



## Clinical trial results:

### A Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of Xyrem with an Open-Label Pharmacokinetic Evaluation and Safety Extension in Pediatric Subjects with Narcolepsy with Cataplexy

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2014-001389-93  |
| Trial protocol           | FI NL IT FR     |
| Global end of trial date | 25 January 2019 |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 16 August 2019 |
| First version publication date | 16 August 2019 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 13-005 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02221869 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                             |
|------------------------------|---------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Jazz Pharmaceuticals                                                                        |
| Sponsor organisation address | 3170 Porter Drive, Palo Alto, United States,                                                |
| Public contact               | Grace Wang, Senior Director, Jazz Pharmaceuticals, +1 6504962687, grace.wang@jazzpharma.com |
| Scientific contact           | Grace Wang, Senior Director, Jazz Pharmaceuticals, +1 6504962687, grace.wang@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? | Yes |

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Interim          |
| Date of interim/final analysis                       | 10 February 2017 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 25 January 2019  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

Primary objectives are:

- 1) To evaluate the efficacy of Xyrem (sodium oxybate) oral solution in the treatment of cataplexy in pediatric subjects with narcolepsy
- 2) To evaluate the safety of Xyrem in the treatment of cataplexy in pediatric subjects with narcolepsy for up to one year

Protection of trial subjects:

Safety was assessed by the incidence of TEAEs, and descriptively for vital signs, 12-lead ECG, PSG parameters, clinical laboratory results, and other assessments.

Background therapy: -

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 01 October 2014 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Netherlands: 8    |
| Country: Number of subjects enrolled | Finland: 1        |
| Country: Number of subjects enrolled | France: 10        |
| Country: Number of subjects enrolled | Italy: 25         |
| Country: Number of subjects enrolled | United States: 62 |
| Worldwide total number of subjects   | 106               |
| 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 months)  | 0  |
| Children (2-11 years)                     | 38 |

|                           |    |
|---------------------------|----|
| Adolescents (12-17 years) | 68 |
| Adults (18-64 years)      | 0  |
| From 65 to 84 years       | 0  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

106 subjects were enrolled. Xyrem-naïve subjects (n=74) entered the Dose Titration Period (3 to 10 weeks). Xyrem-naïve and on Xyrem subjects (n= 99) entered the Stable Dose Period (2 to 3 weeks). 96 subjects then entered the Double-Blind Randomized Withdrawal Period (2 weeks). 95 subjects then entered the Open-label Safety Period (38 to 47 weeks).

### Pre-assignment

Screening details:

Subjects aged 7-17 who were being treated with Xyrem or Xyrem naïve were eligible for the study. 63 subjects were randomized and 33 received open-label Xyrem during the Double-blind Treatment Period. 106 and 63 subjects comprised the Enrolled population and the Efficacy population respectively.

### Period 1

|                              |                                      |
|------------------------------|--------------------------------------|
| Period 1 title               | Double-blind Period (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                 |
| <b>Arm title</b>             | Randomized to Xyrem |

Arm description:

Active Xyrem continued as a double-blind treatment at the stable dose taken and regimen taken in the prior 2 weeks.

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

Dosage and administration details:

Active Xyrem continued as a double-blind treatment at the stable dose taken and regimen taken in the prior 2 weeks.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Randomized to Xyrem Placebo |
|------------------|-----------------------------|

Arm description:

Xyrem placebo was initiated as a double-blind treatment at a volume and regimen equivalent to the Xyrem dose taken in the prior 2 weeks.

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Xyrem Placebo     |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Oral solution     |
| Routes of administration               | Oral use          |

Dosage and administration details:

Xyrem placebo at a volume and regimen equivalent to the stable dose of Xyrem.

| Number of subjects in period<br>1 <sup>[1]</sup> | Randomized to<br>Xyrem | Randomized to<br>Xyrem Placebo |
|--------------------------------------------------|------------------------|--------------------------------|
|                                                  |                        |                                |
| Started                                          | 31                     | 32                             |
| Completed                                        | 30                     | 32                             |
| Not completed                                    | 1                      | 0                              |
| Other                                            | 1                      | -                              |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Subjects reported in the baseline period represent the randomized population in the Double-blind Treatment Period.

## Baseline characteristics

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Randomized to Xyrem |
|-----------------------|---------------------|

Reporting group description:

Active Xyrem continued as a double-blind treatment at the stable dose taken and regimen taken in the prior 2 weeks.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Randomized to Xyrem Placebo |
|-----------------------|-----------------------------|

Reporting group description:

Xyrem placebo was initiated as a double-blind treatment at a volume and regimen equivalent to the Xyrem dose taken in the prior 2 weeks.

| Reporting group values                             | Randomized to Xyrem | Randomized to Xyrem Placebo | Total |
|----------------------------------------------------|---------------------|-----------------------------|-------|
| Number of subjects                                 | 31                  | 32                          | 63    |
| Age categorical<br>Units: Subjects                 |                     |                             |       |
| In utero                                           | 0                   | 0                           | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                   | 0                           | 0     |
| Newborns (0-27 days)                               | 0                   | 0                           | 0     |
| Infants and toddlers (28 days-23 months)           | 0                   | 0                           | 0     |
| Children (2-11 years)                              | 12                  | 14                          | 26    |
| Adolescents (12-17 years)                          | 19                  | 18                          | 37    |
| Adults (18-64 years)                               | 0                   | 0                           | 0     |
| From 65-84 years                                   | 0                   | 0                           | 0     |
| 85 years and over                                  | 0                   | 0                           | 0     |
| Gender categorical<br>Units: Subjects              |                     |                             |       |
| Female                                             | 13                  | 15                          | 28    |
| Male                                               | 18                  | 17                          | 35    |

## End points

### End points reporting groups

|                                                                                                                                          |                             |
|------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Reporting group title                                                                                                                    | Randomized to Xyrem         |
| Reporting group description:                                                                                                             |                             |
| Active Xyrem continued as a double-blind treatment at the stable dose taken and regimen taken in the prior 2 weeks.                      |                             |
| Reporting group title                                                                                                                    | Randomized to Xyrem Placebo |
| Reporting group description:                                                                                                             |                             |
| Xyrem placebo was initiated as a double-blind treatment at a volume and regimen equivalent to the Xyrem dose taken in the prior 2 weeks. |                             |

### Primary: Change in Weekly Number of Cataplexy Attacks

|                                                                                                  |                                              |
|--------------------------------------------------------------------------------------------------|----------------------------------------------|
| End point title                                                                                  | Change in Weekly Number of Cataplexy Attacks |
| End point description:                                                                           |                                              |
| End point type                                                                                   | Primary                                      |
| End point timeframe:                                                                             |                                              |
| From the end of the Stable Dose Period to the end of the Double-blind Treatment Period (2 weeks) |                                              |

| End point values                      | Randomized to Xyrem  | Randomized to Xyrem Placebo |  |  |
|---------------------------------------|----------------------|-----------------------------|--|--|
| Subject group type                    | Reporting group      | Reporting group             |  |  |
| Number of subjects analysed           | 31                   | 32                          |  |  |
| Units: number of attacks              |                      |                             |  |  |
| median (inter-quartile range (Q1-Q3)) | 0.27 (-1.00 to 2.50) | 12.71 (3.44 to 19.77)       |  |  |

### Statistical analyses

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Statistical analysis title              | Change in Weekly Number of Cataplexy Attacks      |
| Comparison groups                       | Randomized to Xyrem Placebo v Randomized to Xyrem |
| Number of subjects included in analysis | 63                                                |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | superiority                                       |
| P-value                                 | < 0.0001                                          |
| Method                                  | ANCOVA                                            |

### Secondary: Clinical Global Impression of Change (CGIc) for Cataplexy Severity

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Clinical Global Impression of Change (CGIc) for Cataplexy Severity |
|-----------------|--------------------------------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the end of the Stable Dose Period to the end of the Double-blind Treatment Period (2 weeks)

| End point values                     | Randomized to<br>Xyrem | Randomized to<br>Xyrem Placebo |  |  |
|--------------------------------------|------------------------|--------------------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group                |  |  |
| Number of subjects analysed          | 29                     | 32                             |  |  |
| Units: score on a scale              |                        |                                |  |  |
| arithmetic mean (standard deviation) | -0.4 (± 1.12)          | -1.5 (± 1.19)                  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the Epworth Sleepiness Scale (ESS) (CHAD) Score

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| End point title | Change in the Epworth Sleepiness Scale (ESS) (CHAD) Score |
|-----------------|-----------------------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the end of the Stable Dose Period to the end of the Double-blind Treatment Period (2 weeks)

| End point values                      | Randomized to<br>Xyrem | Randomized to<br>Xyrem Placebo |  |  |
|---------------------------------------|------------------------|--------------------------------|--|--|
| Subject group type                    | Reporting group        | Reporting group                |  |  |
| Number of subjects analysed           | 30                     | 31                             |  |  |
| Units: score on a scale               |                        |                                |  |  |
| median (inter-quartile range (Q1-Q3)) | 0.0 (-1.0 to 2.0)      | 3.0 (1.0 to 5.0)               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: CGIc for Narcolepsy Overall

|                 |                             |
|-----------------|-----------------------------|
| End point title | CGIc for Narcolepsy Overall |
|-----------------|-----------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|



End point timeframe:

From the end of the Stable Dose Period to the end of the Double-blind Treatment Period (2 weeks)

| End point values                     | Randomized to<br>Xyrem | Randomized to<br>Xyrem Placebo |  |  |
|--------------------------------------|------------------------|--------------------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group                |  |  |
| Number of subjects analysed          | 29                     | 32                             |  |  |
| Units: score on a scale              |                        |                                |  |  |
| arithmetic mean (standard deviation) | -0.4 ( $\pm$ 0.95)     | -1.4 ( $\pm$ 1.13)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Quality of Life (QoL; SF-10 Physical and Psychosocial Summary Score) From the End of the Stable Dose Period to the End of the Double-blind Treatment Period

|                 |                                                                                                                                                                       |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change in Quality of Life (QoL; SF-10 Physical and Psychosocial Summary Score) From the End of the Stable Dose Period to the End of the Double-blind Treatment Period |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the end of the Stable Dose Period to the end of the Double-blind Treatment Period (2 weeks)

| End point values                      | Randomized to<br>Xyrem | Randomized to<br>Xyrem Placebo |  |  |
|---------------------------------------|------------------------|--------------------------------|--|--|
| Subject group type                    | Reporting group        | Reporting group                |  |  |
| Number of subjects analysed           | 30                     | 30                             |  |  |
| Units: score on a scale               |                        |                                |  |  |
| median (inter-quartile range (Q1-Q3)) |                        |                                |  |  |
| SF-10 Physical Summary Score          | 0 (-2.73 to 2.50)      | 0 (-8.42 to 2.73)              |  |  |
| SF-10 Psychosocial Summary Score      | 0 (-6.24 to 2.68)      | -2.67 (-8.02 to 2.67)          |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Safety data are provided through the 120 day update (30 April 2018)

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Safety Population |
|-----------------------|-------------------|

Reporting group description:

Safety population who took study drug

| Serious adverse events                            | Safety Population |  |  |
|---------------------------------------------------|-------------------|--|--|
| Total subjects affected by serious adverse events |                   |  |  |
| subjects affected / exposed                       | 2 / 104 (1.92%)   |  |  |
| number of deaths (all causes)                     | 0                 |  |  |
| number of deaths resulting from adverse events    | 0                 |  |  |
| Psychiatric disorders                             |                   |  |  |
| Acute psychosis                                   |                   |  |  |
| subjects affected / exposed                       | 1 / 104 (0.96%)   |  |  |
| occurrences causally related to treatment / all   | 1 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |
| Suicidal ideation                                 |                   |  |  |
| subjects affected / exposed                       | 1 / 104 (0.96%)   |  |  |
| occurrences causally related to treatment / all   | 1 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |

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

| Non-serious adverse events                            | Safety Population |  |  |
|-------------------------------------------------------|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 74 / 104 (71.15%) |  |  |
| Investigations                                        |                   |  |  |
| Weight decreased                                      |                   |  |  |
| subjects affected / exposed                           | 12 / 104 (11.54%) |  |  |
| occurrences (all)                                     | 12                |  |  |

|                                    |                   |  |  |
|------------------------------------|-------------------|--|--|
| Nervous system disorders           |                   |  |  |
| Dizziness                          |                   |  |  |
| subjects affected / exposed        | 6 / 104 (5.77%)   |  |  |
| occurrences (all)                  | 8                 |  |  |
| Headache                           |                   |  |  |
| subjects affected / exposed        | 17 / 104 (16.35%) |  |  |
| occurrences (all)                  | 18                |  |  |
| Gastrointestinal disorders         |                   |  |  |
| Nausea                             |                   |  |  |
| subjects affected / exposed        | 18 / 104 (17.31%) |  |  |
| occurrences (all)                  | 20                |  |  |
| Vomiting                           |                   |  |  |
| subjects affected / exposed        | 17 / 104 (16.35%) |  |  |
| occurrences (all)                  | 19                |  |  |
| Renal and urinary disorders        |                   |  |  |
| Enuresis                           |                   |  |  |
| subjects affected / exposed        | 19 / 104 (18.27%) |  |  |
| occurrences (all)                  | 20                |  |  |
| Infections and infestations        |                   |  |  |
| Nasopharyngitis                    |                   |  |  |
| subjects affected / exposed        | 7 / 104 (6.73%)   |  |  |
| occurrences (all)                  | 9                 |  |  |
| Upper respiratory tract infection  |                   |  |  |
| subjects affected / exposed        | 5 / 104 (4.81%)   |  |  |
| occurrences (all)                  | 9                 |  |  |
| Metabolism and nutrition disorders |                   |  |  |
| Decreased appetite                 |                   |  |  |
| subjects affected / exposed        | 8 / 104 (7.69%)   |  |  |
| occurrences (all)                  | 9                 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment                                                                     |
|----------------|-------------------------------------------------------------------------------|
| 29 August 2014 | Modified Exclusion Criteria.                                                  |
| 01 April 2015  | Modified Inclusion Criteria and certain study procedures.                     |
| 05 August 2015 | Modified Inclusion and Exclusion Criteria. Modified certain study procedures. |
| 05 April 2016  | Modified Exclusion Criteria. Modified certain study procedures.               |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported