Clinical trial results:
A PROSPECTIVE, OPEN-LABEL, NON-RANDOMIZED, MULTI-CENTER STUDY TO INVESTIGATE THE SAFETY AND TOLERABILITY OF VORICONAZOLE AS PRIMARY THERAPY FOR TREATMENT OF INVASIVE ASPERGILLOSIS AND MOLDS SUCH AS SCEDOSPORIUM OR FUSARIUM SPECIES IN PEDIATRIC PATIENTS

Summary

EudraCT number	2008-005275-10
Trial protocol	NL HU CZ ES DE BG Outside EU/EEA
Global end of trial date	15 May 2013

Results information

Result version number	v2 (current)
This version publication date	18 June 2016
First version publication date	25 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	A1501080

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00836875
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000191-PIP01-08
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 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 May 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of voriconazole as primary treatment of invasive aspergillosis (IA) and rare molds such as Scedosporium or Fusarium species in immunocompromised pediatric subjects from 2 to less than (<) 18 years of age.

Protection of trial subjects:

The study was in compliance with with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation (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	26 May 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	31
EEA total number of subjects	8

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)	11
Adolescents (12-17 years)	20
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study was started on 26 May 2009 and ended on 15 May 2013. Overall, 31 subjects were enrolled into the study across 7 countries.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Voriconazole: 2 to <12 Years

Arm description:

Subjects aged 2 to <12 years with possible, probable or proven IA.

Arm type	Experimental
Investigational medicinal product name	Voriconazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion, Powder for oral suspension, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

For subjects aged 2 to <12 years, voriconazole was administered at a loading dose of 9 milligrams per kg (mg/kg), intravenously (IV) every 12 hours (q12h) for the first 24 hours, followed by maintenance IV dosing regimen of 8 mg/kg IV q12h for a minimum of 7 days. Once significant clinical improvement was observed, subjects could be switched to oral (PO) dosing regimen of 9 mg/kg (a maximum dose of 350 mg) PO q12h. Investigators used subject, tolerability and voriconazole trough plasma levels to facilitate dose adjustments. All subjects received voriconazole therapy for at least 6 weeks, up to a maximum of 12 weeks.

Arm title	Voriconazole: 12 to <18 Years

Arm description:

Subjects aged 12 to <18 years with possible, probable or proven IA.

Arm type	Experimental
Investigational medicinal product name	Voriconazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion, Powder for oral suspension, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

For subjects aged 12 to <18 years (excluding those aged 12--14 years weighing <50 kg), voriconazole was administered at loading doses of 6 mg/kg, IV, q12h for the first 24 hours, followed by maintenance IV dosing regimen of 4 mg/kg IV q12h for a minimum of 7 days. Once significant clinical improvement was observed, subjects could be switched to oral dosing regimen of 200-300 mg PO q12h. Investigators used subject, tolerability and voriconazole trough plasma levels to facilitate dose adjustments. All subjects received voriconazole therapy for at least 6 weeks, up to a maximum of 12 weeks.

Number of subjects in period 1	Voriconazole: 2 to <12 Years	Voriconazole: 12 to <18 Years
Started	11	20
Completed	8	17
Not completed	3	3
Consent withdrawn by subject	-	1
Death	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Voriconazole: 2 to <12 Years
Reporting group description:	
Subjects aged 2 to <12 years with possible, probable or proven IA.	
Reporting group title	Voriconazole: 12 to <18 Years
Reporting group description:	
Subjects aged 12 to <18 years with possible, probable or proven IA.	

Reporting group values	Voriconazole: 2 to <12 Years	Voriconazole: 12 to <18 Years	Total
Number of subjects	11	20	31
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	7.9	14.1	
standard deviation	± 2.3	± 1.7	-
Gender categorical Units: Subjects			
Female	4	11	15
Male	7	9	16

End points

End points reporting groups

Reporting group title	Voriconazole: 2 to <12 Years
Reporting group description:	
Subjects aged 2 to <12 years with possible, probable or proven IA.	
Reporting group title	Voriconazole: 12 to <18 Years
Reporting group description:	
Subjects aged 12 to <18 years with possible, probable or proven IA.	

Primary: Number of Subjects With Adverse Events (AEs)

End point title	Number of Subjects With Adverse Events (AEs)[1]
End point description:	
Safety population: included all subjects who received at least 1 dose of study medication.	
End point type	Primary
End point timeframe:	
Baseline, daily while hospitalized, Days 7, 14, 28, 42, 84, 114, at end of treatment, up to 1 month post treatment	

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 analyzed for the endpoint.

End point values	Voriconazole: 2 to <12 Years	Voriconazole: 12 to <18 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	20		
Units: Subjects				
With AEs	11	19		
With serious AEs	6	9		
With severe AEs	5	8		
Discontinued treatment due to AEs	1	0		
Dose reduced or temporarily discontinued due to AE	0	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Global Response of Success

End point title	Percentage of Subjects With a Global Response of Success
End point description:	
Percentage of subjects with global response of success at Weeks 6 and at end of treatment (EOT) (up to Week 12). Global response of success was defined as a subject who achieved a complete or partial global response per the investigator. Complete response was defined as resolution of all clinical signs and symptoms PLUS resolution of 90 percent (%) or more of the lesions visible on radiological studies and attributed to invasive aspergillosis (IA) at Baseline. Partial response was defined as clinical improvement PLUS 50% to <90 % resolution of the radiological lesions attributed to IA at Baseline.	

Modified intent to treat (MITT) population: all subjects receiving at least 1 dose of study drug and diagnosed with proven or probable aspergillosis (defined by modified European Organization for Research and Treatment of Cancer Mycoses Study Group [EORTC/MSC] criteria) or microbiologically confirmed scedosporium or fusarium infection.

End point type	Secondary

End point timeframe:

Weeks 6, EOT (up to Week 12)

End point values	Voriconazole: 2 to <12 Years	Voriconazole: 12 to <18 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	9		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 6	40 (5.3 to 85.3)	77.8 (40 to 97.2)		
EOT	40 (5.3 to 85.3)	77.8 (40 to 97.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: All-Cause Mortality - Number of Subjects Deaths

End point title	All-Cause Mortality - Number of Subjects Deaths

End point description:

Number of subject deaths reported at Week 6 and at EOT (up to Week 12). Safety population.

End point type	Secondary

End point timeframe:

Week 6, EOT (up to Week 12)

End point values	Voriconazole: 2 to <12 Years	Voriconazole: 12 to <18 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	20		
Units: Subjects				
Week 6	3	1		
EOT	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Attributable Mortality - Number of Subject Deaths

End point title	Attributable Mortality - Number of Subject Deaths

End point description:

Number of subject deaths attributable to study drug reported at Week 6 and at EOT (up to Week 12). Safety population.

End point type	Secondary

End point timeframe:

Weeks 6 and EOT (up to Week 12)

End point values	Voriconazole: 2 to <12 Years	Voriconazole: 12 to <18 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	20		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Death

End point title	Time to Death

End point description:

Safety population; only subjects who died were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline up to 1 month post treatment

End point values	Voriconazole: 2 to <12 Years	Voriconazole: 12 to <18 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: days				
median (full range (min-max))	30 (18 to 38)	47.5 (20 to 75)		

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 treatment

Adverse event reporting additional description:

The same event may appear as both an AE and a Serious AE (SAE). However, what is presented are distinct events. An event may be categorized as serious in one 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	16.0

Reporting groups

Reporting group title	Voriconazole: 2 to <12 Years

Reporting group description:

Subjects aged 2 to <12 years with possible, probable or proven IA.

Reporting group title	Voriconazole: 12 to <18 Years

Reporting group description:

Subjects aged 12 to <18 years with possible, probable or proven IA.

Serious adverse events	Voriconazole: 2 to <12 Years	Voriconazole: 12 to <18 Years	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 11 (54.55%)	9 / 20 (45.00%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Aneurysm ruptured			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			
Endotracheal intubation			

subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Coagulopathy			

subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 11 (9.09%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gingival bleeding			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 11 (9.09%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Aspergillosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 11 (9.09%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	2 / 11 (18.18%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Voriconazole: 2 to <12 Years	Voriconazole: 12 to <18 Years	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 11 (90.91%)	19 / 20 (95.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

Hypotension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Phlebitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Catheter site discharge			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Catheter site pain			
subjects affected / exposed	1 / 11 (9.09%)	2 / 20 (10.00%)	
occurrences (all)	3	2	
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infusion site pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Local swelling			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Mucosal inflammation			
subjects affected / exposed	0 / 11 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	5	
Oedema peripheral			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Pain			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	5	
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	7 / 20 (35.00%)	
occurrences (all)	0	9	
Reproductive system and breast disorders			

Genital swelling			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Vulvar erosion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	2 / 11 (18.18%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Epistaxis			
subjects affected / exposed	2 / 11 (18.18%)	4 / 20 (20.00%)	
occurrences (all)	2	8	
Haemoptysis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypoxia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	1 / 11 (9.09%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Oropharyngeal pain			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Pharyngeal inflammation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rales			

subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Tachypnoea			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Psychiatric disorders			
Affect lability			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Blood phosphorus decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood potassium increased			

subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood pressure increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Blood uric acid increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Cardiac murmur			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Liver function test abnormal			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Oxygen saturation decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Prothrombin time prolonged			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Respirovirus test positive			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Transaminases increased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	4	
Weight decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	1 / 11 (9.09%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Contusion			

subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Excoriation			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Incorrect drug administration rate			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	2 / 11 (18.18%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Central nervous system lesion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Dizziness			
subjects affected / exposed	0 / 11 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	4	
Headache			
subjects affected / exposed	1 / 11 (9.09%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Lethargy			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Paraesthesia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Disseminated intravascular coagulation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Febrile neutropenia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Lymphadenitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Neutrophilia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pancytopenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	1 / 11 (9.09%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Asthenopia			

subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	2		
Cataract				
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Chromatopsia				
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Conjunctival haemorrhage				
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)		
occurrences (all)	1	0		
Conjunctivitis				
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)		
occurrences (all)	0	3		
Diplopia				
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Dry eye				
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)		
occurrences (all)	1	0		
Eye discharge				
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)		
occurrences (all)	1	0		
Eye irritation				
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Eye pain				
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Photophobia				
subjects affected / exposed	1 / 11 (9.09%)	1 / 20 (5.00%)		
occurrences (all)	1	2		
Vision blurred				
subjects affected / exposed	0 / 11 (0.00%)	3 / 20 (15.00%)		
occurrences (all)	0	3		
Visual impairment				

subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	4	
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Anal fissure			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 11 (9.09%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	3 / 11 (27.27%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Dysphagia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Haematemesis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

Lip dry			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Mouth haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Mouth ulceration			
subjects affected / exposed	1 / 11 (9.09%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Painful defaecation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Proctalgia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 11 (9.09%)	1 / 20 (5.00%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Jaundice cholestatic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic			

subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)		
occurrences (all)	1	0		
Dermatitis contact				
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)		
occurrences (all)	1	0		
Dermatitis exfoliative				
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	2		
Dry skin				
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Ecchymosis				
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)		
occurrences (all)	1	0		
Erythema				
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Heat rash				
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Hyperhidrosis				
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)		
occurrences (all)	1	0		
Ingrowing nail				
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Petechiae				
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Pigmentation disorder				
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Post inflammatory pigmentation change				
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)		
occurrences (all)	1	0		

Pruritus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rash macular			
subjects affected / exposed	1 / 11 (9.09%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Rash maculo-papular			
subjects affected / exposed	2 / 11 (18.18%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Red man syndrome			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Scab			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin burning sensation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Toxic skin eruption			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pollakiuria			

subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Renal failure			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	0 / 11 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	4	
Muscle spasms			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 11 (9.09%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Pain in jaw			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Bacteraemia			

subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Cytomegalovirus infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Device related infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Implant site pustules			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Postoperative wound infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Staphylococcal infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Systemic candida			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	3 / 11 (27.27%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Fluid retention			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypercalcaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Hyperuricaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Hypocalcaemia			
subjects affected / exposed	3 / 11 (27.27%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Hypokalaemia			
subjects affected / exposed	1 / 11 (9.09%)	3 / 20 (15.00%)	
occurrences (all)	2	3	
Hypomagnesaemia			
subjects affected / exposed	2 / 11 (18.18%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Hyponatraemia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Hypophosphataemia			
subjects affected / exposed	3 / 11 (27.27%)	0 / 20 (0.00%)	
occurrences (all)	5	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2008	1. Added attributable mortality as a study endpoint. 2. Added Electrocardiography (ECGs) and vital signs to the primary analysis of AEs, tests and added significant ECG and vital signs changes to safety data summaries. 3. Added requirement for formal ophthalmologic exam(including fundoscopic exam) if a treatment-emergent visual AE was noted and added follow-up procedures for subjects with treatment-emergent visual AEs persisting at 1-month follow-up (FU) visit. 4. Expanded eligible diagnoses to include infection due to rare molds such as Scedosporium or Fusarium species and specified that mycology, histology,and cytology assessments were to be done at local site. 5. Clarified definition of discontinuation and required that discontinuations due to AEs be documented, reported immediately to the sponsor, and followed or referred for follow-up. 6. Added EOT as an analysis timepoint and the 6-week timepoint to global response assessment. 7. Changed primary analysis definition to include treatment-emergent AEs,ECGs, vital signs and not include physical examinations. 8. Added ECGs and vital signs to primary analysis of AEs, tests and added significant ECG and vital signs changes to safety data summaries. 9. Added text describing the option of an earlier switch to oral dosing. 10. Revised and clarified exclusion criteria. 11. Added a Week 6 treatment visit and defined the associated assessments and procedures. 12. Changed the time period for monitoring AEs to conclude with the 1-month FU visit. 13. Revised dosing recommendations for subjects with elevated voriconazole levels and clarified collection of plasma peak and trough samples. 14. Included male subjects in contraceptive guidelines and clarified the acceptability of complete abstinence. 15. Added Sections describing dose reductions and describing dose escalations. 16. Revised procedures for subjects discontinued for rescue therapy. 17. Reduced the samples for galactomannan assay at EOT from 2 to 1.
14 July 2010	1. Specified the approximate total blood sampling volume for a subject during the study and restricted the total volume to 150 milliliter (mL) or less. 2. Required that of the 15 subjects with proven or probable IA, a minimum of 10 subjects evaluable for safety were enrolled from the 2 to <12 years age-group and stated that subjects would receive a total of 6 to 12 weeks of therapy. 3. Added the correlation between CYP2C19 genotype status and voriconazole exposure as an exploratory endpoint and added a requirement for the collection of 2 buccal swab samples at baseline or during the study. 4. Clarified the conditions for switching to oral voriconazole therapy and modified the dosing scheme and infusion rates. 5. Revised the requirements and recommendations for voriconazole level plasma sample collection on Day 3 and after dose adjustments. 6. Updated the dosing scheme for children (2 to <12 years of age) and adolescents 12 to 14 years of age weighing less than 50 kg based on the results of 2 recently completed PK studies (A1501081 and A1501088) to allow enrollment in the younger age-group (children). 7. Added the requirement for assent from children who, per the investigator's judgment, were able to comprehend and as required by local regulations.

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.

The study was prematurely terminated due to slow enrollment. The study was not terminated due to any safety issues or concerns. Interpretation of the data are limited due to the small sample size and descriptive design.

Notes: