



Clinical trial results:

A Twelve-week, Double-blind, Placebo-controlled, Randomized, Parallel-group, 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 Narcolepsy

Summary

EudraCT number	2014-005487-15
Trial protocol	DE FI NL FR IT
Global end of trial date	14 February 2017

Results information

Result version number	v1 (current)
This version publication date	02 March 2018
First version publication date	02 March 2018

Trial information

Trial identification

Sponsor protocol code	14-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02348593
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Jazz Pharmaceuticals
Sponsor organisation address	3180 Porter Drive, Palo Alto, United States,
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	13 April 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 February 2017
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 for up to 12 weeks in doses of 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with narcolepsy.

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, 24-hour ABPM, 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	19 May 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	40 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	United States: 172
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 20
Worldwide total number of subjects	236
EEA total number of subjects	44

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)	227
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Note: 239 subjects were randomized. Of these, 236 subjects received at least 1 dose of study medication and comprised the Safety Population. The remaining 3 subjects were randomized in error, did not receive study medication, and were excluded from the Safety Population.

Pre-assignment

Screening details:

After successful completion of the Screening and Baseline visits, subjects were randomized in a stratified manner on the basis of the presence or absence of cataplexy and assigned in a 1:1:1:1 ratio to receive 75, 150, or 300 mg JZP-110 or placebo QD over a 12-week Treatment Phase.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo condition.

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 12 week treatment phase.

Arm title	75 mg JZP-110
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Arm description:

75 mg JZP-110

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:

75 mg JZP-110 administered orally, QD, for the 12-week treatment phase.

Arm title	150 mg JZP-110
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Arm description:

150 mg JZP-110

Arm type	Experimental
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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 randomized to receive 150 mg JZP-110 initially received 75 mg JZP-110 from Day 1 through Day 3 of the Treatment Phase and then received 150 mg JZP-110 starting on Day 4, administered orally, QD.

Arm title	300 mg JZP-110
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Arm description:

300 mg JZP-110

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 randomized to receive 300 mg JZP-110 initially received 150 mg JZP-110 from Day 1 through Day 3 of the Treatment Phase, and received 300 mg JZP-110 starting on Day 4, administered orally, QD.

Number of subjects in period 1	Placebo	75 mg JZP-110	150 mg JZP-110
Started	59	59	59
Completed	52	49	51
Not completed	7	10	8
Consent withdrawn by subject	1	1	1
Adverse event, non-fatal	1	2	4
Sponsor Decision	1	-	-
Other reasons	2	2	1
Lost to follow-up	1	1	-
Lack of efficacy	1	4	1
Protocol deviation	-	-	1

Number of subjects in period 1	300 mg JZP-110
Started	59
Completed	43
Not completed	16
Consent withdrawn by subject	2
Adverse event, non-fatal	5
Sponsor Decision	-
Other reasons	2
Lost to follow-up	-

Lack of efficacy	6
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Placebo condition.	
Reporting group title	75 mg JZP-110
Reporting group description: 75 mg JZP-110	
Reporting group title	150 mg JZP-110
Reporting group description: 150 mg JZP-110	
Reporting group title	300 mg JZP-110
Reporting group description: 300 mg JZP-110	

Reporting group values	Placebo	75 mg JZP-110	150 mg JZP-110
Number of subjects	59	59	59
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	36.0 ± 15.17	36.5 ± 12.78	38.1 ± 13.00
Gender categorical Units: Subjects			
Female	35	37	42
Male	24	22	17

Reporting group values	300 mg JZP-110	Total	
Number of subjects	59	236	
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	34.3 ± 11.51	-	
Gender categorical Units: Subjects			
Female	40	154	
Male	19	82	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo condition.	
Reporting group title	75 mg JZP-110
Reporting group description: 75 mg JZP-110	
Reporting group title	150 mg JZP-110
Reporting group description: 150 mg JZP-110	
Reporting group title	300 mg JZP-110
Reporting group description: 300 mg JZP-110	

Primary: Change in Maintenance of Wakefulness Test (MWT) from Baseline to Week 12

End point title	Change in Maintenance of Wakefulness Test (MWT) from Baseline to Week 12
End point description: Change in mean sleep latency time (in minutes) as determined from the first 4 trials of a 40-minute MWT from baseline to Week 12.	
End point type	Primary
End point timeframe: Baseline to Week 12	

End point values	Placebo	75 mg JZP-110	150 mg JZP-110	300 mg JZP-110
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	59	55	59
Units: minutes				
least squares mean (standard error)	2.12 (± 1.289)	4.74 (± 1.335)	9.77 (± 1.327)	12.27 (± 1.389)

Statistical analyses

Statistical analysis title	Change in the MWT
Statistical analysis description: A hierarchical testing procedure was used to make the following comparisons: JZP-110 300 mg vs. Placebo: p <0.0001 JZP-110 150 mg vs. Placebo: p <0.0001 JZP-110 75 mg vs. Placebo: p =0.1595	
Comparison groups	75 mg JZP-110 v 150 mg JZP-110 v 300 mg JZP-110 v Placebo

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	MMRM

Primary: Change in ESS Score from Baseline to Week 12

End point title	Change in ESS Score from Baseline to Week 12
End point description: Change in ESS score from Baseline to Week 12. A negative change from baseline represents improvement in excessive sleepiness.	
End point type	Primary
End point timeframe: Baseline to Week 12	

End point values	Placebo	75 mg JZP-110	150 mg JZP-110	300 mg JZP-110
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	59	55	59
Units: points on a scale				
least squares mean (standard error)	-1.6 (± 0.65)	-3.8 (± 0.67)	-5.4 (± 0.66)	-6.4 (± 0.68)

Statistical analyses

Statistical analysis title	Change in the ESS
Statistical analysis description: A hierarchical testing procedure was used to make the following comparisons: JZP-110 300 mg vs. Placebo: p <0.0001 JZP-110 150 mg vs. Placebo: p <0.0001 JZP-110 75 mg vs. Placebo: p =0.0211	
Comparison groups	150 mg JZP-110 v 300 mg JZP-110 v 75 mg JZP-110 v Placebo
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	MMRM

Secondary: Subjects Reported Improved on the Patient Global Impression of Change (PGIc) at Week 12

End point title	Subjects Reported Improved on the Patient Global Impression of Change (PGIc) at Week 12
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End point description:

Percentage of subjects reported as improved (minimally, much, or very much) on the PGIC at Week 12.

This is the key secondary endpoint.

End point type	Secondary
End point timeframe:	
Baseline to Week 12.	

End point values	Placebo	75 mg JZP-110	150 mg JZP-110	300 mg JZP-110
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	59	55	59
Units: percentage of subjects				
number (not applicable)	39.7	67.8	78.2	84.7

Statistical analyses

Statistical analysis title	PGIC: Subjects Reported Improved at Week 12
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Statistical analysis description:

A hierarchical testing procedure was used to make the following comparisons:

JZP-110 300 mg vs. Placebo: $p < 0.0001$

JZP-110 150 mg vs. Placebo: $p < 0.0001$

JZP-110 75 mg vs. Placebo: $p = 0.0023$

Comparison groups	300 mg JZP-110 v 75 mg JZP-110 v 150 mg JZP-110 v Placebo
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared

Secondary: Change in Sleep Latency Time on each of the 5 MWT Trials at Week 12

End point title	Change in Sleep Latency Time on each of the 5 MWT Trials at Week 12
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End point description:

Time course of efficacy in MWT: Change in sleep latency (in minutes) on each of the 5 MWT trials at Week 12.

End point type	Secondary
End point timeframe:	
Week 12	

End point values	Placebo	75 mg JZP-110	150 mg JZP-110	300 mg JZP-110
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	59	55	59
Units: minutes				
least squares mean (standard error)				
Trial 1	-0.55 (\pm 1.658)	3.27 (\pm 1.725)	9.87 (\pm 1.713)	9.91 (\pm 1.841)
Trial 2	1.41 (\pm 1.638)	5.70 (\pm 1.697)	9.46 (\pm 1.674)	14.50 (\pm 1.835)
Trial 3	3.79 (\pm 1.799)	6.35 (\pm 1.908)	11.31 (\pm 1.859)	13.99 (\pm 1.996)
Trial 4	2.33 (\pm 1.579)	3.77 (\pm 1.663)	9.77 (\pm 1.606)	13.50 (\pm 1.734)
Trial 5	3.09 (\pm 1.808)	3.92 (\pm 1.928)	9.25 (\pm 1.888)	12.20 (\pm 1.969)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Mean Sleep Latency Time as Determined From the First 4 Trials of a 40-Minute MWT from Baseline to Week 4

End point title	Change in the Mean Sleep Latency Time as Determined From the First 4 Trials of a 40-Minute MWT from Baseline to Week 4
End point description:	Change in mean sleep latency time (in minutes) as determined from the first 4 trials of a 40-minute MWT from Baseline to Week 4.
End point type	Secondary
End point timeframe:	Baseline to Week 4

End point values	Placebo	75 mg JZP-110	150 mg JZP-110	300 mg JZP-110
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	59	55	59
Units: minutes				
least squares mean (standard error)	2.16 (\pm 1.202)	4.67 (\pm 1.223)	9.15 (\pm 1.246)	13.07 (\pm 1.211)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ESS score from Baseline to Weeks 1, 4, and 8

End point title	Change in ESS score from Baseline to Weeks 1, 4, and 8
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End point description:

Change in ESS Score from Baseline to Weeks 1, 4, and 8.

End point type	Secondary
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End point timeframe:

Baseline to Weeks 1, 4, and 8

End point values	Placebo	75 mg JZP-110	150 mg JZP-110	300 mg JZP-110
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	59	55	59
Units: points on a scale				
least squares mean (standard error)				
Week 1	-2.7 (± 0.60)	-3.2 (± 0.60)	-5.5 (± 0.62)	-6.7 (± 0.60)
Week 4	-2.2 (± 0.59)	-3.3 (± 0.59)	-5.6 (± 0.60)	-5.6 (± 0.59)
Week 8	-2.1 (± 0.63)	-3.4 (± 0.64)	-5.2 (± 0.64)	-6.4 (± 0.65)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reported as Improved on the PGIC at Weeks 1, 4, and 8

End point title	Percentage of Subjects Reported as Improved on the PGIC at Weeks 1, 4, and 8
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End point description:

Percentage of subjects reported as improved (minimally, much, very much improved) on the PGIC at Weeks 1, 4, and 8.

End point type	Secondary
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End point timeframe:

Weeks 1, 4, and 8

End point values	Placebo	75 mg JZP-110	150 mg JZP-110	300 mg JZP-110
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	59	55	59
Units: percentage of subjects				
number (not applicable)				
Week 1	53.4	71.2	84.9	84.7
Week 4	53.4	71.2	89.1	88.1
Week 8	44.8	66.1	83.6	88.1

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reported as Improved on the CGIc at Week 1, Week 4, and Week 8

End point title	Percentage of Subjects Reported as Improved on the CGIc at Week 1, Week 4, and Week 8
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End point description:

Percentage of subjects reported as improved (minimally, much, very much) on the CGIc at Weeks 1, 4, and 8.

End point type	Secondary
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End point timeframe:

Weeks 1, 4, and 8

End point values	Placebo	75 mg JZP-110	150 mg JZP-110	300 mg JZP-110
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	59	55	59
Units: percentage of subjects				
number (not applicable)				
Week 1	50.0	67.8	81.8	88.1
Week 4	55.2	67.8	90.9	89.8
Week 8	48.3	66.1	90.9	89.8

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reported as Improved on the CGIc at Week 12

End point title	Percentage of Subjects Reported as Improved on the CGIc at Week 12
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End point description:

Percentage of subjects reported as improved (minimally, much, very much) in CGIc at Week 12.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Placebo	75 mg JZP-110	150 mg JZP-110	300 mg JZP-110
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	59	55	59
Units: percentage of subjects				
number (not applicable)	41.4	69.5	83.6	83.1

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.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	75 mg JZP-110
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Reporting group description: -

Reporting group title	150 mg JZP-110
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Reporting group description: -

Reporting group title	300 mg JZP-110
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Reporting group description: -

Serious adverse events	Placebo	75 mg JZP-110	150 mg JZP-110
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 59 (1.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	300 mg JZP-110		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 59 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from	0		

adverse events			
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	75 mg JZP-110	150 mg JZP-110
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 59 (28.81%)	19 / 59 (32.20%)	32 / 59 (54.24%)
Investigations			
Weight decreased			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	1 / 59 (1.69%)
occurrences (all)	0	1	1
Heart rate increased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	3 / 59 (5.08%)	2 / 59 (3.39%)	0 / 59 (0.00%)
occurrences (all)	3	2	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 59 (5.08%)	6 / 59 (10.17%)	14 / 59 (23.73%)
occurrences (all)	3	9	19
Dizziness			
subjects affected / exposed	2 / 59 (3.39%)	2 / 59 (3.39%)	1 / 59 (1.69%)
occurrences (all)	2	2	1
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	0 / 59 (0.00%) 0	0 / 59 (0.00%) 0	2 / 59 (3.39%) 2
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 1	3 / 59 (5.08%) 4	6 / 59 (10.17%) 8
Dry mouth subjects affected / exposed occurrences (all)	2 / 59 (3.39%) 2	3 / 59 (5.08%) 4	4 / 59 (6.78%) 4
Diarrhoea subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 1	2 / 59 (3.39%) 2	3 / 59 (5.08%) 3
Dyspepsia subjects affected / exposed occurrences (all)	0 / 59 (0.00%) 0	1 / 59 (1.69%) 1	2 / 59 (3.39%) 2
Constipation subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 1	3 / 59 (5.08%) 3	1 / 59 (1.69%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 1	1 / 59 (1.69%) 1	3 / 59 (5.08%) 3
Insomnia subjects affected / exposed occurrences (all)	0 / 59 (0.00%) 0	2 / 59 (3.39%) 2	0 / 59 (0.00%) 0
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	5 / 59 (8.47%) 6	8 / 59 (13.56%) 8
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 1	1 / 59 (1.69%) 1	4 / 59 (6.78%) 4
Influenza subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	2 / 59 (3.39%) 2	1 / 59 (1.69%) 1
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 1	5 / 59 (8.47%) 5	5 / 59 (8.47%) 7
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Non-serious adverse events	300 mg JZP-110		
Total subjects affected by non-serious adverse events subjects affected / exposed	36 / 59 (61.02%)		
Investigations Weight decreased subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3		
Heart rate increased subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4		
Weight increased subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	18 / 59 (30.51%) 26		
Dizziness subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 4		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	6 / 59 (10.17%) 15		
Dry mouth subjects affected / exposed occurrences (all)	6 / 59 (10.17%) 6		
Diarrhoea			

subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3		
Dyspepsia subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 4		
Constipation subjects affected / exposed occurrences (all)	0 / 59 (0.00%) 0		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	5 / 59 (8.47%) 5		
Insomnia subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 59 (0.00%) 0		
Influenza subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	9 / 59 (15.25%) 9		

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 the eligibility criteria.
10 September 2015	This amendment made changes to the eligibility criteria.
08 February 2016	This amendment was made to further support enrollment of a representative patient sample, to clarify enrollment criteria, and to incorporate feedback from FDA about proposed statistical analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported