



Clinical trial results:

A Multi-center, Open-label, Non-controlled Study To Evaluate The Efficacy And Safety Of Lorazepam Intravenously Administered In Subjects With Status Epilepticus Or Repetitive Status Epilepticus Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-000125-13 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 22 August 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 16 February 2017 |
| First version publication date | 16 February 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | B3541002 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02239380 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Pfizer Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer Inc., Pfizer ClinicalTrials.gov Call Center, 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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 | Final |
| Date of interim/final analysis | 14 November 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 August 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of lorazepam intravenously administered in subjects with Status Epilepticus (SE).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 25 November 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Japan: 26 |
| Worldwide total number of subjects | 26 |
| EEA total number of subjects | 0 |

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) | 4 |
| Children (2-11 years) | 10 |
| Adolescents (12-17 years) | 3 |
| Adults (18-64 years) | 9 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted from 25 November 2014 to 22 August 2016 in Japan.

Period 1

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

Arms

| | |
|-----------|-----------|
| Arm title | Lorazepam |
|-----------|-----------|

Arm description:

Subjects aged between 3 months to below 16 years received single intravenous dose (Dose 1) of 0.05 milligram per kilogram (mg/kg) of Lorazepam (up to a maximum dose of 4 mg) on Day 1. Subjects aged above 16 years received single intravenous dose of 4 mg of lorazepam. Subjects whose seizures continued or recurred within 10 minutes following the initial dose, an additional dose (Dose 2) of 4 mg (for subjects above 16 years of age) or 0.05 mg/kg dose (subjects between 3 months to below 16 years of age) was administered accordingly. Subjects were followed up to 7 days after last dose of study drug administration.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lorazepam |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects aged between 3 months to below 16 years received single dose of 0.05 mg/kg of Lorazepam on Day 1. Subjects aged above 16 years received single dose of 4 mg of Lorazepam on Day 1.

| | |
|---------------------------------------|-----------|
| Number of subjects in period 1 | Lorazepam |
| Started | 26 |
| Completed | 26 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Lorazepam |
|-----------------------|-----------|

Reporting group description:

Subjects aged between 3 months to below 16 years received single intravenous dose (Dose 1) of 0.05 milligram per kilogram (mg/kg) of Lorazepam (up to a maximum dose of 4 mg) on Day 1. Subjects aged above 16 years received single intravenous dose of 4 mg of lorazepam. Subjects whose seizures continued or recurred within 10 minutes following the initial dose, an additional dose (Dose 2) of 4 mg (for subjects above 16 years of age) or 0.05 mg/kg dose (subjects between 3 months to below 16 years of age) was administered accordingly. Subjects were followed up to 7 days after last dose of study drug administration.

| Reporting group values | Lorazepam | Total | |
|--|-----------|-------|--|
| Number of subjects | 26 | 26 | |
| 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) | 4 | 4 | |
| Children (2-11 years) | 10 | 10 | |
| Adolescents (12-17 years) | 3 | 3 | |
| Adults (18-64 years) | 9 | 9 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 14 | | |
| standard deviation | ± 12.9 | - | |
| Gender, Male/Female | | | |
| Units: Subjects | | | |
| Female | 10 | 10 | |
| Male | 16 | 16 | |

End points

End points reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Lorazepam |
|-----------------------|-----------|

Reporting group description:

Subjects aged between 3 months to below 16 years received single intravenous dose (Dose 1) of 0.05 milligram per kilogram (mg/kg) of Lorazepam (up to a maximum dose of 4 mg) on Day 1. Subjects aged above 16 years received single intravenous dose of 4 mg of lorazepam. Subjects whose seizures continued or recurred within 10 minutes following the initial dose, an additional dose (Dose 2) of 4 mg (for subjects above 16 years of age) or 0.05 mg/kg dose (subjects between 3 months to below 16 years of age) was administered accordingly. Subjects were followed up to 7 days after last dose of study drug administration.

Primary: Percentage of Subjects Who Achieved Seizure Free Interval of At Least 30 Minutes After Initial Dose (Dose 1) of Study Drug

| | |
|-----------------|---|
| End point title | Percentage of Subjects Who Achieved Seizure Free Interval of At Least 30 Minutes After Initial Dose (Dose 1) of Study Drug ^[1] |
|-----------------|---|

End point description:

Subjects with clinical benefit were defined as subjects whose initial seizure stopped within 10 minutes after initial dose (Dose 1) and who continued seizure-free for at least 30 minutes after the completion of initial dose (Dose 1). Full analysis set (FAS) included all subjects who received at least 1 dose of study drug, excluded those subjects whose status epilepticus (SE) or repetitive SE/cluster seizure was determined on the electroencephalography (EEG).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

30 minutes post Dose 1

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 was planned for this primary endpoing

| | | | | |
|----------------------------------|-------------------|--|--|--|
| End point values | Lorazepam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 48 (27.8 to 68.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Seizure Free Interval of At Least 30 Minutes After Any Dose of Study Drug

| | |
|-----------------|---|
| End point title | Percentage of Subjects Who Achieved Seizure Free Interval of At Least 30 Minutes After Any Dose of Study Drug |
|-----------------|---|

End point description:

Percentage of subjects whose initial seizure stopped within 10 minutes after the administration of study drug (either Dose 1 or 2 [in 10 to 30 minutes from the initial dose]) and who continued seizure-free for at least 30 minutes were analyzed and reported in this endpoint. FAS included all subjects who received at least 1 dose of study drug, excluded those subjects whose SE or repetitive SE/cluster seizure was

determined on the EEG.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 30 minutes post Dose 1 or 2 | |

| | | | | |
|----------------------------------|-----------------|--|--|--|
| End point values | Lorazepam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 64 (42.5 to 82) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Seizure Free Interval of At Least 12 Hours After Administration (Either Initial or Any Dose) of Study Drug

| | |
|-----------------|--|
| End point title | Percentage of Subjects Who Achieved Seizure Free Interval of At Least 12 Hours After Administration (Either Initial or Any Dose) of Study Drug |
|-----------------|--|

End point description:

Percentage of subjects whose seizures stopped within 10 minutes after the administration of initial dose (Dose 1) of study drug and after any study drug dose (either Dose 1 or Dose 2 [in 10 to 30 minutes from the initial dose]), who continued to be seizure-free for at least 12 hours post-dose were analyzed and reported in this endpoint. FAS included all subjects who received at least 1 dose of study drug, excluded those subjects whose SE or repetitive SE/cluster seizure was determined on the EEG.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 12 hour post Dose 1; 12 hour post Dose 1 or 2 | |

| | | | | |
|-------------------------------|-----------------|--|--|--|
| End point values | Lorazepam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Post Dose 1 | 32 | | | |
| Post Dose 1 or 2 | 44 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Seizure Free Interval of At Least 24 Hours After Administration (Either Initial or Any Dose) of Study Drug

| | |
|-----------------|--|
| End point title | Percentage of Subjects Who Achieved Seizure Free Interval of At Least 24 Hours After Administration (Either Initial or Any Dose) of Study Drug |
|-----------------|--|

End point description:

Percentage of subjects whose seizures stopped within 10 minutes after the administration of initial dose (Dose 1) of study drug and after any study drug dose (either Dose 1 or Dose 2 [in 10 to 30 minutes from the initial dose]), who continued to be seizure-free for at least 24 hours post-dose were analyzed and reported in this endpoint. FAS included all subjects who received at least 1 dose of study drug, excluded those subjects whose SE or repetitive SE/cluster seizure was determined on the EEG.

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

End point timeframe:

24 hour post Dose 1; 24 hour post Dose 1 or 2

| | | | | |
|-------------------------------|-----------------|--|--|--|
| End point values | Lorazepam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Post Dose 1 | 24 | | | |
| Post Dose 1 or 2 | 32 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Seizures From The Administration (Either Initial or Any Dose) of Study Drug

| | |
|-----------------|---|
| End point title | Time to Resolution of Seizures From The Administration (Either Initial or Any Dose) of Study Drug |
|-----------------|---|

End point description:

Time to resolution (in minutes) was defined as the duration between the administration of study drug until the seizure resolved without receiving the prohibited medications. FAS included all subjects who received at least 1 dose of study drug, excluded those subjects whose SE or repetitive SE/cluster seizure was determined on the EEG. Here, 'n' signifies those subjects who were evaluable for specific category.

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

End point timeframe:

10 minutes post Dose 1; 10 minutes post Dose 1 or 2

| | | | | |
|-------------------------------|-----------------|--|--|--|
| End point values | Lorazepam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: minutes | | | | |
| median (full range (min-max)) | | | | |
| Post Dose 1 (n =15) | 1 (0 to 10) | | | |
| Post Dose 1 or 2 (n =17) | 1 (0 to 10) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Relapse Following The Administration (Either Initial or Any Dose) of Study Drug

| | |
|-----------------|---|
| End point title | Time to Relapse Following The Administration (Either Initial or Any Dose) of Study Drug |
|-----------------|---|

End point description:

Time to relapse (in minutes) was defined duration from the time of study drug administration to the time of relapse, as determined by investigator. Subjects whose seizure stops within 10 minutes without receiving the prohibited medications were analyzed in this endpoint. FAS included all subjects who received at least 1 dose of study drug, excluded those subjects whose SE or repetitive SE/cluster seizure was determined on the EEG. Here, number of subjects analyzed (N) signifies those subjects who were evaluable for this endpoint.

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

End point timeframe:

24 hour post Dose 1; 24 hour post Dose 1 or 2

| | | | | |
|-------------------------------|------------------|--|--|--|
| End point values | Lorazepam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: minutes | | | | |
| median (full range (min-max)) | | | | |
| Post Dose 1 | 62 (11 to 879) | | | |
| Post Dose 1 or 2 | 103 (23 to 1246) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) |
|-----------------|---|

End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to

possibility of causal relationship. An SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug to the end of study (Day 12), that were absent before treatment or that worsened relative to pre-treatment state. AEs include both serious and non-serious adverse events. Safety analysis set included all participants who received at least 1 dose of study drug.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to 7 days after last dose of study drug administration (up to 12 days) | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Lorazepam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 26 | | | |
| Units: subjects | | | | |
| AEs | 12 | | | |
| SAEs | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 7 days after last dose of study drug administration (up to 12 days)

Adverse event reporting additional description:

The same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in one event and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Lorazepam |
|-----------------------|-----------|

Reporting group description:

Subjects aged between 3 months to below 16 years received single intravenous dose (Dose 1) of 0.05 milligram per kilogram (mg/kg) of Lorazepam (up to a maximum dose of 4 mg) on Day 1. Subjects aged above 16 years received single intravenous dose of 4 mg of lorazepam. Subjects whose seizures continued or recurred within 10 minutes following the initial dose, an additional dose (Dose 2) of 4 mg (for subjects above 16 years of age) or 0.05 mg/kg dose (subjects between 3 months to below 16 years of age) was administered accordingly. Subjects were followed up to 10 days after last dose of study drug administration.

| Serious adverse events | Lorazepam | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Lorazepam | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 26 (46.15%) | | |
| Investigations | | | |

| | | | |
|--|---|--|--|
| Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 1 / 26 (3.85%) 1 | | |
| Injury, poisoning and procedural complications Laceration subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all) | 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1 | | |
| Nervous system disorders Balance disorder subjects affected / exposed occurrences (all) Ataxia subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) | 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1 2 / 26 (7.69%) 2 | | |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 1 / 26 (3.85%) 1 | | |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) | 1 / 26 (3.85%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 1 / 26 (3.85%) 1 | | |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 1 / 26 (3.85%) 1 | | |

| | | | |
|---|--|--|--|
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 | | |
| Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all) | 1 / 26 (3.85%) 1 | | |
| Infections and infestations Pneumonia subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported