Clinical trial results:
An Open-Label Safety Study of USL261 in the Outpatient Treatment of Subjects with Seizure Clusters

Summary

EudraCT number	2011-004109-25
Trial protocol	ES DE HU PL IT
Global end of trial date	22 February 2017

Results information

Result version number	v2 (current)
This version publication date	24 October 2019
First version publication date	21 September 2019
Version creation reason	• Correction of full data set Minor change: Change in End of trial date only

Trial information

Trial identification

Sponsor protocol code	P261-402

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01529034
WHO universal trial number (UTN)	-
Other trial identifiers	US IND Number: 77,421

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,, +1 952-658-7438, dsequeira@proximagen.com
Scientific contact	David Sequeira, Proximagen, LLC,, +1 952-658-7438, 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	31 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 February 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The study objectives were to evaluate the long-term safety and tolerability of USL261 in the treatment of seizure clusters using the following:
• Respiration rate: caregiver-recorded at approximately 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours after study drug administration
• Adverse events (AEs)
• Clinical laboratory tests
• Physical, nasal, and neurological examinations
• Vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiration rate, and temperature) as recorded by the study center staff
• Brief Smell Identification Test (B-SIT)
• Columbia-Suicide Severity Rating Scale (C-SSRS)
• Requirement for unscheduled emergency room (ER) or Emergency Medical Service (EMS) visits within 24 hours after study drug administration.

Protection of trial subjects:

Before the initiation of the clinical trial, the protocol, consent form, and advertisements for the recruitment of participants were reviewed and approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of the participating study center, in accordance with current Good Clinical Practices (GCP) and all applicable regulatory requirements. All protocol amendments and changes to the informed consent form (ICF) occurring during the study were also approved by the IRB or IEC. This clinical trial 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 Council for Harmonisation's (ICH's) GCP Guidelines, effective in 1997. Before study entry, each study participant or the participant's legally acceptable representative (LAR) was required to read, sign, and date an IRB- or IEC-approved consent form, explaining the nature, purpose, potential and possible risks, benefits, and duration of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 August 2012
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	Poland: 12
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 56

Country: Number of subjects enrolled	Ukraine: 53
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Australia: 12
Worldwide total number of subjects	161
EEA total number of subjects	34

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)	8
Adults (18-64 years)	153
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter trial was conducted at 63 trial sites in the following 9 countries: United States of America (USA), Canada, Australia, Hungary, Poland, Ukraine, Spain, Germany, and Israel.

Pre-assignment

Screening details:

After informed consent was obtained, participants underwent screening procedures at Visit 1, which could have occurred at the same time as, or up to 28 days after, Visit 4 of Study P261-401. The participant disposition refers to the enrolled population and includes participants who did not treat a seizure cluster episode.

Period 1

Period 1 title	USL261 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study.

Arms

Arm title	USL261

Arm description:

Participants received at least 1 dose of open-label study drug (USL261) in Study P261-402
Note: A total of 175 participants were screened and enrolled, but only 161 were treated with study drug; 14 discontinued without being treated with study drug.

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 midazolam) was delivered with a single actuation of the unit dose pump.

Number of subjects in period 1	USL261
Started	161
Completed	1
Not completed	160
Withdrawal by Participant	25
Adverse Event	4
Protocol violation	4
Study termination	29
No treated seizure clusters within protocol window	13
Caregiver no longer available	7

Study drug not available	2
Principal Investigator no longer available	2
Site closure	62
Noncompliance	8
Lack of efficacy	4

Baseline characteristics

Reporting groups	
Reporting group title	USL261
Reporting group description:	
Participants received at least 1 dose of open-label study drug (USL261) in Study P261-402 Note: A total of 175 participants were screened and enrolled, but only 161 were treated with study drug; 14 discontinued without being treated with study drug.	

Reporting group values	USL261	Total	
Number of subjects	161	161	
Age categorical 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)	8	8	
Adults (18-64 years)	153	153	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	32.9		
standard deviation	± 11.96	-	
Gender categorical Units: Subjects			
Female	80	80	
Male	81	81	
Ethnicity Units: Subjects			
Hispanic or Latino	8	8	
Not Hispanic or Latino	153	153	
Race			
Participant in Race other category reported race as "Slavic"			
Units: Subjects			
White	152	152	
Asian	1	1	
Black or African American	4	4	
American Indian or Alaska Native	2	2	
Other	2	2	
Body Mass Index			
Measure Analysis Population Description: Height not reported for some participants			
Units: kg/m2			
median	24.70		
full range (min-max)	17.7 to 43.0	-	
Seizure cluster episodes in year before			

Visit 1 in Study P261-401			
Units: Seizure cluster episodes			
median	18.0		
full range (min-max)	3 to 999	-	
Number of years participant had seizure cluster episodes prior to Study P261-401			
Measure Analysis Population Description: Unknown or data entered as indefinite (eg >3) for some participants. Number analyzed (n) = 157			
Units: Years			
median	5.00		
full range (min-max)	0.3 to 48.0	-	
Typical number of seizures in seizure cluster episode			
Units: Seizures			
median	6.0		
full range (min-max)	2 to 170	-	
Typical duration of seizure cluster episode			
Measure Analysis Population Description: Non-numerical duration (eg "several" hours) reported for some participants. n = 154			
Units: Hours			
median	1.00		
full range (min-max)	0.0 to 72.0	-	

End points

End points reporting groups

Reporting group title	USL261

Reporting group description:

Participants received at least 1 dose of open-label study drug (USL261) in Study P261-402
Note: A total of 175 participants were screened and enrolled, but only 161 were treated with study drug; 14 discontinued without being treated with study drug.

Subject analysis set title	USL261
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Population included all participants who were enrolled in Study P261-402 and received at least 1 dose of study drug during the open-label study.

Participants received USL261 5 mg or USL261 5 mg + 5 mg for a treated seizure cluster episode.

Primary: Duration of Safety Observation

End point title	Duration of Safety Observation[1]

End point description:

Duration of participant study participation for collection of long term safety data. Participants received at least 1 dose of USL261 5mg on study.

End point type	Primary

End point timeframe:

From Baseline/(Screening) to End of Safety-Follow-up (up to 56 months) as per assessment table of the study.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is available for this primary end point.

End point values	USL261			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: Months				
median (full range (min-max))	16.80 (1.0 to 55.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Participants Meeting Predefined Safety Criteria for Vital Signs

End point title	Participants Meeting Predefined Safety Criteria for Vital Signs[2]

End point description:

Participants meeting predefined safety criteria for vital signs (systolic blood pressure [SBP] <85 mm Hg, SBP change from baseline ≥ 40 mm Hg, diastolic BP [DBP] <50 mm Hg, DBP change from baseline ≥ 30 mm Hg, pulse rate <50 beats per minute (bpm), pulse rate >120 bpm, pulse rate change from baseline ≥ 40) at any visit post baseline or for caregiver recorded participant respiration rate [RR] <8 breaths per minute (brpm) or >24 brpm) after any USL261 treated seizure cluster episode. Abnormal vital signs were assessed separately by Investigator and recorded as adverse events if applicable.

End point type	Primary

End point timeframe:

From Baseline/(Screening) to End of Safety-Follow-up (up to 56 months) as per assessment table of the study.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is available for this primary end point.

End point values	USL261			
Subject group type	Subject analysis set			
Number of subjects analysed	161			
Units: Participants				
number (not applicable)				
SBP <85 mm Hg	0			
SBP change from baseline ≥ 40 mm Hg	1			
DBP <50 mm Hg	2			
DBP change from baseline ≥ 30 mm Hg	3			
Pulse rate < 50 bpm	2			
Pulse rate > 120 bpm	1			
Pulse rate change from baseline ≥ 40 bpm	4			
Caregiver recorded RR <8 brpm, n = 159	1			
Caregiver recorded RR >24 brpm, n = 159	29			

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Laboratory Abnormalities Meeting Predefined Criteria

End point title	Participants With Laboratory Abnormalities Meeting Predefined Criteria[3]

End point description:

Participants with abnormal laboratory finding, at any time post baseline, meeting predefined criteria. Abnormal laboratory findings were assessed separately by Investigator and recorded as adverse events if applicable. Alanine aminotransferase (ALT); Alkaline phosphatase (ALP); Aspartate aminotransferase (AST); Gamma glutamyl transferase (GGT); upper limit of normal (ULN)

End point type	Primary

End point timeframe:

From Baseline/(Screening) to End of Safety-Follow-up (up to 56 months) as per assessment table of the study.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is available for this primary end point.

End point values	USL261			
Subject group type	Subject analysis set			
Number of subjects analysed	161			
Units: Participants				
number (not applicable)				
ALT >ULN & ≤3xULN	26			
Albumin <30 g/L	2			
ALP >2.5xULN	1			
AST >ULN & ≤3xULN	17			
AST >5x ULN & <20xULN	1			
Bicarbonate <15.9 mmol/L	6			
Cholesterol >7.75 mmol/L	5			
Creatinine >1.5xULN	1			
Creatinine >2x baseline	2			
GGT >2.5xULN	14			
Glucose <3 mmol/L	3			
Glucose <8.9 mmol/L	5			
Phosphate <0.8 mmol/L	13			
Potassium >5.5 mmol/L	5			
Sodium <130 mmol/L	11			
Sodium >150 mmol/L	1			
Hemoglobin <100 g/L	5			
Hemoglobin decrease 20 g/L	10			
Leukocytes <3x10^9/L	4			
Lymphocytes <0.8x10^9/L	4			
Neutrophils <1.5x10^9/L	8			

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Clinically Significant Abnormalities Physical Examination

End point title	Participants With Clinically Significant Abnormalities Physical Examination[4]

End point description:

Participants with abnormal findings, at any time post baseline, on physical examination considered clinically significant by the investigator.

End point type	Primary

End point timeframe:

From Baseline/(Screening) to End of Safety-Follow-up (up to 56 months) as per assessment table of the study.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is available for this primary end point.

End point values	USL261			
Subject group type	Subject analysis set			
Number of subjects analysed	161			
Units: Participants				
number (not applicable)				
Skin	2			
Head/Eyes/Ears/Nose/Throat	0			
Neck	1			
Thyroid	0			
Lungs	0			
Heart	0			
Abdomen	0			
Lymph nodes	0			
Extremities	0			

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Clinically Significant Abnormalities on Neurologic Examination

End point title	Participants With Clinically Significant Abnormalities on Neurologic Examination[5]

End point description:

Participants with abnormal findings, at any time post baseline, on neurologic examination considered clinically significant by the investigator.

End point type	Primary

End point timeframe:

From Baseline/(Screening) to End of Safety-Follow-up (up to 56 months) as per assessment table of the study.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is available for this primary end point.

End point values	USL261			
Subject group type	Subject analysis set			
Number of subjects analysed	161			
Units: Participants				
number (not applicable)				
Mental status	10			
Cranial nerves II-XII	1			
Motor strength of limbs	2			
Deep tendon reflexes	2			
Sensory exam	1			
Station and gait	5			
Hopping	0			
Romberg test	0			
Finger-to-nose test	1			
Heel-to-shin test	1			

Rapid alternating movements	2			
Nystagmus	0			
Tremor/Other abnormal movements	0			

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Clinically Significant Abnormalities on Nasal Examination

End point title	Participants With Clinically Significant Abnormalities on Nasal Examination[6]

End point description:

Participants with abnormal findings, at any time post baseline, on nasal examination considered clinically significant by the investigator.

End point type	Primary

End point timeframe:

From Baseline/(Screening) to End of Safety-Follow-up (up to 56 months) as per assessment table of the study.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is available for this primary end point.

End point values	USL261			
Subject group type	Subject analysis set			
Number of subjects analysed	161			
Units: Participants				
number (not applicable)	1			

Statistical analyses

No statistical analyses for this end point

Primary: Participant Change in Brief Smell Identification Test (B-SIT) Score

End point title	Participant Change in Brief Smell Identification Test (B-SIT) Score[7]

End point description:

Change in participant B-SIT score from baseline to last visit with assessment. The BSIT is a self-administered 12-item test; the score indicates odors correctly identified (0 to 12). The B-SIT was added while the study was already ongoing (Protocol Amendment 4, 20 May 2015) in response to a regulatory request. The test was only implemented at sites in the United States and included only participants considered by the investigator to have adequate cognitive ability to perform the test. Baseline was defined as the latest non-missing value prior to administration of USL261 in the Test Dose Phase of Study P261-401.

End point type	Primary

End point timeframe:

From Baseline/(Screening) to End of Safety-Follow-up (up to 56 months) as per assessment table of the study.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is available for this primary end point.

End point values	USL261			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.6 (± 1.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Suicidal Ideation

End point title	Participants With Suicidal Ideation[8]

End point description:

Participants with suicidal ideation reported on Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire at any post-baseline visit. Responses including: Wish to be Dead; Non-Specific Active Suicidal Thoughts; Active Suicidal Ideation with Some Intent to Act, without Specific Plan; Active Suicidal Ideation with Specific Plan and Intent; and Any Suicidal Ideation Regardless of Type.

End point type	Primary

End point timeframe:

From Baseline/(Screening) to End of Safety-Follow-up (up to 56 months) as per assessment table of the study.

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is available for this primary end point.

End point values	USL261			
Subject group type	Subject analysis set			
Number of subjects analysed	161			
Units: Participants				
number (not applicable)				
Wish to be dead	3			
Non-specific active	3			
Active without specific plan	3			
Active with specific plan/intent	1			
Any suicidal ideation	4			

Statistical analyses

No statistical analyses for this end point

Primary: Emergency Room/Emergency Medical Service Visits

End point title	Emergency Room/Emergency Medical Service Visits[9]

End point description:

Participants requiring emergency room (ER)/emergency medical service (EMS) visit within 24 hours after any USL261 treated seizure cluster (including for continued seizures).

End point type	Primary

End point timeframe:

From Baseline/(Screening) to End of Safety-Follow-up (up to 56 months) as per assessment table of the study.

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is available for this primary end point.

End point values	USL261			
Subject group type	Subject analysis set			
Number of subjects analysed	161			
Units: Participants				
number (not applicable)	20			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Treated Seizure Clusters Meeting Criteria for Treatment Success

End point title	Number of Treated Seizure Clusters Meeting Criteria for Treatment Success[10]

End point description:

Number of Treated Seizure Clusters Meeting Criteria for Treatment Success: Termination of seizure(s) within 10 minutes and no recurrence within 6 hours after administration of first dose of USL261 (intranasal midazolam 5 mg)

End point type	Primary

End point timeframe:

6 hours after first dose of USL261 for each treated seizure cluster

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is available for this primary end point.

End point values	USL261			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: Seizure cluster episodes				
number (not applicable)	1108			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Original protocol-each participant 2 years from enrollment; Amended protocol-each participant open-ended from enrollment(up to 4 years or longer as approved by Health Authority). Actual individual participant duration 1.0 to 55 months.

Adverse event reporting additional description:

Due to intermittent treatment (qualifying seizure clusters), short systemic half-life of active (midazolam), and long participant duration, treatment emergent adverse event within 2 days after each treated seizure cluster are reported. Seizures were not considered adverse events unless worsening from underlying condition.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	USL261

Reporting group description:

USL261 5 mg or USL261 5 mg + 5 mg for a treated seizure cluster episode

Serious adverse events	USL261		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 161 (4.97%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure cluster			
subjects affected / exposed	2 / 161 (1.24%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	2 / 161 (1.24%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			

subjects affected / exposed	2 / 161 (1.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	USL261		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 161 (20.50%)		
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 161 (6.21%)		
occurrences (all)	27		
Somnolence			
subjects affected / exposed	15 / 161 (9.32%)		
occurrences (all)	92		
Respiratory, thoracic and mediastinal disorders			
Nasal discomfort			
subjects affected / exposed	20 / 161 (12.42%)		
occurrences (all)	96		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2013	Amendment 1: • Changes were made to the study objectives, safety endpoints, and safety analyses; • The instructions for administering the second dose of 5 mg of USL261 were modified; • The duration of the study was increased to a maximum of 2 years from the date of enrollment; • The number of study centers listed in the study design was removed; • Changes were made to the inclusion and exclusion criteria; • Changes were made to permitted and prohibited medications and substances; • The reporting requirements for serious adverse events (SAEs) that occurred greater than 30 days after Final Visit or Early termination (ET) Visit were corrected; • Caregivers were required to follow the rescue protocol specified in the participant's patient management plan (PMP) if the participant had < 8 breaths per minute, was excessively and uncharacteristically sedated, had persistent or recurrent seizure activity, or other safety concern; • Changes to the efficacy endpoints and analyses: − Time to return to baseline functionality was to be summarized instead of time to cessation of seizures, − Definition of recurrence of seizures was clarified, − Recurrence of seizures was expanded from between 10 minutes and 4 hours after study drug administration to between 10 minutes and 6 hours after study drug administration, − The occurrence of seizures between 10 minutes and 4 hours after study drug administration was to be included as an exploratory analysis.
09 May 2014	Amendment 2: • Duration of the study was extended from up to 2 years from date of enrollment (Visit 1) to up to marketing of the study drug in the United States. After the first 2 years of participation in the study, only the date and start time of the next seizure beginning > 10 minutes and ≤ 24 hours after study drug administration were to be captured; • "Requirement for emergency rescue treatment with assisted breathing or intubation within 24 hours after study drug administration" was removed from the study objectives. These events were to be captured as adverse events; • Clarification that pregnancy tests were only required for females of childbearing potential; • Addition information was provided regarding the formulation of study drug used in the study; • Information regarding completed and ongoing studies was updated to reflect studies completed and initiated since Amendment 1; • Resource utilization questions were removed from the Caregiver Questionnaire as this information was collected elsewhere; • Clarification that caregiver withdrawal of consent could be documented as a reason for discontinuation from the study; • Clarification of the statistical analyses planned for the study.

19 March 2015	Amendment 3: • The protocol was amended to allow participants in Study P261-401 who completed the Test Dose Visit (Visit 2) and met the inclusion criteria for Visit 2 to enroll in Study P261-402 upon termination of Study P261-401; • The sample size of this study was increased from 155 to 240 as a result of an increase in the sample size of Study P261-401; • Inclusion Criterion 3 was modified to redefine age restriction; • Inclusion Criterion 8 requiring participants to weigh 40 to 125 kg, inclusive, at Visit 1 was removed; • Exclusion Criterion 1 was updated to exclude only those participants whose seizure cluster progresses to status epilepticus during or since his/her participation in Study P261-401; • Exclusion Criterion 17 excluding participants who had a vagal nerve stimulator implanted since completion of Study P261-401 was removed; • The duration of a participant's participation was modified to up to approximately 4 years from the date of enrollment (Visit 1); • The list of efficacy assessments was modified to remove the date and time of recognition of seizure cluster(s) eligible for treatment with study drug; • The adverse event reporting time frame was reduced from 30 days after the last administration of study drug to 7 days after the last administration of study drug; • The introduction section was updated to reflect studies completed and ongoing since Amendment 1; • Several mild and moderate inhibitors of cytochrome P450 3A4 metabolism were removed from the list of prohibited concomitant substances, while others have had modifications made to the required washout period; • The required washout period for fentanyl, morphine, and propofol was modified from 7 days to 1 day, following brief intravenous (IV) administration of these drugs; • The procedures to be completed at Visits 2 through X, Final Visit or ET Visit, and on the telephone follow-up every 30 days were updated.
20 May 2015	Amendment 4: • The B-SIT was added to assess the long-term effects of USL261 on olfaction (United States only); • The introduction section was updated to include the results of Study P261-201, a single-center, inpatient trial investigating the safety, tolerability, PK, and pharmacodynamics of escalating single- and 2-dose regimens of USL261 compared with placebo in adult participants with epilepsy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 February 2017	Study P261-402 was to continue up until marketing approval or a time period as approved by the Health Authority where the study was being conducted. Because of the early termination of Study P261-401 for business reasons not related to safety or efficacy, the present study (Study P261-402) was also terminated early.	-

Notes:

Limitations and caveats

None reported