Clinical trial results:
A Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of JZP-258 in Subjects with Narcolepsy with Cataplexy

Summary

EudraCT number	2016-000426-20
Trial protocol	GB CZ DE ES FR BE FI HR NL
Global end of trial date	10 July 2019

Results information

Result version number	v1 (current)
This version publication date	23 July 2020
First version publication date	23 July 2020

Trial information

Trial identification

Sponsor protocol code	15-006

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Jazz Pharmaceuticals
Sponsor organisation address	3180 Porter Drive, Palo Alto, California, United States,
Public contact	Director, Clinical Trial Disclosure & Transparency, Jazz Pharmaceuticals, ClinicalTrialDisclosure@JazzPharma.com
Scientific contact	Director, Clinical Trial Disclosure & Transparency, Jazz Pharmaceuticals, ClinicalTrialDisclosure@JazzPharma.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	10 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of JZP-258 in the treatment of cataplexy and excessive daytime sleepiness (EDS) in subjects with narcolepsy.

Protection of trial subjects:

Safety was assessed by the incidence of observed and reported adverse events (AEs), and changes in electrocardiograms (ECGs), clinical laboratory tests, vital signs, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Safety was assessed throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 March 2017
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 States: 79
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Czech Republic: 26
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 16
Worldwide total number of subjects	201
EEA total number of subjects	122

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	195
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were evaluated for eligibility during the Screening Period (up to 30 days).

Period 1

Period 1 title	Open Label Treatment and Titration
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Open-label JZP-258

Arm description:

All 201 subjects entered the Open Label Optimized Treatment and Titration Period (OL OTTP) and received at least 1 dose of study drug. During the OL OTTP (12 weeks), eligible subjects were transitioned to JZP-258 treatment based on their pre-treatment status.

Arm type	Experimental
Investigational medicinal product name	JZP-258
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

During the Open-label Treatment and Titration Period (12 weeks), eligible subjects were transitioned to JZP-258 (0.5 g/mL.) treatment based on their pretreatment status (Xyrem, Xyrem and a non-Xyrem anticataplетic, non-Xyrem anticataplectic only, or no anticataplectic).

Number of subjects in period 1	Open-label JZP-258
Started	201
Completed	155
Not completed	46
Physician decision	3
Consent withdrawn by subject	6
Non-Compliance with Study Drug	4
Adverse event, non-fatal	18
Other	1
Sponsor Decision	2
Lost to follow-up	3
Lack of efficacy	1
Protocol deviation	8

Period 2

Period 2 title	Stable Dose
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Open-label JZP-258

Arm description:

During the Stable Dose Period, subjects received open-label JZP-258 at the same unchanged dose that they received during the last 2 weeks of the Open Label Treatment and Titration Period.

Arm type	Experimental
Investigational medicinal product name	JZP-258
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Open-label JZP-258 (0.5 g/ mL) at the same unchanged dose as during the last 2 weeks of the Open Label Treatment and Titration Period.

Number of subjects in period 2[1]	Open-label JZP-258
Started	149
Completed	144
Not completed	5
Adverse event, non-fatal	1
Lost to follow-up	1
Protocol deviation	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Of the 201 subjects that entered the Open-label Treatment and Titration Period, 149 achieved a tolerable and efficacious dose of JZP-258 and entered the Stable Dose Period. Of those subjects, 136 were randomized.

Period 3

Period 3 title	Double Blind Randomized Withdrawal
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	JZP-258

Arm description:

JZP-258 at the dose taken during the last 2 weeks of the Stable Dose Period.

Arm type	Experimental
Investigational medicinal product name	JZP-258
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

JZP-258 (0.5 g/mL) at the dose taken during the last 2 weeks of the Stable Dose Period

Arm title	Placebo

Arm description:

A matching oral solution to JZP-258.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

A matching oral solution to JZP-258.

Number of subjects in period 3[2]	JZP-258	Placebo
Started	69	67
Completed	69	59
Not completed	0	8
Randomized in error	-	2
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	3
Lack of efficacy	-	2

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: After completing the Stable Dose Period, 136 subjects were randomized. Two subjects were randomized in error, but did not receive any dose of study drug in the DB RWP. Therefore, 134 subjects received at least 1 dose of study drug in the DB RWP.

Baseline characteristics

Reporting groups	
Reporting group title	Open Label Treatment and Titration

Reporting group description: -

Reporting group values	Open Label Treatment and Titration	Total	
Number of subjects	201	201	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	195	195	
From 65-84 years	6	6	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	122	122	
Male	79	79	

End points

End points reporting groups

Reporting group title	Open-label JZP-258

Reporting group description:

All 201 subjects entered the Open Label Optimized Treatment and Titration Period (OL OTTP) and received at least 1 dose of study drug. During the OL OTTP (12 weeks), eligible subjects were transitioned to JZP-258 treatment based on their pre-treatment status.

Reporting group title	Open-label JZP-258

Reporting group description:

During the Stable Dose Period, subjects received open-label JZP-258 at the same unchanged dose that they received during the last 2 weeks of the Open Label Treatment and Titration Period.

Reporting group title	JZP-258

Reporting group description:

JZP-258 at the dose taken during the last 2 weeks of the Stable Dose Period.

Reporting group title	Placebo

Reporting group description:

A matching oral solution to JZP-258.

Primary: Change in Average Weekly Number of Cataplexy Attacks

End point title	Change in Average Weekly Number of Cataplexy Attacks

End point description:

Subjects completed a daily Cataplexy Frequency Diary each night prior to bedtime. Subjects were to record the number of cataplexy attacks that they had each day.

End point type	Primary

End point timeframe:

From the two weeks of the Stable-Dose Period to the two weeks of the Double Blind Randomized Withdrawal Period.

End point values	JZP-258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	65		
Units: Number				
median (inter-quartile range (Q1-Q3))	0.00 (-0.49 to 1.75)	2.35 (0.00 to 11.61)		

Statistical analyses

Statistical analysis title	Change in Weekly Number of Cataplexy Attacks
Comparison groups	JZP-258 v Placebo

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Rank-based ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.044
upper limit	-1.5

Secondary: Change in Epworth Sleepiness Scale (ESS) Score

End point title	Change in Epworth Sleepiness Scale (ESS) Score

End point description:

This is the key secondary endpoint.

The Epworth Sleepiness Scale (ESS) is a self-administered questionnaire with 8 questions asking the subject how likely they would be to doze off or fall asleep in different situations.

End point type	Secondary

End point timeframe:

From the end of the Stable Dose Period to the end of the Double Blind Randomized Withdrawal Period

End point values	JZP-258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	65		
Units: Point on Scale				
median (inter-quartile range (Q1-Q3))	0.00 (-1.0 to 1.0)	2.0 (0.00 to 5.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIc) for Narcolepsy Overall

End point title	Patient Global Impression of Change (PGIc) for Narcolepsy Overall

End point description:

At the end of the Double Blind Randomized Withdrawal Period, subjects rated the change in their condition on a 7-point scale ranging from 1 = "very much improved" to 7 = "very much worse" since the last visit. This endpoint measures the percentage of subjects with worsening PGIc scores for narcolepsy overall (defined as scores of Much Worse or Very Much Worse).

End point type	Secondary

End point timeframe:

At the end of the Double Blind Randomized Withdrawal Period.

End point values	JZP-258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	65		
Units: subjects				
number (not applicable)	3	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression of Change (CGIc) for Narcolepsy Overall

End point title	Clinical Global Impression of Change (CGIc) for Narcolepsy Overall

End point description:

At the end of the Double Blind Randomized Withdrawal Period, Investigators rated their impression of any change in the severity of the subject's narcolepsy overall condition since the start of the Double Blind Randomized Withdrawal Period on a 7-point scale ranging from 1 = "very much improved" to 7 = "very much worse". This endpoint measures the percentage of subjects with worsening CGIc scores for narcolepsy overall, defined as scores of Much Worse or Very Much Worse.

End point type	Secondary

End point timeframe:

At the end of the Double Blind Randomized Withdrawal Period.

End point values	JZP-258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	65		
Units: subjects				
number (not applicable)	4	39		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 36-Item Short Form Health Survey Version 2 (SF-36v2) Scores

End point title	Change in 36-Item Short Form Health Survey Version 2 (SF-36v2) Scores

End point description:

The SF-36v2 is a multi-purpose, short-form health survey with 36 questions/ items. It yields an 8-scale profile of functional health and well-being scores as well as a psychometrically-based physical and mental overall component summary measures.

Two summary scores were derived using the SF-36v2. Physical Component Summary measures dimensions of functional health that are meaningful to respondents, including the impact of health and health-related changes on physical function, pain, and the ability to carry out daily roles. The Mental Component Summary component scale measures the impact of health and health-related changes on well-being, including vitality, social function, and emotional well-being.

End point type	Secondary

End point timeframe:

At the end of the Double Blind Randomized Withdrawal Period.

End point values	JZP-258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	65		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Physical Component Summary	-0.03 (-2.07 to 2.41)	-1.92 (-3.46 to 1.73)		
Mental Component Summary	1.55 (-1.88 to 3.78)	-1.92 (-6.28 to 1.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in EQ-5D-5L Crosswalk Index Score and Visual Analog Scale

End point title	Change in EQ-5D-5L Crosswalk Index Score and Visual Analog Scale

End point description:

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome that includes a descriptive system consisting of 5 dimensions (mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression). The EQ-5D-5L includes five levels of severity for each of the 5 dimensions of the descriptive system(1= no problems, 2= slight problems, 3= moderate problems, 4= severe problems, and 5= extreme problems) that reflect increasing levels of difficulty. Subjects completed the EQ-5D-5L at the end of the OL SDP and the end of the DB RWP by selecting the most appropriate level in each of the 5 dimensions.

End point type	Secondary

End point timeframe:

At the end of the Double Blind Randomized Withdrawal Period.

End point values	JZP-258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[1]	65		
Units: score				
median (inter-quartile range (Q1-Q3))				
Crosswalk index	0.00 (-0.01 to 0.03)	0.00 (-0.05 to 0.03)		
VAS Score	0.00 (0.00 to 5.00)	-5.00 (-10.00 to 5.00)		

Notes:
[1] - There were 68 JZP-258 subjects included in the Crosswalk Index, and 69 in the VAS Score.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety data are summarized for all subjects who received at least 1 dose of study medication across all periods.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	JZP-258
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	JZP-258	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 201 (2.49%)	2 / 65 (3.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Muscle enzyme increased			
subjects affected / exposed	0 / 201 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 201 (0.50%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 201 (0.50%)	0 / 65 (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			

Peripheral nerve paresis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 201 (0.50%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 201 (0.50%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 201 (0.50%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 201 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral cardiomyopathy			
subjects affected / exposed	1 / 201 (0.50%)	0 / 65 (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	JZP-258	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 201 (53.73%)	12 / 65 (18.46%)	
Nervous system disorders			

Cataplexy			
subjects affected / exposed	21 / 201 (10.45%)	5 / 65 (7.69%)	
occurrences (all)	23	6	
Dizziness			
subjects affected / exposed	23 / 201 (11.44%)	0 / 65 (0.00%)	
occurrences (all)	34	0	
Headache			
subjects affected / exposed	45 / 201 (22.39%)	1 / 65 (1.54%)	
occurrences (all)	85	1	
Somnolence			
subjects affected / exposed	5 / 201 (2.49%)	6 / 65 (9.23%)	
occurrences (all)	5	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 201 (6.47%)	0 / 65 (0.00%)	
occurrences (all)	16	0	
Nausea			
subjects affected / exposed	27 / 201 (13.43%)	0 / 65 (0.00%)	
occurrences (all)	32	0	
Infections and infestations			
Influenza			
subjects affected / exposed	17 / 201 (8.46%)	1 / 65 (1.54%)	
occurrences (all)	21	1	
Nasopharyngitis			
subjects affected / exposed	19 / 201 (9.45%)	2 / 65 (3.08%)	
occurrences (all)	21	2	
Upper respiratory tract infection			
subjects affected / exposed	11 / 201 (5.47%)	0 / 65 (0.00%)	
occurrences (all)	16	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 201 (7.46%)	1 / 65 (1.54%)	
occurrences (all)	16	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2016	Clinical Protocol Amendment 1.0
07 November 2016	Updates to the efficacy population and statistical methodology.
10 April 2017	Updates to the efficacy population.
15 December 2017	Addition of a 6-month OLE.
15 May 2018	Addition of a planned interim analysis in order to ensure the availability of study results at the earliest possible date in order to provide a low sodium treatment option alternative.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported