Clinical trial results:
PROSPECTIVE STUDY OF OPHTHALMOLOGIC FUNCTION IN PATIENTS RECEIVING LINEZOLID FOR SIX WEEKS OR GREATER

Summary

EudraCT number	2006-002303-14
Trial protocol	SE IT
Global end of trial date	27 December 2013

Results information

Result version number	v2 (current)
This version publication date	07 April 2016
First version publication date	15 July 2015
Version creation reason	• Correction of full data set Reporting periods and duplicate Adverse Events in their data.

Trial information

Trial identification

Sponsor protocol code	A5951110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00359632
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 ClinicalTrials.gov Call Center, Pfizer, Inc., 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 December 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To prospectively identify and characterize optic nerve toxicity in subjects receiving long-term (two months or greater) linezolid therapy.

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 Conference on 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	17 November 2008
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	Italy: 6
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	Sweden: 5
Worldwide total number of subjects	33
EEA total number of subjects	11

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)	0
Adults (18-64 years)	26
From 65 to 84 years	7

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Nine centers (2 centers in Italy, 1 center in Sweden, and 6 centers in the US) enrolled subjects for inclusion in the study. Sites were selected based on their capability to perform the comprehensive testing and to treat types of infections that might require therapy with linezolid for 6 weeks or longer.

Pre-assignment

Screening details:

There were separate selection criteria for subjects in the treated and control groups. At the Screening/Baseline visit (Day 1), subjects were eligible for the study after verification that they met the relevant inclusion/exclusion criteria and the study had been explained to them.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Linezolid

Arm description:

Subjects received linezolid. Mode of administration and duration of treatment was at the discretion of the investigator, but for study purposes, the subject had to receive linezolid treatment for a minimum of 6 weeks (at least 42 days) prior to the baseline visit.

Arm type	Experimental
Investigational medicinal product name	Linezolid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Subjects received linezolid either as tablets or as an intravenous (IV) infusion at a dose of 600 milligrams (mg), twice daily (BID).

Arm title	Control

Arm description:

Control subjects individually matched to linezolid subjects (on age, gender, and type of infection) received antibiotics other than linezolid per standard of care at the discretion of the treating investigator, for at least 6 weeks (at least 42 days) prior to the baseline visit. The control group was only assessed at the baseline visit to identify the presence of background abnormalities in the study test panel.

Arm type	Active comparator
Investigational medicinal product name	Antibiotics
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received antibiotics matching to Linezolid as per standard of care at the discretion of the treating investigator, for at least 6 weeks (at least 42 days).

Number of subjects in period 1	Linezolid	Control
Started	24	9
Completed	20	9
Not completed	4	0
Death	2	-
Adverse event	1	-
Non-compliance with visit schedule	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Linezolid
Reporting group description:	
Subjects received linezolid. Mode of administration and duration of treatment was at the discretion of the investigator, but for study purposes, the subject had to receive linezolid treatment for a minimum of 6 weeks (at least 42 days) prior to the baseline visit.	
Reporting group title	Control
Reporting group description:	
Control subjects individually matched to linezolid subjects (on age, gender, and type of infection) received antibiotics other than linezolid per standard of care at the discretion of the treating investigator, for at least 6 weeks (at least 42 days) prior to the baseline visit. The control group was only assessed at the baseline visit to identify the presence of background abnormalities in the study test panel.	

Reporting group values	Linezolid	Control	Total
Number of subjects	24	9	33
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	53.4	50.1	
standard deviation	± 13.38	± 11.86	-
Gender categorical			
Units: Subjects			
Female	10	3	13
Male	14	6	20

End points

End points reporting groups

Reporting group title	Linezolid

Reporting group description:

Subjects received linezolid. Mode of administration and duration of treatment was at the discretion of the investigator, but for study purposes, the subject had to receive linezolid treatment for a minimum of 6 weeks (at least 42 days) prior to the baseline visit.

Reporting group title	Control

Reporting group description:

Control subjects individually matched to linezolid subjects (on age, gender, and type of infection) received antibiotics other than linezolid per standard of care at the discretion of the treating investigator, for at least 6 weeks (at least 42 days) prior to the baseline visit. The control group was only assessed at the baseline visit to identify the presence of background abnormalities in the study test panel.

Primary: Percentage of Subjects with an Adverse Event

End point title	Percentage of Subjects with an Adverse Event[1]

End point description:

End point type	Primary

End point timeframe:

Through and including 28 calendar days after the last administration of the investigational product

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: Only descriptive data was planned to be reported for this endpoint.

End point values	Linezolid	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: percentage of subjects				
number (not applicable)				
Adverse events, percent (%)	83.3	11.1		
Serious adverse events, %	25	0		
Severe adverse events, %	12.5	0		
Discontinued due to adverse events, %	29.2	0		
Dose Reduced or Temporary Discontinuation,%	12.5	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects by Clinical Outcome of Infection at End of Study

End point title	Percentage of Subjects by Clinical Outcome of Infection at End of Study[2]

End point description:

Clinical response was evaluated at the End of Study visit as Cure, Improvement, Failure, Unknown or Other. Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at that evaluation timepoint.

End point type	Secondary

End point timeframe:

At End of Study visit

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification:
Comparison between groups not planned. Data not collected at end of study visit for Control Arm.

End point values	Linezolid			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of subjects				
number (not applicable)				
Cure, %	47.6			
Improvement, %	42.9			
Failure, %	0			
Unknown, %	0			
Other, %	9.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs/SAEs: Recorded from signing of informed consent form and up to 28 calendar days after the last administration of the investigational product

Adverse event reporting additional description:

The same event may appear as both an adverse event (AE) and a serious AE (SAE). However, what is presented are distinct events. An event may be categorized as serious in 1 subject and as non serious in another subject, or one subject may have experienced both a serious and non serious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Linezolid

Reporting group description:

Subjects received linezolid either as tablets, by mouth (PO) or as an intravenous (IV) infusion at a dose of 600 milligrams (mg), twice daily (BID). Mode of administration and duration of treatment was at the discretion of the investigator, but for study purposes, the subjects had to receive linezolid treatment for a minimum of 6 weeks (at least 42 days) prior to the baseline visit.

Reporting group title	Control

Reporting group description:

Control subjects individually matched to linezolid subjects (on age, gender, and type of infection) received antibiotics other than linezolid per standard of care at the discretion of the treating investigator, for at least 6 weeks (at least 42 days) prior to the baseline visit. The control group was only assessed at the baseline visit to identify the presence of background abnormalities in the study test panel.

Serious adverse events	Linezolid	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 24 (25.00%)	0 / 9 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	2 / 24 (8.33%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Erythropoiesis abnormal			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sideroblastic anaemia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Linezolid	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 24 (83.33%)	1 / 9 (11.11%)	
Investigations			

Blood lactic acid increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Platelet count increased			
subjects affected / exposed	2 / 24 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Protein total increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Vitamin B1 decreased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Vitamin B12 decreased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Complications of transplant surgery			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Neuropathy peripheral			

subjects affected / exposed	3 / 24 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Paraesthesia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Polyneuropathy			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Sinus headache			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 24 (25.00%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Leukopenia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Neutropenia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Chest pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Malaise			

subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Diabetic retinal oedema			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Narrow anterior chamber angle			
subjects affected / exposed	0 / 24 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Optic neuropathy			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Retinal disorder			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Toxic optic neuropathy			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Visual impairment			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorder			
subjects affected / exposed	2 / 24 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Nausea			

subjects affected / exposed	3 / 24 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Tooth discolouration			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	3 / 24 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Folliculitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Folate deficiency			
subjects affected / exposed	3 / 24 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Hyperkalaemia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Vitamin B1 deficiency			
subjects affected / exposed	2 / 24 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Vitamin B12 deficiency			
subjects affected / exposed	2 / 24 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Vitamin B6 deficiency			
subjects affected / exposed	2 / 24 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Malnutrition			
subjects affected / exposed	1 / 24 (4.17%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2006	1- The color vision testing was modified to include D15 Hue Test de-saturated as a primary test and the 28 Hue Test as a secondary test to increase the sensitivity of the testing in order to detect the more subtle changes in color vision that may be characteristic of linezolid-related optic neuropathy. 2- The Humphrey Visual Fields Test was added as a primary eye test to include the test of fovea sensitivity to better detect early signs of optic neuropathy. 3- The neurological examination requirements were updated to enable confirmation of peripheral neuropathy to be assessed by either a neurologist's examination or a laboratory study (such as a nerve conduction study). 4- Additional instruction was included on how to follow-up on significant abnormalities (optic or peripheral neuropathy) noted during the study that had not resolved or stabilized either by the End of Study (EOS) visit and/or after 6 months of follow-up testing.
06 November 2007	1- Plasma lactate was included as a required laboratory test for all study visits rather than designated as a secondary test to be run only if the bicarbonate was determined to be less than the lower limit of normal. This was done to ensure that laboratory findings suggestive of lactic acidosis were detected as soon as possible. 2- Vitamin B6 testing was added for all study visits in the treated and control groups as an indicator for potential underlying causes of neuropathy. 3- Glycosylated hemoglobin (HbA1c) testing was added at Baseline in the treated and control groups as an indicator for the risk of progression of diabetic complications, including diabetic neuropathy. 4- Hepatitis C serology was added at Baseline in the treated and control groups as an indicator for potential underlying causes of neuropathy. 5- The primary ophthalmologic examination for the treated and control groups at all visits was modified to include Intraocular pressure (IOP) and test for relative afferent pupillary defect. 6- The stereo optic nerve head photograph was added as a primary ophthalmologic test at Baseline to increase the likelihood of prospectively identifying optic nerve toxicity.
26 June 2008	1- Optical Coherence Tomography -3 (OCT-3) test moved from 'Secondary Ophthalmologic Testing' to 'Ophthalmologic Examination'. 2- 'To evaluate newer research ophthalmologic testing in the assessment of optic neuropathy' deleted from Study objectives. 3- Adverse events reporting, including suspected serious unexpected adverse reactions, were carried out in accordance with applicable local regulations. 4- Added Phosphorylated neurofilament, heavy subunit (PNF-H) to be collected if subject's primary ophthalmologic testing was consistent with optic neuropathy.
09 May 2012	1-The addition of pregnancy tests for safety and for enhanced monitoring of women of child bearing potential. 2- Birth control and pregnancy information were added in lifestyle guidelines for the safety of subjects. 3- Inclusion criteria changed to allow subjects receiving linezolid 600 mg BID for a minimum of 6 weeks. Previously, inclusion criteria allowed subjects who had received a minimum of 60 days of linezolid 600 mg BID to be eligible.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This pilot study was exploratory and not designed to be powered for safety or efficacy. Controls were not followed post-baseline whereas linezolid patients returned for multiple study visits. The study was terminated early due to slow enrollment.

Notes: