Clinical trial results:
An open, intravenous multiple dose, multi-centre study to investigate the pharmacokinetics, safety and toleration of Voriconazole in children aged 2-12 years who require treatment for the prevention of systemic fungal infection

Summary

EudraCT number	2014-004183-38
Trial protocol	Outside EU/EEA
Global end of trial date	13 December 2000
Results information	
Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	01 August 2015

Trial information

Trial identification	
Sponsor protocol code	A1501007
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	ClinicalTrials.gov Call Center, Pfizer Inc. , 001 8007181021, ClinicalTrials.govCallCenter@pfizer.com
Scientific contact	ClinicalTrials.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?	Yes
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 April 2001
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 December 2000
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the pharmacokinetics of voriconazole following multiple dosing with intravenous voriconazole in children aged 2 to less than (<)12 years.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 July 2000
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	Panama: 3
Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Costa Rica: 7
Worldwide total number of subjects	28
EEA total number of subjects	2

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)	28
Adolescents (12-17 years)	0
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:

The study was conducted in 4 countries and total 28 subjects were assigned to receive treatment. The study started on 18 July 2000 and completed on 13 December 2000.

Period 1

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

Arms

Arm title	Voriconazole Intravenous

Arm description:

Voriconazole was administered intravenously 6 milligram per kilogram (mg/kg) every 12 hours on Day 1. Subjects received reduced intravenous dose of voriconazole 3 mg/kg every 12 hours from Day 2 until start of Day 4. Provided that clinical signs and symptoms and laboratory safety tests did not indicate a clinical concern, the dose was increased to 4 mg/kg every 12 hours from the evening of Day 4 to the morning of Day 8.

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 6mg/kg, 3mg/kg or 4mg/kg was administered as an intravenous infusion over 120, 60 or 80 minutes at every 12 hours up to Day 8. The intravenous formulation was administered at an infusion rate of 3mg/kg/hour.

Number of subjects in period 1	Voriconazole Intravenous
Started	28
Completed	19
Not completed	9
Adverse Event	3
Death	1
Unspecified	3
Laboratory abnormality	2

Baseline characteristics

Reporting groups	
Reporting group title	Voriconazole Intravenous

Reporting group description:

Voriconazole was administered intravenously 6 milligram per kilogram (mg/kg) every 12 hours on Day 1. Subjects received reduced intravenous dose of voriconazole 3 mg/kg every 12 hours from Day 2 until start of Day 4. Provided that clinical signs and symptoms and laboratory safety tests did not indicate a clinical concern, the dose was increased to 4 mg/kg every 12 hours from the evening of Day 4 to the morning of Day 8.

Reporting group values	Voriconazole Intravenous	Total	
Number of subjects	28	28	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 6 ± 3	 -	
Gender categorical Units: Subjects			
Female	11	11	
Male	17	17	

End points

End points reporting groups

Reporting group title	Voriconazole Intravenous

Reporting group description:

Voriconazole was administered intravenously 6 milligram per kilogram (mg/kg) every 12 hours on Day 1. Subjects received reduced intravenous dose of voriconazole 3 mg/kg every 12 hours from Day 2 until start of Day 4. Provided that clinical signs and symptoms and laboratory safety tests did not indicate a clinical concern, the dose was increased to 4 mg/kg every 12 hours from the evening of Day 4 to the morning of Day 8.

Primary: Trough Concentration (Cmin) on Day 4 (Pre-dose)

End point title	Trough Concentration (Cmin) on Day 4 (Pre-dose)[1]

End point description:

Cmin at 3 mg/kg Intravenous every 12 hour regimen. Pharmacokinetic population included those subjects who had at least one evaluable concentration available.

End point type	Primary

End point timeframe:

Pre-dose on Day 4

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Voriconazole Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	26[2]			
Units: nanogram per millilitre (ng/mL)				
geometric mean (standard deviation)	303.7 (± 1097.9)			

Notes:

[2] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Peak Concentration (Cmax) on Day 4 (End of Infusion)

End point title	Peak Concentration (Cmax) on Day 4 (End of Infusion)[3]

End point description:

Cmax at 3 mg/kg every 12 hour regimen. Pharmacokinetic population included those subjects who had at least one evaluable concentration available.

End point type	Primary

End point timeframe:

End of Infusion on Day 4

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 for this endpoint.

End point values	Voriconazole Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	22[4]			
Units: ng/mL				
geometric mean (standard deviation)	2610.8 (± 3874.5)			

Notes:

[4] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Cmin of Voriconazole on Day 8 (Pre-dose)

End point title	Cmin of Voriconazole on Day 8 (Pre-dose)[5]

End point description:

Cmin at 4 mg/kg intravenous every 12 hour regimen. Pharmacokinetic population included those subjects who had at least one evaluable concentration available.

End point type	Primary

End point timeframe:

Pre-dose on Day 8

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 for this endpoint.

End point values	Voriconazole Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	23[6]			
Units: ng/mL				
geometric mean (standard deviation)	437.5 (± 1301.4)			

Notes:

[6] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of Voriconazole on Day 8 (End of Infusion)

End point title	Cmax of Voriconazole on Day 8 (End of Infusion)[7]

End point description:

Cmax at 4 mg/kg intravenous every 12 hour. Pharmacokinetic population included those subjects who had at least one evaluable concentration available.

End point type	Primary

End point timeframe:

End of Infusion on Day 8

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 for this endpoint.

End point values	Voriconazole Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	20[8]			
Units: ng/mL				
geometric mean (standard deviation)	2368.7 (± 2499.8)			

Notes:

[8] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Voriconazole (N-oxide) on Day 4 and Day 8

End point title	Plasma Concentration of Voriconazole (N-oxide) on Day 4 and Day 8

End point description:

Plasma Concentration of Voriconazole (N-oxide) UK-121,265 was reported for Day 4 and Day 8. Pharmacokinetic population included those subjects who had at least one evaluable concentration available. (n)= number of evaluable subjects at specified time points.

End point type	Secondary

End point timeframe:

Pre-dose on Day 4, 8; End of Infusion on Day 4, 8

End point values	Voriconazole Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: ng/mL				
geometric mean (standard deviation)				
Pre-dose Day 4: 3mg/kg (n= 25)	665.8 (± 660)			
End infusion Day 4: 3mg/kg (n= 22)	1583.5 (± 806.8)			
Pre-dose Day 8: 4 mg/kg (n= 23)	1027.4 (± 711.2)			
End infusion Day 8: 4 mg/kg (n= 20)	2418 (± 646)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after last dose of study drug

Adverse event reporting additional description:

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

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Voriconazole Intravenous

Reporting group description:

Voriconazole was administered intravenously 6 milligram per kilogram (mg/kg) every 12 hours on Day 1. Subjects received reduced intravenous dose of voriconazole 3 mg/kg every 12 hours from Day 2 until start of Day 4. Provided that clinical signs and symptoms and laboratory safety tests did not indicate a clinical concern, the dose was increased to 4 mg/kg every 12 hours from the evening of Day 4 to the morning of Day 8.

Serious adverse events	Voriconazole Intravenous		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 28 (17.86%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Encephalitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		

Streptococcal bacteraemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Voriconazole Intravenous		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 28 (89.29%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Hypotension			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Phlebitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
General disorders and administration site conditions			
Catheter site erythema			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Catheter site haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Device occlusion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Fatigue			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Localised oedema			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	7		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Graft versus host disease			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	6		
Nasal congestion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Oropharyngeal pain			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pulmonary mass			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Respiratory failure			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Tachypnoea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Disorientation			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Blood pressure increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Blood triglycerides increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Heart sounds abnormal			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Gastroenteritis radiation			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Radiation mucositis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cardiac disorders			
Cardiomegaly			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Syncope			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Febrile neutropenia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		

Pancytopenia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Eye disorders			
Eye pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Eye pruritus			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Eyelid oedema			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Photophobia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Retinal haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Scleral haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Strabismus			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Abdominal distension			

subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Abdominal pain upper				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	4			
Abdominal tenderness				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Anal ulcer				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Anorectal discomfort				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	2			
Diarrhoea				
subjects affected / exposed	6 / 28 (21.43%)			
occurrences (all)	6			
Frequent bowel movements				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	2			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	2			
Gastrointestinal pain				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	2			
Gingival hypertrophy				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Haematemesis				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Nausea				
subjects affected / exposed	3 / 28 (10.71%)			
occurrences (all)	8			
Pancreatitis				

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	11		
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	6		
Rash erythematous			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Red man syndrome			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Skin disorder			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Renal failure			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Urinary retention			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Arthropathy			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Device related infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Oral herpes			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Sepsis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Streptococcal bacteraemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Fluid overload			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Fluid retention			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported