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
Arm title	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.

Arm title	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 1[1]	Randomized to Xyrem	Randomized to Xyrem Placebo
Started	31	32
Completed	30	32
Not completed	1	0
Other	1	-

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 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 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 Xyrem	Randomized to 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 Xyrem	Randomized to 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 Xyrem	Randomized to 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 (± 0.95)	-1.4 (± 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 Xyrem	Randomized to 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 occurrences (all) Headache subjects affected / exposed occurrences (all)	 6 / 104 (5.77%) 8 17 / 104 (16.35%) 18		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 18 / 104 (17.31%) 20 17 / 104 (16.35%) 19		
Renal and urinary disorders Enuresis subjects affected / exposed occurrences (all)	 19 / 104 (18.27%) 20		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 7 / 104 (6.73%) 9 5 / 104 (4.81%) 9		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 8 / 104 (7.69%) 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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported