



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 | <ul style="list-style-type: none">• 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/m ² | | | |
| 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 \geq 40 mm Hg, diastolic BP [DBP] <50 mm Hg, DBP change from baseline \geq 30 mm Hg, pulse rate <50 beats per minute (bpm), pulse rate >120 bpm, pulse rate change from baseline \geq 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 \geq 40 mm Hg | 1 | | | |
| DBP <50 mm Hg | 2 | | | |
| DBP change from baseline \geq 30 mm Hg | 3 | | | |
| Pulse rate < 50 bpm | 2 | | | |
| Pulse rate > 120 bpm | 1 | | | |
| Pulse rate change from baseline \geq 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.

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|----------------|---------|
| 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