# 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 | Efficacy, Safety |
| 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<br>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<br>Units: years | | | |
| arithmetic mean | 54.8 | | |
| standard deviation | ± 10.5 | - | |
| Gender categorical<br>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:<br>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:<br>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