Clinical trial results:
Voriconazole in High-Risk Patients With Invasive Fungal Infections in Slovakia. An Open, Prospective, Non-Comparative Study. (Ve-RIFI)

Summary

EudraCT number	2017-000501-20
Trial protocol	Outside EU/EEA
Global end of trial date	16 November 2009

Results information

Result version number	v1 (current)
This version publication date	09 June 2017
First version publication date	09 June 2017

Trial information

Trial identification

Sponsor protocol code	A1501082

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01137292
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 April 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 November 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To collect data on treatment outcomes (clinical and mycological cure), safety and tolerability of treatment with voriconazole in subjects with invasive fungal infections in Slovakia.

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	12 April 2007
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	Slovakia: 177
Worldwide total number of subjects	177
EEA total number of subjects	177

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)	3
Children (2-11 years)	8
Adolescents (12-17 years)	6
Adults (18-64 years)	134
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted from 12 April 2007 to 16 November 2009 in Slovakia.

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	Voriconazole

Arm description:

Subjects received Voriconazole intravenously at a loading dose of 6 milligram per kilogram (mg/kg) every 12 hours (during the first 24 hours) followed by the maintenance dose of 4 mg/kg twice daily up to 2 weeks. Subjects weighing greater than (>) 40 kg, received oral formulation at a loading dose of 400 mg twice during the first 24 hours followed by maintenance dose of 200 mg twice daily up to 2 weeks. Subjects weighing less than (<) 40 kg received oral formulation at a loading dose of 200 mg twice during the first 24 hours followed by maintenance dose of 100 mg twice daily up to 2 weeks. Paediatric subjects <12 years received 7 mg/kg intravenously or 200 mg orally twice daily up to 2 weeks.

Arm type	Experimental
Investigational medicinal product name	Voriconazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Voriconazole at a loading dose of 6 mg/kg every 12 hours (during the first 24 hours) followed by the maintenance dose of 4 mg/kg twice daily up to 2 weeks. Paediatric subjects <12 years received 7 mg/kg or 200 mg twice daily up to 2 weeks.

Investigational medicinal product name	Voriconazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects weighing >40 kg, received formulation at a loading dose of 400 mg twice during the first 24 hours followed by maintenance dose of 200 mg twice daily up to 2 weeks. Subjects weighing <40 kg received formulation at a loading dose of 200 mg twice during the first 24 hours followed by maintenance dose of 100 mg twice daily up to 2 weeks.

Number of subjects in period 1	Voriconazole
Started	177
Completed	123
Not completed	54
Other unspecified	7
Death	30
Adverse event	3
Lost to follow-up	1
Lack of efficacy	13

Baseline characteristics

Reporting groups	
Reporting group title	Voriconazole

Reporting group description:

Subjects received Voriconazole intravenously at a loading dose of 6 milligram per kilogram (mg/kg) every 12 hours (during the first 24 hours) followed by the maintenance dose of 4 mg/kg twice daily up to 2 weeks. Subjects weighing greater than (>) 40 kg, received oral formulation at a loading dose of 400 mg twice during the first 24 hours followed by maintenance dose of 200 mg twice daily up to 2 weeks. Subjects weighing less than (<) 40 kg received oral formulation at a loading dose of 200 mg twice during the first 24 hours followed by maintenance dose of 100 mg twice daily up to 2 weeks. Paediatric subjects <12 years received 7 mg/kg intravenously or 200 mg orally twice daily up to 2 weeks.

Reporting group values	Voriconazole	Total	
Number of subjects	177	177	
Age Categorical Units: Subjects			
<2 years	3	3	
2 to 18 years	16	16	
19 to 44 years	52	52	
45 to 64 years	80	80	
>=65 years	26	26	
Age continuous Units: years			
arithmetic mean	45.9		
standard deviation	± 19.1	-	
Gender, Male/Female Units: Subjects			
Female	73	73	
Male	104	104	

End points

End points reporting groups

Reporting group title	Voriconazole

Reporting group description:

Subjects received Voriconazole intravenously at a loading dose of 6 milligram per kilogram (mg/kg) every 12 hours (during the first 24 hours) followed by the maintenance dose of 4 mg/kg twice daily up to 2 weeks. Subjects weighing greater than (>) 40 kg, received oral formulation at a loading dose of 400 mg twice during the first 24 hours followed by maintenance dose of 200 mg twice daily up to 2 weeks. Subjects weighing less than (<) 40 kg received oral formulation at a loading dose of 200 mg twice during the first 24 hours followed by maintenance dose of 100 mg twice daily up to 2 weeks. Paediatric subjects <12 years received 7 mg/kg intravenously or 200 mg orally twice daily up to 2 weeks.

Primary: Number of Subjects With Clinical and/or Mycological Efficacy by Response at the End of Treatment (EOT) Visit

End point title	Number of Subjects With Clinical and/or Mycological Efficacy by Response at the End of Treatment (EOT) Visit[1]

End point description:

Clinical, mycological responses: clinical cure, clinical improvement, no clinical cure, mycological cure, no mycological cure and no mycological culture performed. Subjects could have more than one responses. Responses were based on the investigator's judgement according to the Infectious Disease Society of America, European Conference on Infections in Leukemia, and European Committee on Antimicrobial Susceptibility Testing guidelines. Full analysis set (FAS) included all enrolled subjects who were administered the study medication and had post baseline documentation of efficacy available.

End point type	Primary

End point timeframe:

Baseline up to 2 Weeks (EOT visit)

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 analysis was planned to be analysed in this end point.

End point values	Voriconazole			
Subject group type	Reporting group			
Number of subjects analysed	177			
Units: subjects				
Clinical Cure	64			
Clinical Improvement	64			
No Clinical Cure	36			
Mycological Cure	34			
No Mycological Cure	10			
No Mycological Culture Performed	40			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinical and/or Mycological Efficacy by Response at the Test-of-Cure Visit

End point title	Number of Subjects With Clinical and/or Mycological Efficacy by Response at the Test-of-Cure Visit[2]

End point description:

Clinical, mycological responses: clinical cure, clinical improvement, no clinical cure, mycological cure, no mycological cure, no mycological culture performed, death, and lost from follow-up. Subjects could have more than one responses. Responses were based on the investigator's judgement according to the Infectious Disease Society of America, European Conference on Infections in Leukemia, and European Committee on Antimicrobial Susceptibility Testing guidelines. FAS included all enrolled subjects who were administered the study medication and had post baseline documentation of efficacy available.

End point type	Primary

End point timeframe:

6 weeks after last dose of study drug

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: Only descriptive analysis was planned to be analysed in this end point.

End point values	Voriconazole			
Subject group type	Reporting group			
Number of subjects analysed	177			
Units: subjects				
Clinical Cure	54			
Clinical Improvement	46			
No Clinical Cure	7			
Mycological Cure	31			
No Mycological Cure	1			
No Mycological Culture Performed	19			
Death	41			
Lost From Follow-Up	11			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Investigator's Satisfaction with the Efficacy of Voriconazole Assessment at the End of Treatment (EOT) Visit

End point title	Number of Subjects With Investigator's Satisfaction with the Efficacy of Voriconazole Assessment at the End of Treatment (EOT) Visit[3]

End point description:

Investigator's Satisfaction Responses: very good, good, moderate, poor. Responses were based on the investigator's judgement. FAS included all enrolled subjects who were administered the study medication and had post baseline documentation of efficacy available. Here, 'number of subjects analyzed' signifies the subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to 2 weeks (EOT visit)

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: Only descriptive analysis was planned to be analysed in this end point.

End point values	Voriconazole			
Subject group type	Reporting group			
Number of subjects analysed	172			
Units: subjects				
Very Good	85			
Good	49			
Moderate	33			
Poor	5			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Investigator's Satisfaction with the Tolerability of Voriconazole Assessment at the End of Treatment (EOT) Visit

End point title	Number of Subjects With Investigator's Satisfaction with the Tolerability of Voriconazole Assessment at the End of Treatment (EOT) Visit[4]

End point description:

Investigator's Satisfaction Responses: very good, good, moderate, poor. Responses were based on the investigator's judgement. Safety population included subjects who received at least 1 dose of the study medication. Here, 'number of subjects analyzed' signifies the subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to 2 weeks (EOT visit)

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: Only descriptive analysis was planned to be analysed in this end point.

End point values	Voriconazole			
Subject group type	Reporting group			
Number of subjects analysed	174			
Units: subjects				
Very Good	105			
Good	61			
Moderate	8			
Poor	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days after the last dose of study drug

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject 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	12.1

Reporting groups

Reporting group title	Voriconazole

Reporting group description:

Subjects received Voriconazole intravenously at a loading dose of 6 milligram per kilogram (mg/kg) every 12 hours (during the first 24 hours) followed by the maintenance dose of 4 mg/kg twice daily up to 2 weeks. Subjects weighing greater than (>) 40 kg, received oral formulation at a loading dose of 400 mg twice during the first 24 hours followed by maintenance dose of 200 mg twice daily up to 2 weeks. Subjects weighing less than (<) 40 kg received oral formulation at a loading dose of 200 mg twice during the first 24 hours followed by maintenance dose of 100 mg twice daily up to 2 weeks. Paediatric subjects <12 years received 7 mg/kg intravenously or 200 mg orally twice daily up to 2 weeks.

Serious adverse events	Voriconazole		
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 177 (19.21%)		
number of deaths (all causes)	41		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Lymphocytic leukaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Neoplasm			

alternative assessment type: Systematic				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neoplasm malignant				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Non-Hodgkin’s lymphoma				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Injury, poisoning and procedural complications				
Multiple injuries				
alternative assessment type: Systematic				
subjects affected / exposed	2 / 177 (1.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Subdural haematoma				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Traumatic brain injury				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac disorders				
Acute myocardial infarction				
alternative assessment type: Systematic				

subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
alternative assessment type: Systematic				
subjects affected / exposed	5 / 177 (2.82%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 4			
Cardiopulmonary failure				
alternative assessment type: Systematic				
subjects affected / exposed	4 / 177 (2.26%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Haemorrhage intracranial				
alternative assessment type: Systematic				
subjects affected / exposed	3 / 177 (1.69%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 3			
Haemorrhagic stroke				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Locked-in syndrome				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Bone marrow disorder				
alternative assessment type: Systematic				

subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pancytopenia				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
General disorders and administration site conditions				
Disease progression				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Multi-organ failure				
alternative assessment type: Systematic				
subjects affected / exposed	8 / 177 (4.52%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 6			
Sudden death				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
alternative assessment type: Systematic				

subjects affected / exposed	3 / 177 (1.69%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 3		
Renal and urinary disorders			
Crush syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nephropathy toxic			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Aspergillosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 177 (2.82%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 3		
Sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 177 (2.26%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 3		
Septic shock			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Voriconazole		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 177 (3.39%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Vascular disorders			
Hypertensive crisis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Hepatobiliary disorders			
Liver disorder			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acrodermatitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Rash pruritic			
alternative assessment type:			

Systematic subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Infections and infestations Bronchitis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 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