Clinical trial results:
A Six-Week, Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Safety and Efficacy of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Obstructive Sleep Apnea (OSA)

Summary

EudraCT number	2014-005515-16
Trial protocol	FI SE
Global end of trial date	11 November 2016

Results information

Result version number	v1 (current)
This version publication date	15 December 2017
First version publication date	15 December 2017

Trial information

Trial identification

Sponsor protocol code	14-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02348619
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 2158323750,
Scientific contact	Clinical Trial Disclosure & Transparency, Jazz Pharmaceuticals Inc., 001 2158323750,

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	25 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of JZP-110 administered once daily compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.

Protection of trial subjects:

The following measures were repeatedly assessed throughout the course of the study to monitor subject safety: (1) Assessment of adverse events and serious adverse events, (2) clinical laboratory tests, (3) medical history, (4) full review of body system through physical examination, (5) vital signs assessment, (6) polysomnography, and (7) administration of the columbia-suicide severity rating scale.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 May 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Finland: 18
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	United States: 141
Worldwide total number of subjects	174
EEA total number of subjects	33

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)	140
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The Screening phase involved a standard medical screening visit. Following screening, subjects entered the Titration phase.

Period 1

Period 1 title	Titration Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	JZP-110

Arm description: -

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:

Start at 75 mg, titrate up to 150 or 300 mg, or down at any time.

Number of subjects in period 1	JZP-110
Started	174
Completed	157
Not completed	17
Consent withdrawn by subject	1
Adverse event, non-fatal	6
Other	7
Lost to follow-up	1
Treatment noncompliant	1
Protocol deviation	1

Period 2	
Period 2 title	Stable-Dose Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	JZP-110
Arm description: -	
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:

Subjects who were titrated to an efficacious and tolerable dose in the Titration phase remained on the same dose regimen in the Stable-Dose phase.

Number of subjects in period 2	JZP-110
Started	157
Completed	124
Not completed	33
Consent withdrawn by subject	4
Other	2
Randomization criteria not met	21
Lost to follow-up	3
Sponsor decision	1
Protocol deviation	1
Lack of efficacy	1

Period 3	
Period 3 title	Double-Blind Withdrawal Phase
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	Placebo
Arm description: -	
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:

Subjects in the Double-Blind Withdrawal phase who did not receive JZP-110 received placebo for 2 weeks.

Arm title	JZP-110
Arm description: -	
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:

Subjects who received JZP-110 in the Double-Blind Withdrawal phase received the same dose as received in the Stable-Dose phase.

Number of subjects in period 3	Placebo	JZP-110
Started	62	62
Completed	62	60
Not completed	0	2
Consent withdrawn by subject	-	1
Randomization criteria not met	-	1

Baseline characteristics

Reporting groups

Reporting group title	Titration Phase

Reporting group description: -

Reporting group values	Titration Phase	Total	
Number of subjects	174	174	
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)	140	140	
From 65-84 years	34	34	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	54.8		
standard deviation	± 10.5	-	
Gender categorical Units: Subjects			
Female	67	67	
Male	107	107	

End points

End points reporting groups	
Reporting group title	JZP-110
Reporting group description: -	
Reporting group title	JZP-110
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	JZP-110
Reporting group description: -	

Primary: Change in the Maintenance of Wakefulness Test (MWT)	
End point title	Change in the Maintenance of Wakefulness Test (MWT)
End point description: Change in the mean sleep latency time as determined from the first four trials of a 40-minute MWT from the end of the Stable Dose Phase to the end of the Double-blind Withdrawal Phase.	
End point type	Primary
End point timeframe: Week 4 to Week 6	

End point values	Placebo	JZP-110		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	60		
Units: minutes				
least squares mean (standard error)	-12.11 (± 1.326)	-0.96 (± 1.350)		

Statistical analyses

Statistical analysis title	Change in the MWT
Comparison groups	JZP-110 v Placebo
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Primary: Change in the Epworth Sleepiness Scale (ESS)	
End point title	Change in the Epworth Sleepiness Scale (ESS)

End point description:

Change in ESS score from the end of the Stable Dose Phase to the end of the Double-blind Withdrawal phase.

End point type	Primary

End point timeframe:

Week 4 to Week 6

End point values	Placebo	JZP-110		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	60		
Units: points on a scale				
least squares mean (standard error)	4.5 (± 0.71)	-0.1 (± 0.73)		

Statistical analyses

Statistical analysis title	Change in the ESS
Comparison groups	Placebo v JZP-110
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Secondary: Patient Global Impression of Change (PGIc)

End point title	Patient Global Impression of Change (PGIc)

End point description:

Percentage of subjects reported as worse (minimally, much, or very much) on the PGIc at the end of the Double-blind Withdrawal Phase.

End point type	Secondary

End point timeframe:

Week 4 to Week 6

End point values	Placebo	JZP-110		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	60		
Units: percentage of subjects				
number (not applicable)	50	20		

Statistical analyses

Statistical analysis title	PGIc
Comparison groups	Placebo v JZP-110
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	Chi-squared

Secondary: Clinical Global Impression of Change (CGIc)

End point title	Clinical Global Impression of Change (CGIc)
End point description:	
Percentage of subjects reported as worse (minimally, much, and very much) on the CGIc at the end of the Double-blind Withdrawal Phase.	
End point type	Secondary
End point timeframe:	
Week 4 to Week 6	

End point values	Placebo	JZP-110		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	60		
Units: percentage of subjects				
number (not applicable)	59	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Functional Outcomes of Sleep Questionnaire (FOSQ-10)

End point title	Change in Functional Outcomes of Sleep Questionnaire (FOSQ-10)
End point description:	
Change is total score from the end of the stable dose phase to the end of the double blind withdrawal phase.	
End point type	Secondary
End point timeframe:	
Week 4 to Week 6	

End point values	Placebo	JZP-110		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	60		
Units: points				
least squares mean (standard error)	-1.31 (± 0.381)	-0.15 (± 0.393)		

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 phases.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Placebo (randomized withdrawal)
Reporting group description:	
During the randomized withdrawal phase only	
Reporting group title	JZP-110 (entire study)
Reporting group description:	
Across the entire study	

Serious adverse events	Placebo (randomized withdrawal)	JZP-110 (entire study)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)	0 / 174 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Placebo (randomized withdrawal)	JZP-110 (entire study)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)	58 / 174 (33.33%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 62 (0.00%)	9 / 174 (5.17%)	
occurrences (all)	0	9	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 62 (0.00%)	20 / 174 (11.49%)	
occurrences (all)	0	27	
Dizziness			

subjects affected / exposed	0 / 62 (0.00%)	14 / 174 (8.05%)	
occurrences (all)	0	14	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	0 / 62 (0.00%)	13 / 174 (7.47%)	
occurrences (all)	0	16	
Nausea			
subjects affected / exposed	0 / 62 (0.00%)	13 / 174 (7.47%)	
occurrences (all)	0	14	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 62 (0.00%)	11 / 174 (6.32%)	
occurrences (all)	0	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2015	This amendment made changes to the inclusion/exclusion criteria.
09 February 2016	This amendment was made to further support enrollment of a representative patient sample and clarify enrollment criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported