35 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Seizure | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 35 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Hernia pain | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 35 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 35 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | LJPC-401 | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 33 / 34 (97.06%) | 30 / 35 (85.71%) | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 35 (5.71%) | |
| occurrences (all) | 0 | 2 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 2 / 35 (5.71%) | |
| occurrences (all) | 2 | 2 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 35 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Headache | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 3 / 35 (8.57%) | |
| occurrences (all) | 2 | 3 | |
| Presyncope | | | |

| | | | |
|--|------------------|-----------------|--|
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 35 (5.71%) | |
| occurrences (all) | 0 | 3 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 5 / 35 (14.29%) | |
| occurrences (all) | 4 | 5 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 35 (5.71%) | |
| occurrences (all) | 0 | 2 | |
| Injection site bruising | | | |
| subjects affected / exposed | 6 / 34 (17.65%) | 0 / 35 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Injection site erythema | | | |
| subjects affected / exposed | 17 / 34 (50.00%) | 0 / 35 (0.00%) | |
| occurrences (all) | 56 | 0 | |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 35 (5.71%) | |
| occurrences (all) | 0 | 2 | |
| Injection site induration | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 35 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Injection site mass | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 0 / 35 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Injection site nodule | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 0 / 35 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Injection site pain | | | |
| subjects affected / exposed | 8 / 34 (23.53%) | 0 / 35 (0.00%) | |
| occurrences (all) | 40 | 0 | |
| Injection site pruritus | | | |
| subjects affected / exposed | 14 / 34 (41.18%) | 1 / 35 (2.86%) | |
| occurrences (all) | 50 | 1 | |
| Injection site rash | | | |

| | | | |
|---|-----------------------|-----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 0 / 35 (0.00%) 0 | |
| Injection site reaction subjects affected / exposed occurrences (all) | 4 / 34 (11.76%) 29 | 0 / 35 (0.00%) 0 | |
| Injection site swelling subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 6 | 0 / 35 (0.00%) 0 | |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 2 / 35 (5.71%) 2 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 5 / 34 (14.71%) 10 | 4 / 35 (11.43%) 5 | |
| Nausea subjects affected / exposed occurrences (all) | 4 / 34 (11.76%) 7 | 1 / 35 (2.86%) 1 | |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 1 / 35 (2.86%) 1 | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 4 / 34 (11.76%) 4 | 10 / 35 (28.57%) 1 | |
| Rash subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 3 | 1 / 35 (2.86%) 1 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 6 / 34 (17.65%) 8 | 4 / 35 (11.43%) 6 | |
| Back pain subjects affected / exposed occurrences (all) | 4 / 34 (11.76%) 4 | 2 / 35 (5.71%) 2 | |

| | | | |
|---|---------------------|---------------------|--|
| Muscle spasms subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 1 / 35 (2.86%) 1 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 1 / 35 (2.86%) 1 | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 3 | 1 / 35 (2.86%) 1 | |
| Rhinitis subjects affected / exposed occurrences (all) | 1 / 34 (2.94%) 1 | 3 / 35 (8.57%) 4 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 3 | 3 / 35 (8.57%) 3 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 3 / 35 (8.57%) 4 | |
| Metabolism and nutrition disorders | | | |
| Type 2 diabetes mellitus subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 2 / 35 (5.71%) 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 30 November 2017 | <ul style="list-style-type: none">- Clarified study endpoints- Updated to use the 2011 Iron Disorders Institute (IDI) phlebotomy guidelines for patients with hereditary hemochromatosis (HH)- Updated to require standard-of-care phlebotomy for all randomized patients on Day 1. Thereafter, phlebotomy decisions by the investigator were to be assessed at Weeks 4, 8 and 12 per the 2011 IDI guidelines- Added a secondary endpoint to assess the number of phlebotomy events- Added HH diagnosis and genotype as part of medical history data collection- Added that complete iron lab samples should be drawn predose at the same time of day each visit, whenever possible- Added contraception language- Revised TSAT stratification factor- Amended statistical methods to align with the revisions to study endpoints |
| 08 March 2018 | <ul style="list-style-type: none">- Updated adverse event reporting to start at the time of consent- Revised statistical methods to align with the statistical analysis plan- Modified phlebotomy language to allow investigator to remove blood volume based on weight- Specified diabetes Type 2 exclusion criteria to exclude patients with poorly controlled diabetes- Amended a phlebotomy event in subgroups as either based on a phlebotomy or having a fasting TSAT > 45%- Update planned enrollment to at least 48 evaluable patients- Revised excluded medications and therapies- Revised the comparability group to include subgroups of interest |
| 18 June 2018 | <ul style="list-style-type: none">- Study design changed from double-blind to single-blind- Extended the screening period to 90 days- Added rescreening specifics- Blood collections for TSAT and other iron parameters were changed from weekly to extended durations- Dosage was revised to a more fixed design- Added glycemic control as an exploratory objective and change in hemoglobin A1c from baseline to Week 16 as an exploratory endpoint- Added additional endpoint and blood sample collection at Week 17 for complete iron studies- Revised inclusion criteria for serum ferritin from 150 to greater than or equal to 100 ng/mL to < 1,000 ng/mL- Updated exclusion criteria to exclude patients receiving chelation therapy within 7 days prior to the first dose of study drug- Updated exclusion criteria to exclude patients initiation phlebotomy therapy less than 3 months from first dose of study drug- Removed type 2 diabetes as an exclusion criteria- Removed clinically significant arrhythmias as an exclusion criteria- Specified the timing of certain screening evaluations- Removed requirement for a formal DMC- Revised randomizations by baseline of phlebotomy frequency over the last 12 months |

| | |
|------------------|---|
| 02 October 2018 | <ul style="list-style-type: none"> - Revised primary endpoint to account for patients who received phlebotomy and patients who did not receive a phlebotomy after Week 1 - Added an iron parameter endpoint at Week 17 - Revised statistical methods - Added 10 mg/mL concentration to the IMP description - Corrected dose adjustment information - Added a safety monitoring committee - Added an interim analysis to evaluate initial data after the first 16 patients completed Week 16 assessments or had a phlebotomy after the SOC phlebotomy on Day 1 and before Week 16 - Added an exclusion criteria based on ECG findings and clinical significant arrhythmias - Added an exclusion criteria to exclude patients with poorly controlled Type 2 diabetes |
| 14 December 2018 | - Amended the Efficacy Analysis Population to include those patients enrolled under global protocol version 4.0 or later only |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported