Clinical trial results:
A Randomized, Double-Blind, Placebo Controlled Trial Examining the Safety and Efficacy of Midazolam Intranasal Spray (USL261) for the Treatment of Intermittent Bouts of Increased Seizure Activity in the Epilepsy Monitoring Unit (EMU)

Summary

EudraCT number	2014-003961-49
Trial protocol	BE CZ IT DE ES AT LT
Global end of trial date	26 August 2015

Results information

Result version number	v1 (current)
This version publication date	19 January 2019
First version publication date	19 January 2019

Trial information

Trial identification

Sponsor protocol code	P261-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01999777
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Proximagen, LLC
Sponsor organisation address	505 North Highway 169, Plymouth, MN , United States, 55441
Public contact	David Sequeira, Proximagen, LLC, +1 9526587437, dsequeira@proximagen.com
Scientific contact	David Sequeira, Proximagen, LLC, +1 9526587437, dsequeira@proximagen.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study objective was to evaluate the efficacy, safety, and tolerability of USL261 compared with that of Intranasal (IN) placebo for the treatment of intermittent bouts of increased seizure activity.

Protection of trial subjects:

Prior to the initiation of the clinical study, the protocol, consent form, assent form and advertisements for the recruitment of subjects were reviewed and approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of the participating study center in the relevant country in accordance with current Good Clinical Practices (GCP) and all applicable regulatory requirements. This clinical study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, 1964, and with adherence to the principles of GCP, outlined by the International Conference on Harmonisation's GCP Guidelines, effective 1997. An IRB/IEC-approved written informed consent was obtained from each subject or legally acceptable representative (LAR) and the subject's caregiver prior to the initiation of any subject-specific procedures.

Background therapy:

Background therapy was permitted, but changes were not allowed during the treatment period.

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 November 2013
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	Spain: 7
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Lithuania: 5
Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	62
EEA total number of subjects	18

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)	4
Adults (18-64 years)	58
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter trial was conducted at 61 trial sites in the following 10 countries: Australia, Austria, Belgium, Czech Republic, France, Germany, Italy, Lithuania, Spain and the United States of America (USA). This includes sites/countries that may have screened a subject(s) but had no subjects who were enrolled.

Pre-assignment

Screening details:

Eligible subjects entered Pretreatment Observation during which they were monitored in Epilepsy monitoring unit (EMU) for seizure events. Only subjects who met entry criteria and presented with seizure events meeting the treatment decision criteria were eligible to enter the Treatment Phase.

Period 1

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

Blinding implementation details:

Drug supplies were labeled in a double-blind fashion with information including the protocol number, kit identification number, and instructions for use. The label did not specify whether the kit contained USL261 or placebo, and the investigator, study center staff, and subject did not know the identity of the randomized study drug.

Arms

Are arms mutually exclusive?	Yes
Arm title	USL261

Arm description:

Randomized subjects received a single dose of IN USL261 according to randomized assignment. A dose of USL261 (5 mg midazolam [MDZ]) was delivered with a single actuation of the unit dose pump.

Arm type	Experimental
Investigational medicinal product name	USL261
Investigational medicinal product code	USL261
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

A dose of USL261 (5 mg MDZ) was delivered with a single actuation of the unit dose pump.

Arm title	Placebo

Arm description:

Randomized subjects received single doses of IN placebo according to randomized assignment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	USL261
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

Matching placebo was administered.

Number of subjects in period 1	USL261	Placebo
Started	31	31
Completed	31	31

Baseline characteristics

Reporting groups	
Reporting group title	USL261
Reporting group description:	
Randomized subjects received a single dose of IN USL261 according to randomized assignment. A dose of USL261 (5 mg midazolam [MDZ]) was delivered with a single actuation of the unit dose pump.	
Reporting group title	Placebo
Reporting group description:	
Randomized subjects received single doses of IN placebo according to randomized assignment.	

Reporting group values	USL261	Placebo	Total
Number of subjects	31	31	62
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)	0	0	0
Adolescents (12-17 years)	2	2	4
Adults (18-64 years)	29	29	58
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	32.7	35.9	
standard deviation	± 12.94	± 13.56	-
Gender categorical			
Units: Subjects			
Female	18	21	39
Male	13	10	23
Race			
Units: Subjects			
White	26	27	53
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Black or African American	3	3	6
Native Hawaiian or other Pacific Islander	0	0	0
Other	2	0	2
Ethnicity			
Units: Subjects			
Hispanic or Latino	3	2	5
Non-Hispanic or Latino	28	29	57

End points

End points reporting groups

Reporting group title	USL261
Reporting group description:	
Randomized subjects received a single dose of IN USL261 according to randomized assignment. A dose of USL261 (5 mg midazolam [MDZ]) was delivered with a single actuation of the unit dose pump.	
Reporting group title	Placebo
Reporting group description:	
Randomized subjects received single doses of IN placebo according to randomized assignment.	

Primary: Number of subjects that were seizure-free

End point title	Number of subjects that were seizure-free
End point description:	
A subject was considered "seizure-free" if he or she completed the 6-hour Treatment Phase without any seizures recorded, premature discontinuation of study drug, rescue intervention for acute central respiratory depression adverse event (AE), and alteration to background anti-epileptic drug (AED) therapy; all criteria needed to be met to be considered seizure-free.	
End point type	Primary
End point timeframe:	
6 hours	

End point values	USL261	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	31		
Units: Subjects				
number (not applicable)	17	12		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Assumptions included that the proportion of seizures occurring within 6 hours after placebo administration was ~65% and a relative reduction of 50% would result in a reduction of ≥ 32.5 percentage points. Based on a 2-sided 95% confidence interval (CI) for the differences in proportions, a sample size of 62 analyzable subjects was chosen to detect a 0.35 difference between group. Sample size estimations were based on nQuery Version 7.0 using the table for CIs for differences in 2 proportions.	
Comparison groups	USL261 v Placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1972 [1]
Method	Wald asymptotic
Parameter estimate	Proportions
Point estimate	16.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	40.6

Notes:

[1] - The p-value was based on a standard Wald asymptotic test for equality without a continuity correction.

Secondary: Time to first seizure following treatment (TFSFT)

End point title	Time to first seizure following treatment (TFSFT)

End point description:

TFSFT was defined as the time from treatment with study drug to the onset of the next seizure, rescue intervention (for acute central respiratory depression AE) to maintain subject safety, alterations to background AED therapy, early termination, or 6 hours, whichever came first. An arbitrary value of '99999' indicates value was not estimable. Unable to estimate median in USL261 group as > 50% were seizure-free throughout the 6-hour treatment phase. No upper CI boundary as observations stopped at 6 hours.

End point type	Secondary

End point timeframe:

6 hours

End point values	USL261	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	31		
Units: Hours				
median (confidence interval 95%)	99999 (4.0 to 99999)	3.9 (1.8 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	USL261 v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1388
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent until up to 48 hours of completion of the Treatment Phase.

Adverse event reporting additional description:

Adverse events were collected from time informed consent until subject completion or early termination. Exit assessments were to be conducted within 48 hours of completion of the Treatment Phase (6 hours) and prior to discharge for the EMU. Treatment-Emergent Adverse Events have been presented in the following table.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	USL261

Reporting group description:

Randomized subjects received a single dose of IN USL261 according to randomized assignment. A dose of USL261 (5 mg MDZ) was delivered with a single actuation of the unit dose pump.

Reporting group title	Placebo

Reporting group description:

Randomized subjects received single doses of IN placebo according to randomized assignment.

Serious adverse events	USL261	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	USL261	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 31 (51.61%)	17 / 31 (54.84%)	
Injury, poisoning and procedural complications			
Tongue injury			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 31 (3.23%)	5 / 31 (16.13%)	
occurrences (all)	1	5	
Somnolence			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Product taste abnormal			
subjects affected / exposed	2 / 31 (6.45%)	6 / 31 (19.35%)	
occurrences (all)	2	6	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 31 (9.68%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Nasal discomfort			
subjects affected / exposed	5 / 31 (16.13%)	5 / 31 (16.13%)	
occurrences (all)	5	5	
Throat irritation			
subjects affected / exposed	3 / 31 (9.68%)	3 / 31 (9.68%)	
occurrences (all)	3	3	
Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2014	•The primary efficacy measure analysis was changed in 2 ways. •The sample size was changed from N = 48 to N = 62.•The secondary efficacy endpoint and analysis were clarified to state that the time to event data would be presented with Kaplan-Meier estimates of median and 2-sided 95% CI.•The exploratory efficacy variables and analysis were updated.•A statistical gatekeeping procedure was specified to control for multiplicity effects for Type 1 error across the primary and secondary efficacy outcomes.•Inclusion Criterion 4 was modified to remove the upper age restriction (previously </= 65 years of age). •Exclusion Criterion 4 was modified to exempt the requirement for a Urine drug screen (UDS) in individuals with cognitive disability that precluded the collection of a urine sample by conventional methods.•Exclusion Criterion 14 was modified to specify that exclusion (current or prior use of investigational device within 60 days of screening) did not apply to non-interventional devices. •The pharmacokinetic assessments were modified in 2 ways. •The analysis of clinical laboratory parameters was altered to no longer specify that urinalysis results would be described with summary statistics and shift tables. •The AE reporting timeframe was reduced from 30 days after administration of study drug to 7 days after administration of study drug.•The analysis of electrocardiogram results was changed to reflect that baseline parameters would not be presented. •The requirement for the UDS to be performed by the local laboratory was changed that if the local laboratory could not provide the results within a 24 hour period for any particular drug, a commercially available dipstick test kit that included the drug could be used for that particular drug.•Several mild and moderate inhibitors of cytochrome P450 3A4 metabolism were removed from the list of prohibited concomitant substances in Appendix 1. •The required washout period for fentanyl, morphine, and propofol were modified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported