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) Post Dose 1 or 2 (n =17)	1 (0 to 10) 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 Post Dose 1 or 2	62 (11 to 879) 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

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