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 (± 20.53)	-2.5 (± 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	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Injection site reaction			
subjects affected / exposed	4 / 34 (11.76%)	0 / 35 (0.00%)	
occurrences (all)	29	0	
Injection site swelling			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	6	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	5 / 34 (14.71%)	4 / 35 (11.43%)	
occurrences (all)	10	5	
Nausea			
subjects affected / exposed	4 / 34 (11.76%)	1 / 35 (2.86%)	
occurrences (all)	7	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 34 (11.76%)	10 / 35 (28.57%)	
occurrences (all)	4	1	
Rash			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 34 (17.65%)	4 / 35 (11.43%)	
occurrences (all)	8	6	
Back pain			
subjects affected / exposed	4 / 34 (11.76%)	2 / 35 (5.71%)	
occurrences (all)	4	2	

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2017	- 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	- 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	- 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	- 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