Clinical trial results:
An open label, intravenous to oral switch, multiple dose study to evaluate the pharmacokinetics, safety and tolerability of voriconazole in immunocompromised adolescents aged 12 to less than (<) 17 years who were at high risk for systemic fungal infection

Summary

EudraCT number	2012-001151-39
Trial protocol	Outside EU/EEA
Global end of trial date	02 December 2009

Results information

Result version number	v1 (current)
This version publication date	13 April 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	A1501081

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00556998
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 East 42nd Street, New York, United States, NY 10017
Public contact	Pfizer Clinical Trials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.govCallCenter@pfizer.com
Scientific contact	Pfizer Clinical Trials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.govCallCenter@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	24 May 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 December 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the pharmacokinetics of voriconazole following an intravenous (IV) to oral switch regimen in immunocompromised adolescent subjects aged 12 to <17 years who were at high risk for systemic fungal infection.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 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	United States: 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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	26
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:

Total 26 subjects were recruited from 10 sites in United States. Study started on 10 June 2008 and completed on 02 December 2009.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All Subjects

Arm description:

Voriconazole intravenous (IV) loading doses every 12 hours on Day 1 and maintenance IV doses every 12 hours on Days 2 to 7 (up to Day 20 if clinically indicated). The oral maintenance dosing regimen was administered following voriconazole IV and lasted 6.5 days (up to Day 30 if clinically indicated).

Arm type	Experimental
Investigational medicinal product name	Voriconazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Oral suspension
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Voriconazole IV loading dose of 6 milligram per kilogram (mg/kg) in the morning and evening on Day 1 and multiple IV doses of 4 mg/kg in the morning and evening on Days 2 to 7, up to Day 20 if clinically indicated. Oral maintenance dosing regimen of 300 mg every 12 hours or 150 mg every 12 hours if subject weighed less than 40 kg was administered following voriconazole IV and lasted 6.5 days, up to Day 30 if clinically indicated. One subject received 2 days of oral regimen then received IV again before discontinuing from study.

Number of subjects in period 1	All Subjects
Started	26
Completed	26

Period 2	
Period 2 title	Voriconazole IV
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Voriconazole IV

Arm description:

Voriconazole IV loading doses every 12 hours on Day 1 and maintenance IV doses every 12 hours on Days 2 to 7 (up to Day 20 if clinically indicated).

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

Dosage and administration details:

Voriconazole IV loading dose (6 mg/kg every 12 hours) in the morning and evening on Day 1 and multiple IV doses (4 mg/kg every 12 hours) in the morning and evening on Days 2 to 7, up to Day 20 if clinically indicated. One subject received 2 days of oral regimen then received IV again before discontinuing from

Number of subjects in period 2	Voriconazole IV
Started	26
Completed	21
Not completed	5
Adverse event	1
Unspecified	4

Period 3	
Period 3 title	Voriconazole Oral
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Voriconazole Oral

Arm description:

Voriconazole oral doses were administered following voriconazole IV and lasted 6.5 days (up to Day 30 if clinically indicated).

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

Dosage and administration details:

The oral maintenance dosing regimen of 300 mg every 12 hours or 150 mg every 12 hours if subject weighed less than 40 kg was administered following voriconazole IV and lasted 6.5 days, up to Day 30 if clinically indicated. One subject received voriconazole 150 mg every 12 hours during oral phase.

Number of subjects in period 3	Voriconazole Oral
Started	21
Completed	20
Not completed	1
Adverse event	1

Baseline characteristics

Reporting groups	
Reporting group title	All Subjects

Reporting group description:

Voriconazole intravenous (IV) loading doses every 12 hours on Day 1 and maintenance IV doses every 12 hours on Days 2 to 7 (up to Day 20 if clinically indicated). The oral maintenance dosing regimen was administered following voriconazole IV and lasted 6.5 days (up to Day 30 if clinically indicated).

Reporting group values	All Subjects	Total	
Number of subjects	26	26	
Age categorical			
Units: Subjects			
12 years	4	4	
13 years	10	10	
Greater than (>) 13 to >17 years	12	12	
Age continuous			
Units: years			
arithmetic mean	13.7		
standard deviation	± 1.3	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	17	17	

End points

End points reporting groups

Reporting group title	All Subjects

Reporting group description:

Voriconazole intravenous (IV) loading doses every 12 hours on Day 1 and maintenance IV doses every 12 hours on Days 2 to 7 (up to Day 20 if clinically indicated). The oral maintenance dosing regimen was administered following voriconazole IV and lasted 6.5 days (up to Day 30 if clinically indicated).

Reporting group title	Voriconazole IV

Reporting group description:

Voriconazole IV loading doses every 12 hours on Day 1 and maintenance IV doses every 12 hours on Days 2 to 7 (up to Day 20 if clinically indicated).

Reporting group title	Voriconazole Oral

Reporting group description:

Voriconazole oral doses were administered following voriconazole IV and lasted 6.5 days (up to Day 30 if clinically indicated).

Primary: Area Under the Curve Over Dosing Interval at Steady State (AUC12,ss) Following IV Administration

End point title	Area Under the Curve Over Dosing Interval at Steady State (AUC12,ss) Following IV Administration[1]

End point description:

AUC12,ss = Area under the plasma concentration-time profile from time zero (predose) to twelve hours at steady-state. AUC12,ss was obtained by the Linear/Log trapezoidal method. Intent to treat (ITT) population of subjects who had completed pharmacokinetic (PK) blood sampling for at least one day.

End point type	Primary

End point timeframe:

Day 7 (up to Day 20) at predose, 40, 78 minutes, 4, 6, 8 and 12 hours after start of infusion

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.

End point values	Voriconazole IV			
Subject group type	Reporting group			
Number of subjects analysed	23[2]			
Units: microgram (mcg)*hour (h)/milliliter (mL)				
geometric mean (standard deviation)	22.39 (± 21.47)			

Notes:

[2] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Primary: Peak Plasma Concentration at Steady State (Cmax,ss) Following IV Administration

End point title	Peak Plasma Concentration at Steady State (Cmax,ss) Following IV Administration[3]

End point description:

ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Primary

End point timeframe:

Day 7 (up to Day 20) at predose, 40, 78 minutes, 4, 6, 8 and 12 hours after start of infusion

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 data was planned to be reported.

End point values	Voriconazole IV			
Subject group type	Reporting group			
Number of subjects analysed	23[4]			
Units: mcg/mL				
geometric mean (standard deviation)	3.89 (± 2.59)			

Notes:

[4] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach Cmax (Tmax) Following IV Administration

End point title	Time to Reach Cmax (Tmax) Following IV Administration[5]

End point description:

ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Primary

End point timeframe:

Day 7 (up to Day 20) at predose, 40, 78 minutes, 4, 6, 8 and 12 hours after start of infusion

Notes:

[5] - 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.

End point values	Voriconazole IV			
Subject group type	Reporting group			
Number of subjects analysed	23[6]			
Units: hours				
median (full range (min-max))	1.3 (1.17 to 3.95)			

Notes:

[6] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Primary: AUC12,ss Following Oral Administration

End point title	AUC12,ss Following Oral Administration[7]

End point description:

AUC12,ss = Area under the plasma concentration-time profile from time zero (predose) to twelve hours at steady-state. AUC12,ss was obtained by the Linear/Log trapezoidal method. ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Primary

End point timeframe:

Day 7 (up to Day 30) at predose, 1, 2, 4, 6, 8, and 12 hours postdose

Notes:

[7] - 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.

End point values	Voriconazole Oral			
Subject group type	Reporting group			
Number of subjects analysed	19[8]			
Units: mcg*h/mL				
geometric mean (standard deviation)	16.74 (± 13.5)			

Notes:

[8] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Primary: Cmax,ss Following Oral Administration

End point title	Cmax,ss Following Oral Administration[9]

End point description:

ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Primary

End point timeframe:

Day 7 (up to Day 30) at predose, 1, 2, 4, 6, 8, and 12 hours postdose

Notes:

[9] - 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.

End point values	Voriconazole Oral			
Subject group type	Reporting group			
Number of subjects analysed	19[10]			
Units: mcg/mL				
geometric mean (standard deviation)	2.35 (± 1.41)			

Notes:

[10] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Primary: Tmax Following Oral Administration

End point title	Tmax Following Oral Administration[11]

End point description:

ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Primary

End point timeframe:

Day 7 (up to Day 30) Predose, 1, 2, 4, 6, 8, and 12 hours postdose

Notes:

[11] - 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.

End point values	Voriconazole Oral			
Subject group type	Reporting group			
Number of subjects analysed	19[12]			
Units: hours				
median (full range (min-max))	2 (0.67 to 8.1)			

Notes:

[12] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: AUC12 Following IV Loading Dose

End point title	AUC12 Following IV Loading Dose

End point description:

AUC12 = Area under the plasma concentration-time profile from time zero (predose) to twelve hours. AUC12 was obtained by the Linear/Log trapezoidal method. ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Secondary

End point timeframe:

Day 1 at predose, 60, 118 minutes, 4, 6, 8 and 12 hours after start of infusion

End point values	Voriconazole IV			
Subject group type	Reporting group			
Number of subjects analysed	22[13]			
Units: mcg*h/mL				
geometric mean (standard deviation)	9.14 (± 4.9)			

Notes:

[13] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax Following an IV Loading Dose

End point title	Tmax Following an IV Loading Dose

End point description:

ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Secondary

End point timeframe:

Day 1 at predose, 60, 118 minutes, 4, 6, 8 and 12 hours after start of infusion

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	22[14]			
Units: hours				
median (full range (min-max))	1.97 (1.9 to 2.08)			

Notes:

[14] - N signifies number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax Following an IV Loading Dose

End point title	Cmax Following an IV Loading Dose

End point description:

ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Secondary

End point timeframe:

Day 1 at predose, 60, 118 minutes, 4, 6, 8 and 12 hours after start of infusion

End point values	Voriconazole IV			
Subject group type	Reporting group			
Number of subjects analysed	22[15]			
Units: mcg/mL				
geometric mean (standard deviation)	2.25 (± 0.86)			

Notes:

[15] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Plasma Trough Concentration (Cmin)

End point title	Minimum Observed Plasma Trough Concentration (Cmin)

End point description:

ITT population of subjects who had completed PK blood sampling for at least one day. Here 'n', signifies the number of subjects who contributed to the data.

End point type	Secondary

End point timeframe:

Day 7 (up to Day 20) for IV; Day 7 (up to Day 30) for oral at predose

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	21[16]			
Units: mcg/mL				
geometric mean (standard deviation)				
IV Day 7 (up to Day 20) (n=21) Oral Day 7 (up to Day 30) (n=19)	1.05 (± 1.85) 0.72 (± 0.81)			

Notes:

[16] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: AUC12,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following IV Administration

End point title	AUC12,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following IV Administration

End point description:

AUC12,ss = Area under the plasma concentration-time profile from time zero (predose) to twelve hours at steady-state. AUC12,ss was obtained by the Linear/Log trapezoidal method. ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Secondary

End point timeframe:

Day 1 at predose, 60, 118 minutes, 4, 6, 8 and 12 hours after start of infusion, Day 7 (up to Day 20) at predose, 40, 78 minutes, 4, 6 8 and 12 hours after start of infusion

End point values	Voriconazole IV			
Subject group type	Reporting group			
Number of subjects analysed	25[17]			
Units: mcg*h/mL				
geometric mean (standard deviation)				
Day 1 Day 7 (up to Day 20)	21.18 (± 6.8) 36.21 (± 9.2)			

Notes:

[17] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following IV Administration

End point title	Cmax,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following IV Administration

End point description:

ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Secondary

End point timeframe:

Day 1 at predose, 60, 118 minutes, 4, 6, 8 and 12 hours after start of infusion and on Day 7 (up to Day 20) at predose, 40, 78 minutes, 4, 6 8 and 12 hours after start of infusion

End point values	Voriconazole IV			
Subject group type	Reporting group			
Number of subjects analysed	25[18]			
Units: mcg/mL				
geometric mean (standard deviation)				
Day 1	2.5 (± 0.84)			
Day 7 (up to Day 20)	3.48 (± 0.73)			

Notes:

[18] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of N-oxide Voriconazole Metabolite (UK-121, 265) Following IV Administration

End point title	Tmax of N-oxide Voriconazole Metabolite (UK-121, 265) Following IV Administration

End point description:

ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Secondary

End point timeframe:

Day 1 at predose, 60, 118 minutes, 4, 6, 8 and 12 hours after start of infusion and on Day 7 (up to Day 20) at predose, 40, 78 minutes, 4, 6 8 and 12 hours after start of infusion

End point values	Voriconazole IV			
Subject group type	Reporting group			
Number of subjects analysed	25[19]			
Units: mcg*h/mL				
median (full range (min-max))				
Day 1 Day 7 (up to Day 20)	4 (1.97 to 8.03) 4.03 (0 to 12.1)			

Notes:

[19] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: AUC12,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following Oral Administration

End point title	AUC12,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following Oral Administration

End point description:

AUC12,ss = Area under the plasma concentration-time profile from time zero (predose) to twelve hours at steady-state. AUC12,ss was obtained by the Linear/Log trapezoidal method. ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Secondary

End point timeframe:

On Day 7 (up to Day 30) at predose, 1, 2, 4, 6, 8, and 12 hours postdose

End point values	Voriconazole Oral			
Subject group type	Reporting group			
Number of subjects analysed	19[20]			
Units: mcg*h/mL				
geometric mean (standard deviation)	44.07 (± 13.86)			

Notes:

[20] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following Oral Administration

End point title	Cmax,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following Oral Administration

End point description:

ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Secondary

End point timeframe:

Day 7 (up to Day 30) at predose, 1, 2, 4, 6, 8, and 12 hours postdose

End point values	Voriconazole Oral			
Subject group type	Reporting group			
Number of subjects analysed	19[21]			
Units: µg/mL				
geometric mean (standard deviation)	4.44 (± 1.43)			

Notes:

[21] - Number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of N-oxide Voriconazole Metabolite (UK-121, 265) Following Oral Administration

End point title	Tmax of N-oxide Voriconazole Metabolite (UK-121, 265) Following Oral Administration

End point description:

ITT population of subjects who had completed PK blood sampling for at least one day.

End point type	Secondary

End point timeframe:

Day 7 (up to Day 30) at predose, 1, 2, 4, 6, 8, and 12 hours postdose

End point values	Voriconazole Oral			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: hours				
median (full range (min-max))	5.97 (1 to 8.1)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic Parameters of Voriconazole in Adolescents Compared to Historical Adult Data - AUC12 IV Loading Dose

End point title	Pharmacokinetic Parameters of Voriconazole in Adolescents

	Compared to Historical Adult Data - AUC12 IV Loading Dose

End point description:

Data for this Outcome Measure was not reported here because the analysis population included subjects who were not enrolled in this study.

End point type	Other pre-specified

End point timeframe:

Day 1

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	0[22]			
Units: mcg*h/mL				
geometric mean (standard deviation)	()			

Notes:

[22] - Data was not reported because the analysis included subjects who were not enrolled in this study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters of voriconazole in adolescents compared to historical adult data - AUC12 IV steady state

End point title	Pharmacokinetic parameters of voriconazole in adolescents compared to historical adult data - AUC12 IV steady state

End point description:

Data for this Outcome Measure was not reported here because the analysis population includes subjects who were not enrolled in this study.

End point type	Other pre-specified

End point timeframe:

Day 7 of IV dosing

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	0[23]			
Units: mcg*h/mL				
geometric mean (standard deviation)	()			

Notes:

[23] - Data was not reported because the analysis included subjects who were not enrolled in this study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters of voriconazole in adolescents compared to historical adult data - AUC12 oral dose all subjects

End point title	Pharmacokinetic parameters of voriconazole in adolescents

	compared to historical adult data - AUC12 oral dose all subjects

End point description:

Data for this Outcome Measure was not reported here because the analysis population includes subjects who were not enrolled in this study.

End point type	Other pre-specified

End point timeframe:

Day 7 Oral dosing

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	0[24]			
Units: mcg*h/mL				
geometric mean (standard deviation)	()			

Notes:

[24] - Data was not reported because the analysis included subjects who were not enrolled in this study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters of voriconazole in adolescents compared to historical adult data - AUC12 Oral 300mg

End point title	Pharmacokinetic parameters of voriconazole in adolescents compared to historical adult data - AUC12 Oral 300mg

End point description:

Data for this Outcome Measure was not reported here because the analysis population includes subjects who were not enrolled in this study.

End point type	Other pre-specified

End point timeframe:

Day 7 oral dosing

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	0[25]			
Units: mcg*h/mL				
geometric mean (standard deviation)	()			

Notes:

[25] - Data was not reported because the analysis included subjects who were not enrolled in this study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters of voriconazole in adolescents compared to historical adult data - Cmax IV Loading dose

End point title	Pharmacokinetic parameters of voriconazole in adolescents

	compared to historical adult data - Cmax IV Loading dose

End point description:

Data for this Outcome Measure was not reported here because the analysis population includes subjects who were not enrolled in this study.

End point type	Other pre-specified

End point timeframe:

Day 1

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	0[26]			
Units: mcg/mL				
geometric mean (standard deviation)	()			

Notes:

[26] - Data was not reported because the analysis included subjects who were not enrolled in this study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters of voriconazole in adolescents compared to historical adult data - Cmax IV steady state

End point title	Pharmacokinetic parameters of voriconazole in adolescents compared to historical adult data - Cmax IV steady state

End point description:

Data for this Outcome Measure was not reported here because the analysis population includes subjects who were not enrolled in this study.

End point type	Other pre-specified

End point timeframe:

Day 7 of Intravenous dosing

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	0[27]			
Units: mcg*h/mL				
geometric mean (standard deviation)	()			

Notes:

[27] - Data was not reported because the analysis included subjects who were not enrolled in this study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters of voriconazole in adolescents compared to historical adult data - Cmax Day 7 oral all subjects

End point title	Pharmacokinetic parameters of voriconazole in adolescents

	compared to historical adult data - Cmax Day 7 oral all subjects

End point description:

Data for this Outcome Measure was not reported here because the analysis population includes subjects who were not enrolled in this study.

End point type	Other pre-specified

End point timeframe:

Day 7 of oral dosing

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	0[28]			
Units: mcg/mL				
geometric mean (standard deviation)	()			

Notes:

[28] - Data was not reported because the analysis included subjects who were not enrolled in this study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters of voriconazole in adolescents compared to historical adult data - Cmax 300 mg oral dose

End point title	Pharmacokinetic parameters of voriconazole in adolescents compared to historical adult data - Cmax 300 mg oral dose

End point description:

Data for this Outcome Measure was not reported here because the analysis population includes subjects who were not enrolled in this study.

End point type	Other pre-specified

End point timeframe:

Day 7 of oral dosing

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	0[29]			
Units: mcg/mL				
geometric mean (standard deviation)	()			

Notes:

[29] - Data was not reported because the analysis included subjects who were not enrolled in this study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 1 month after last dose of investigational product

Adverse event reporting additional description:

The same event may appear as both an adverse event (AE) and a serious AE (SAE). An event may be categorized as serious in one subject and as nonserious in an other subject. EU BR specific AE tables were generated separately as per EU format using latest coding.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Voriconazole Oral

Reporting group description:

Voriconazole oral maintenance dosing regimen (300 mg every 12 hours or 150 mg every 12 hours if subject weighed less than 40 kg) was administered following voriconazole IV and lasted 6.5 days (up to Day 30 if clinically indicated).

Reporting group title	Voriconazole IV

Reporting group description:

Voriconazole IV loading doses (6 mg/kg every 12 hours) hours on Day 1 and maintenance IV doses (4 mg/kg every 12 hours) on Days 2 to 7 (up to Day 20 if clinically indicated).

Serious adverse events	Voriconazole Oral	Voriconazole IV	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 22 (18.18%)	4 / 26 (15.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			

subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
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			
Neutropenia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in liver			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Alpha haemolytic streptococcal infection			

subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (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: 0 %

Non-serious adverse events	Voriconazole Oral	Voriconazole IV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	26 / 26 (100.00%)	
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Hypotension			

subjects affected / exposed	5 / 22 (22.73%)	2 / 26 (7.69%)	
occurrences (all)	5	3	
Hypertension			
subjects affected / exposed	6 / 22 (27.27%)	4 / 26 (15.38%)	
occurrences (all)	6	4	
Vena cava thrombosis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Oxygen supplementation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Chills			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Device occlusion			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Drug withdrawal syndrome			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Face oedema			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Gait disturbance			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Generalised oedema			

subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation			
subjects affected / exposed	9 / 22 (40.91%)	11 / 26 (42.31%)	
occurrences (all)	13	13	
Oedema			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	4 / 22 (18.18%)	1 / 26 (3.85%)	
occurrences (all)	4	1	
Pain			
subjects affected / exposed	2 / 22 (9.09%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Pyrexia			
subjects affected / exposed	5 / 22 (22.73%)	13 / 26 (50.00%)	
occurrences (all)	11	17	
Suprapubic pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Engraftment syndrome			
subjects affected / exposed	1 / 22 (4.55%)	3 / 26 (11.54%)	
occurrences (all)	1	3	
Graft versus host disease			
subjects affected / exposed	3 / 22 (13.64%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Graft versus host disease in skin			

subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Social circumstances			
Refusal of treatment by patient			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Perineal pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Pruritus genital			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Scrotal pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Vulvovaginal discomfort			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	4 / 22 (18.18%)	1 / 26 (3.85%)	
occurrences (all)	4	1	
Epistaxis			
subjects affected / exposed	3 / 22 (13.64%)	2 / 26 (7.69%)	
occurrences (all)	3	3	
Hypoxia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			

subjects affected / exposed	1 / 22 (4.55%)	3 / 26 (11.54%)	
occurrences (all)	1	3	
Pulmonary oedema			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Rales			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Respiratory depression			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Respiratory distress			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Sneezing			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Tachypnoea			
subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Confusional state			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Drug dependence			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

Flat affect			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Mental status changes			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	3 / 22 (13.64%)	2 / 26 (7.69%)	
occurrences (all)	3	2	
Nightmare			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Blood bilirubin increased			
subjects affected / exposed	2 / 22 (9.09%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Blood cortisol decreased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	2 / 22 (9.09%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Blood pressure systolic increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Blood triglycerides increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Blood urea increased			

subjects affected / exposed	1 / 22 (4.55%)	2 / 26 (7.69%)		
occurrences (all)	1	4		
Breath sounds abnormal				
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)		
occurrences (all)	1	0		
CSF protein increased				
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)		
occurrences (all)	1	0		
Cardiac function test abnormal				
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)		
occurrences (all)	1	1		
Cytomegalovirus test positive				
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)		
occurrences (all)	1	1		
Electrocardiogram QT prolonged				
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)		
occurrences (all)	0	1		
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)		
occurrences (all)	1	1		
Hepatic enzyme increased				
subjects affected / exposed	3 / 22 (13.64%)	3 / 26 (11.54%)		
occurrences (all)	3	4		
Immunosuppressant drug level increased				
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)		
occurrences (all)	1	1		
Oxygen saturation decreased				
subjects affected / exposed	5 / 22 (22.73%)	1 / 26 (3.85%)		
occurrences (all)	6	1		
Transaminases increased				
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)		
occurrences (all)	2	1		
Viral test positive				

subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Weight decreased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
White blood cell count increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Ear abrasion			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Head injury			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Radiation pneumonitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Refractoriness to platelet transfusion			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Colour blindness			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	

Dizziness			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Drooling			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Dystonia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Encephalopathy			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	3 / 22 (13.64%)	4 / 26 (15.38%)	
occurrences (all)	3	4	
Mental impairment			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Myoclonus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Neuralgia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Neuropathy peripheral			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Nystagmus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Restless legs syndrome			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	

Sedation			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Tremor			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Anaemia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Leukopenia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Febrile neutropenia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	2 / 22 (9.09%)	3 / 26 (11.54%)	
occurrences (all)	2	3	
Pancytopenia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Thrombocytopenia			
subjects affected / exposed	3 / 22 (13.64%)	3 / 26 (11.54%)	
occurrences (all)	3	3	
Ear and labyrinth disorders			
Ear canal erythema			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Conjunctivitis allergic			

subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Conjunctival irritation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Dry eye			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Hypermetropia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Photophobia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Strabismus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Abdominal pain			
subjects affected / exposed	3 / 22 (13.64%)	2 / 26 (7.69%)	
occurrences (all)	3	2	
Anorectal disorder			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Ascites			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	2	1	

Breath odour			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Chapped lips			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	5 / 22 (22.73%)	5 / 26 (19.23%)	
occurrences (all)	6	5	
Constipation			
subjects affected / exposed	4 / 22 (18.18%)	2 / 26 (7.69%)	
occurrences (all)	4	2	
Dyspepsia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Dysphagia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Faecal volume increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Frequent bowel movements			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Gingival bleeding			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Haematemesis			
subjects affected / exposed	3 / 22 (13.64%)	2 / 26 (7.69%)	
occurrences (all)	3	2	

Haematochezia				
subjects affected / exposed	3 / 22 (13.64%)	2 / 26 (7.69%)		
occurrences (all)	3	2		
Haemorrhoids				
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)		
occurrences (all)	1	0		
Lip dry				
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)		
occurrences (all)	0	1		
Lip haemorrhage				
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)		
occurrences (all)	0	1		
Lower gastrointestinal haemorrhage				
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)		
occurrences (all)	0	1		
Localised intraabdominal fluid collection				
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)		
occurrences (all)	1	1		
Nausea				
subjects affected / exposed	6 / 22 (27.27%)	6 / 26 (23.08%)		
occurrences (all)	6	6		
Mouth haemorrhage				
subjects affected / exposed	1 / 22 (4.55%)	2 / 26 (7.69%)		
occurrences (all)	1	2		
Oral pain				
subjects affected / exposed	1 / 22 (4.55%)	3 / 26 (11.54%)		
occurrences (all)	1	3		
Pancreatitis				
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)		
occurrences (all)	1	0		
Rectal fissure				
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)		
occurrences (all)	1	1		
Rectal haemorrhage				

subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	0 / 22 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Toothache			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	5 / 22 (22.73%)	5 / 26 (19.23%)	
occurrences (all)	5	6	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Hepatomegaly			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Hyperbilirubinaemia			
subjects affected / exposed	3 / 22 (13.64%)	4 / 26 (15.38%)	
occurrences (all)	3	4	
Jaundice			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 22 (13.64%)	2 / 26 (7.69%)	
occurrences (all)	3	2	
Dry skin			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Petechiae			

subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Ingrowing nail			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Purpura			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	1 / 22 (4.55%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Rash			
subjects affected / exposed	5 / 22 (22.73%)	4 / 26 (15.38%)	
occurrences (all)	5	4	
Rash macular			
subjects affected / exposed	3 / 22 (13.64%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Rash maculo-papular			
subjects affected / exposed	3 / 22 (13.64%)	3 / 26 (11.54%)	
occurrences (all)	3	3	
Rash morbilliform			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Skin disorder			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Skin lesion			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Skin mass			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Renal and urinary disorders			

Cystitis haemorrhagic			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	6 / 22 (27.27%)	1 / 26 (3.85%)	
occurrences (all)	6	1	
Haematuria			
subjects affected / exposed	5 / 22 (22.73%)	3 / 26 (11.54%)	
occurrences (all)	5	3	
Glycosuria			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Ketonuria			
subjects affected / exposed	1 / 22 (4.55%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Micturition disorder			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Oliguria			
subjects affected / exposed	1 / 22 (4.55%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Proteinuria			
subjects affected / exposed	2 / 22 (9.09%)	2 / 26 (7.69%)	
occurrences (all)	3	3	
Renal impairment			
subjects affected / exposed	2 / 22 (9.09%)	2 / 26 (7.69%)	
occurrences (all)	3	2	
Urinary retention			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 22 (13.64%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Back pain			

subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Bone pain			
subjects affected / exposed	5 / 22 (22.73%)	2 / 26 (7.69%)	
occurrences (all)	5	2	
Limb discomfort			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Osteopenia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	5 / 22 (22.73%)	3 / 26 (11.54%)	
occurrences (all)	5	3	
Pain in jaw			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
BK virus infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Bacteraemia			
subjects affected / exposed	2 / 22 (9.09%)	2 / 26 (7.69%)	
occurrences (all)	2	2	

Bacterial infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Cellulitis orbital			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Cytomegalovirus infection			
subjects affected / exposed	3 / 22 (13.64%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Conjunctivitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Cytomegalovirus viraemia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Device related infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Escherichia bacteraemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Herpes simplex			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Human polyomavirus infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Klebsiella bacteraemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	

Lung infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Oral herpes			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Pneumonia fungal			
subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	3 / 22 (13.64%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Staphylococcal infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 22 (4.55%)	3 / 26 (11.54%)	
occurrences (all)	1	3	
Streptococcal sepsis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Urethritis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

Varicella			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 22 (13.64%)	3 / 26 (11.54%)	
occurrences (all)	4	4	
Fluid overload			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Electrolyte imbalance			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	
occurrences (all)	2	2	
Fluid retention			
subjects affected / exposed	5 / 22 (22.73%)	4 / 26 (15.38%)	
occurrences (all)	5	4	
Hyperglycaemia			
subjects affected / exposed	4 / 22 (18.18%)	3 / 26 (11.54%)	
occurrences (all)	5	3	
Hypoalbuminaemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Hypocalcaemia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Hypokalaemia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Hypomagnesaemia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Malnutrition			

subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2008	Addition of safety assessments to be performed every 5-7 days during the extended IV or oral treatment period and on the last day of voriconazole dosing and flexibility in urine pregnancy test (the serum pregnancy test can be used instead).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported