Clinical trial results:
A Long-Term, Safety and Maintenance of Efficacy Study of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy or Obstructive Sleep Apnea

Summary

EudraCT number	2014-005489-31
Trial protocol	FI DE NL FR
Global end of trial date	08 December 2017

Results information

Result version number	v1 (current)
This version publication date	23 December 2018
First version publication date	23 December 2018

Trial information

Trial identification

Sponsor protocol code	14-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02348632
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Jazz Pharmaceuticals
Sponsor organisation address	3180 Porter Drive, Palo Alto, United States, 94304
Public contact	Clinical Trial Disclosure & Transparency, Jazz Pharmaceuticals Inc., 001 2158323661,
Scientific contact	Clinical Trial Disclosure & Transparency, Jazz Pharmaceuticals Inc., 001 2158323661,

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	08 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of JZP-110 administered once daily for up to 52 weeks in doses of 75, 150, and 300 mg.

Protection of trial subjects:

Safety was assessed by the incidence of observed and reported adverse events (AEs), and changes in physical examination findings, 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	01 April 2015
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	Netherlands: 6
Country: Number of subjects enrolled	Finland: 17
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	United States: 545
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	643
EEA total number of subjects	70

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)	547
From 65 to 84 years	96
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Note: Subjects who had completed prior studies with JZP-110 (14-002, 14-003, 14-004, 15-004, 15-005, ADXN05 201, or ADXN05 202) and met the screening criteria were eligible to enroll. 643 subjects comprised the safety population.

Pre-assignment

Screening details:

The Screening phase involved a standard medical screening visit.

Period 1

Period 1 title	Open-label period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Combined JZP-110

Arm description:

Subjects completed a 2-week titration phase. They then entered the maintenance phase of up to 50 weeks at the stable dose that was reached at the end of the Titration Phase.

Arm type	Experimental
Investigational medicinal product name	JZP-110
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Titration phase: Start at 75 mg, titrate up 1 dose level once every 3 days to a maximum of 300 mg. Subjects could also titrate down if needed.

Subjects entered the maintenance phase at the stable dose that was reached at the end of the Titration Phase. Only 3 dose adjustments were allowed during the first 12 weeks of the maintenance phase after which no changes were permitted.

Number of subjects in period 1	Combined JZP-110
Started	643
Completed	458
Not completed	185
Consent withdrawn by subject	27
Adverse event, non-fatal	61
Other	1
Lost to follow-up	14
Treatment noncompliant	7
Sponsor decision	10
Lack of efficacy	54

Protocol deviation	11

Period 2

Period 2 title	Randomized Withdrawal Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo administered orally, QD, for the 2-week randomized withdrawal period.

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

Dosage and administration details:

Placebo administered orally, QD, for the 2-week randomized withdrawal period.

Arm title	JZP-110

Arm description:

JZP-110 administered orally, QD, for the 2-week randomized withdrawal period, at the same dose subjects were currently receiving.

Arm type	Experimental
Investigational medicinal product name	JZP-110
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

JZP-110 administered orally, QD, at the dose subjects were receiving during the open-label maintenance phase.

Number of subjects in period 2[1]	Placebo	JZP-110
Started	142	140
Completed	141	137
Not completed	1	3
Consent withdrawn by subject	-	1
Lost to follow-up	1	-
Treatment noncompliant	-	1
Protocol deviation	-	1

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: 282 subjects were treated in the Randomized Withdrawal Period, and 278 subjects completed the Randomized Withdrawal Period.

Baseline characteristics

Reporting groups	
Reporting group title	Open-label period

Reporting group description: -

Reporting group values	Open-label period	Total	
Number of subjects	643	643	
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)	547	547	
From 65-84 years	96	96	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	49.31		
standard deviation	± 14.155	-	
Gender categorical Units: Subjects			
Female	306	306	
Male	337	337	

End points

End points reporting groups

Reporting group title	Combined JZP-110
Reporting group description:	
Subjects completed a 2-week titration phase. They then entered the maintenance phase of up to 50 weeks at the stable dose that was reached at the end of the Titration Phase.	
Reporting group title	Placebo
Reporting group description:	
Placebo administered orally, QD, for the 2-week randomized withdrawal period.	
Reporting group title	JZP-110
Reporting group description:	
JZP-110 administered orally, QD, for the 2-week randomized withdrawal period, at the same dose subjects were currently receiving.	

Primary: Change in Epworth Sleepiness Scale (ESS) Score

End point title	Change in Epworth Sleepiness Scale (ESS) Score
End point description:	
Change in ESS score during the 2-week randomized withdrawal period. The beginning of the randomized withdrawal period represents efficacy baseline. A negative change from baseline represents improvement in excessive sleepiness.	
End point type	Primary
End point timeframe:	
Start of randomized withdrawal phase to end of randomized withdrawal (2 weeks)	

End point values	Placebo	JZP-110		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: points on a scale				
least squares mean (standard error)	5.3 (± 0.41)	1.6 (± 0.41)		

Statistical analyses

Statistical analysis title	Change in ESS Score
Statistical analysis description:	
JZP-110 v. Placebo: <0.0001	
Comparison groups	Placebo v JZP-110
Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Secondary: Subjects Reported as Worse on the Patient Global Impression of Change (PGIc)

End point title	Subjects Reported as Worse on the Patient Global Impression of Change (PGIc)

End point description:

Percentage of subjects reported as worse (minimally worse, much worse, or very much worse) on the PGIc during the 2-week randomized withdrawal period. The beginning of the randomized withdrawal period represents efficacy baseline.

End point type	Secondary

End point timeframe:

Beginning of randomized withdrawal phase to end of the randomized withdrawal phase (2 weeks)

End point values	Placebo	JZP-110		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: percentage of subjects				
number (not applicable)	64.5	28.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects Reported as Worse on the Clinical Global Impression of Change (CGIc)

End point title	Subjects Reported as Worse on the Clinical Global Impression of Change (CGIc)

End point description:

Subjects reported as worse (very much worse, much worse, and minimally worse) on the CGIc during the 2-week randomized withdrawal period. The beginning of the randomized withdrawal period represents efficacy baseline.

End point type	Secondary

End point timeframe:

Beginning of randomized withdrawal phase to end of the randomized withdrawal phase (2 weeks)

End point values	Placebo	JZP-110		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: percentage of subjects				
number (not applicable)	63.8	28.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The Safety Population consisted of all subjects who received at least 1 dose of study medication. Adverse events are reported across the entire study (e.g., the open-label and randomized withdrawal periods combined).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Combined JZP-110

Reporting group description: -

Serious adverse events	Placebo	Combined JZP-110	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 142 (0.00%)	27 / 643 (4.20%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events		0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer stage I			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			

subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stillbirth			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
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			
Chest pain			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatomegaly			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 142 (0.00%)	2 / 643 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar I disorder			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, auditory			
subjects affected / exposed	0 / 142 (0.00%)	2 / 643 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	0 / 142 (0.00%)	2 / 643 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ear canal injury			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 142 (0.00%)	4 / 643 (0.62%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 142 (0.00%)	2 / 643 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cluster headache			
subjects affected / exposed	0 / 142 (0.00%)	2 / 643 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 142 (0.00%)	2 / 643 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			

subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 142 (0.00%)	1 / 643 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Combined JZP-110	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 142 (2.11%)	269 / 643 (41.84%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 142 (0.00%)	71 / 643 (11.04%)	
occurrences (all)	0	92	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	1 / 142 (0.70%)	57 / 643 (8.86%)	
occurrences (all)	1	68	
Dry mouth			
subjects affected / exposed	0 / 142 (0.00%)	47 / 643 (7.31%)	
occurrences (all)	0	55	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 142 (0.00%)	46 / 643 (7.15%)	
occurrences (all)	0	52	
Insomnia			
subjects affected / exposed	1 / 142 (0.70%)	51 / 643 (7.93%)	
occurrences (all)	1	68	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 142 (0.70%)	54 / 643 (8.40%)	
occurrences (all)	1	65	
Upper respiratory tract infection			
subjects affected / exposed	0 / 142 (0.00%)	32 / 643 (4.98%)	
occurrences (all)	0	39	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 142 (0.00%)	32 / 643 (4.98%)	
occurrences (all)	0	33	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2015	This amendment made changes to clarify enrollment criteria.
11 September 2015	This amendment made changes to clarify enrollment criteria.
02 February 2016	This amendment added the randomized withdrawal period, along with additional study procedures and data analyses as a result of this period, and also increased the maximum enrollment. Changes to clarify the enrollment criteria were also made.
17 November 2016	This amendment was made to clarify the number of subjects to be randomized into the randomized withdrawal period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported