Clinical trial results:
A Multicenter, Open-Label, Ascending Multiple-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Tigecycline in Patients 8 to 11 Years of Age With Selected Serious Infections

Summary

EudraCT number	2007-002120-14
Trial protocol	BE GB Outside EU/EEA
Global end of trial date	25 September 2009

Results information

Result version number	v1 (current)
This version publication date	13 April 2016
First version publication date	05 June 2015

Trial information

Trial identification

Sponsor protocol code	3074K4-2207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00488345
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., +1 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800-718-1021, 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-000120-PIP01-07
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	26 March 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 September 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the pharmacokinetics (PK) profile and to evaluate the safety and tolerability of ascending multiple doses of tigecycline in patients aged 8 to 11 years with selected serious infections (complicated intra-abdominal infection [cIAI], complicated skin and skin structure infection [cSSSI], or community-acquired pneumonia [CAP]).

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 January 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	Taiwan: 1
Country: Number of subjects enrolled	Ukraine: 26
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	South Africa: 12
Worldwide total number of subjects	58
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)	58
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:

Fifty-nine subjects were screened and enrolled in the study, and 58 subjects received at least 1 dose of tigecycline.

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	Tigecycline 0.75 mg/kg

Arm description:

0.75 milligram per kilogram (mg/kg) intravenous (IV) infusion every 12 hours

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

Dosage and administration details:

A dose of 0.75 mg/kg of tigecycline was administered as IV infusion every 12 hours.

Arm title	Tigecycline 1 mg/kg

Arm description:

1 mg/kg IV infusion every 12 hours

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

Dosage and administration details:

A dose of 1 mg/kg of tigecycline was administered as IV infusion every 12 hours.

Arm title	Tigecycline 1.25 mg/kg

Arm description:

1.25 mg/kg IV infusion every 12 hours

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

Dosage and administration details:

A dose of 1.25 mg/kg of tigecycline was administered as IV infusion every 12 hours.

Number of subjects in period 1	Tigecycline 0.75 mg/kg	Tigecycline 1 mg/kg	Tigecycline 1.25 mg/kg
Started	17	21	20
Completed	17	17	17
Not completed	0	4	3
Unable to administer antibiotics at home	-	1	-
Parent/legal guardian request	-	1	1
Adverse event	-	1	1
Institutional Review Board review	-	-	1
Surgical team recommendation	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Tigecycline 0.75 mg/kg
Reporting group description:	
0.75 milligram per kilogram (mg/kg) intravenous (IV) infusion every 12 hours	
Reporting group title	Tigecycline 1 mg/kg
Reporting group description:	
1 mg/kg IV infusion every 12 hours	
Reporting group title	Tigecycline 1.25 mg/kg
Reporting group description:	
1.25 mg/kg IV infusion every 12 hours	

Reporting group values	Tigecycline 0.75 mg/kg	Tigecycline 1 mg/kg	Tigecycline 1.25 mg/kg
Number of subjects	17	21	20
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	10.21	10.2	9.72
standard deviation	± 1.15	± 1.06	± 0.94
Gender, Male/Female			
Units: subjects			
Female	9	10	8
Male	8	11	12
Selected Serious Infections			
Units: Subjects			
Community Acquired Pneumonia	7	8	4
Complicated Intra-abdominal Infection	6	6	12
Complicated Skin and Skin Structure Infection	4	7	4

Reporting group values	Total		
Number of subjects	58		
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: subjects			
Female	27		
Male	31		

Selected Serious Infections Units: Subjects			
Community Acquired Pneumonia	19		
Complicated Intra-abdominal Infection	24		
Complicated Skin and Skin Structure Infection	15		

End points

End points reporting groups

Reporting group title	Tigecycline 0.75 mg/kg
Reporting group description:	
0.75 milligram per kilogram (mg/kg) intravenous (IV) infusion every 12 hours	
Reporting group title	Tigecycline 1 mg/kg
Reporting group description:	
1 mg/kg IV infusion every 12 hours	
Reporting group title	Tigecycline 1.25 mg/kg
Reporting group description:	
1.25 mg/kg IV infusion every 12 hours	
Subject analysis set title	Tigecycline 0.75 mg/kg, 1 mg/kg, 1.25 mg/kg
Subject analysis set type	Full analysis
Subject analysis set description:	
0.75, 1 mg/kg, and 1.25 mg/kg IV infusions every 12 hours	

Primary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)[1]
End point description:	
Cmax: tigecycline serum concentration measured in nanograms per milliliter (ng/mL) determined by a validated liquid chromatography with mass spectrophotometric (LC/MS/MS) detection method. Peak concentration was taken directly from the observed data. Modified intent to treat (mITT) population: subjects who were screened, assigned to study medication and received at least one dose of study medication.	
End point type	Primary
End point timeframe:	
Day 3 (immediately post-dose, 0.75, 2 hours post-dose)	

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 outcome measure.

End point values	Tigecycline 0.75 mg/kg	Tigecycline 1 mg/kg	Tigecycline 1.25 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	19[2]	16[3]	
Units: ng/mL				
arithmetic mean (standard deviation)	456 (± 347)	1515 (± 1457)	2599 (± 3643)	

Notes:

[2] - N = number of subjects with evaluable tigecycline concentration data.

[3] - N = number of subjects with evaluable tigecycline concentration data.

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach Maximum Observed Plasma Concentration (Tmax)

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax)[4]
End point description:	
Time of peak concentration taken directly from the observed data. mITT population.	
End point type	Primary

End point timeframe:

Day 3 (immediately post-dose, 0.75, 2 hours post-dose)

Notes:

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

End point values	Tigecycline 0.75 mg/kg	Tigecycline 1 mg/kg	Tigecycline 1.25 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	19[5]	16[6]	
Units: hours				
arithmetic mean (standard deviation)	0.6 (± 0.2)	0.5 (± 0.1)	0.8 (± 0.6)	

Notes:

[5] - N = number of subjects with evaluable tigecycline concentration data.

[6] - N = number of subjects with evaluable tigecycline concentration data.

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Curve (AUCT) From Time Zero to Time of Estimated Concentration at 12 Hours

End point title	Area Under the Curve (AUCT) From Time Zero to Time of Estimated Concentration at 12 Hours[7]

End point description:

AUCT: AUC between doses from time zero to the time of estimated concentration at 12 hours reported in nanograms * hours divided by milliliters (ng*h/mL) was calculated using the log-trapezoidal rule for decreasing concentrations and the linear-trapezoidal rule for increasing concentrations estimating the 12 hour drug concentration if necessary. mITT population.

End point type	Primary

End point timeframe:

Day 3 (just before and immediately after infusion, 0.75, 2, 6 hours post-dose)

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 outcome measure.

End point values	Tigecycline 0.75 mg/kg	Tigecycline 1 mg/kg	Tigecycline 1.25 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[8]	18[9]	13[10]	
Units: ng*h/mL				
arithmetic mean (standard deviation)	1650 (± 529)	2557 (± 1196)	3196 (± 1704)	

Notes:

[8] - N = number of subjects with sufficient reported tigecycline concentration data to estimate AUC.

[9] - N = number of subjects with sufficient reported tigecycline concentration data to estimate AUC.

[10] - N = number of subjects with sufficient reported tigecycline concentration data to estimate AUC.

Statistical analyses

No statistical analyses for this end point

Primary: Weight Normalized Drug Clearance (CLW)

End point title	Weight Normalized Drug Clearance (CLW)[11]

End point description:

Weight normalized drug clearance measured in liters per hour per kilogram (L/hr/kg). Drug clearance (CL) was determined as the ratio of dose/area under the concentration-time curve from time zero (start of infusion) to 12 hours (start of next infusion) (AUC_T). CLW was determined as the ratio of CL/weight. mITT population.

End point type	Primary

End point timeframe:

Day 3 (just before and immediately after infusion, 0.75, 2, 6 hours post-dose)

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 for this outcome measure.

End point values	Tigecycline 0.75 mg/kg	Tigecycline 1 mg/kg	Tigecycline 1.25 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[12]	18[13]	13[14]	
Units: L/hr/kg				
arithmetic mean (standard deviation)	0.49 (± 0.13)	0.498 (± 0.335)	0.528 (± 0.384)	

Notes:

[12] - N = number of subjects with sufficient reported tigecycline concentration data to estimate AUC.

[13] - N = number of subjects with sufficient reported tigecycline concentration data to estimate AUC.

[14] - N = number of subjects with sufficient reported tigecycline concentration data to estimate AUC.

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Clinical Response (CR) to Tigecycline at Last Day of Therapy (LDOT) and Test-of-Cure (TOC) Assessment

End point title	Percentage of Subjects With Clinical Response (CR) to Tigecycline at Last Day of Therapy (LDOT) and Test-of-Cure (TOC) Assessment[15]

End point description:

CR = Cure: resolution of all signs, symptoms (SS) of infection (INF) or improvement, no further antibacterial therapy (AT) necessary; Improved (IMP): SS IMP to extent that switch to oral AT deemed appropriate; Failure: lack of response, required additional AT, initial recovery then deterioration requiring further AT, death due to the INF after day 2, death due to treatment (TR)-related adverse event (AE), required non-routine surgical TR >48 hours after 1st dose of TR due to failure to IMP or clinical worsening. TOC = CR, vital signs, physical exam, laboratory results, concomitant TR, and AEs. mITT population.

End point type	Primary

End point timeframe:

Day 14 or LDOT, TOC Visit (10 to 21 days after last dose of total antibiotic therapy)

Notes:

[15] - 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 outcome measure.

End point values	Tigecycline 0.75 mg/kg	Tigecycline 1 mg/kg	Tigecycline 1.25 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	21	20	
Units: percentage of subjects				
number (not applicable)				
Cure: LDOT	82.4	52.4	30	

Improved: LDOT	17.6	28.6	55	
Failure: LDOT	0	0	0	
Indeterminate: LDOT	0	19	15	
Cure: TOC	94.1	76.2	75	
Failure: TOC	5.9	4.8	10	
Indeterminate: TOC	0	19	15	

Statistical analyses

No statistical analyses for this end point

Secondary: Population Pharmacokinetic (PK) Model: Volume of Distribution

End point title	Population Pharmacokinetic (PK) Model: Volume of Distribution

End point description:

Two compartment model with linear clearance and effect of weight on clearance using pooled PK data from 2 pediatric studies. All concentration-time data were combined and analyzed using population PK methods to investigate potential influence of age, weight, and height (dose, tigecycline concentrations, times, subject weight, height, age, body surface area, serum creatinine, estimated creatinine clearance, serum bilirubin. Separate population pharmacokinetic analysis results were not available for the current study as more than 1 study was involved in this analysis based on pooled data from pediatric studies 3074A1-110 and 3074K4-2207.

End point type	Secondary

End point timeframe:

3074K4-2207: Day 3 just before and immediately after infusion, 0.75, 2, 6 hours post-dose; 3074A1-110: just before, 0.5, 0.75, 1, 2, 3, 4, 8, 12, 24, 36, 48 hours after start of infusion

End point values	Tigecycline 0.75 mg/kg, 1 mg/kg, 1.25 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	0[16]			
Units: liters				
arithmetic mean (standard error)	()			

Notes:

[16] - Separate population pharmacokinetic analysis results were not available for the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Population Pharmacokinetic (PK) Model: Clearance

End point title	Population Pharmacokinetic (PK) Model: Clearance

End point description:

Two compartment model with linear clearance and effect of weight on clearance using pooled PK data from 2 pediatric studies. All concentration-time data were combined and analyzed using population PK methods to investigate potential influence of age, weight, and height (dose, tigecycline concentrations, times, subject weight, height, age, body surface area, serum creatinine, estimated creatinine clearance, serum bilirubin. Separate population pharmacokinetic analysis results were not available for the current study as more than 1 study was involved in this analysis based on pooled data from pediatric studies

3074A1-110 and 3074K4-2207.

End point type	Secondary

End point timeframe:

3074K4-2207: Day 3 just before and immediately after infusion, 0.75, 2, 6 hours post-dose; 3074A1-110: just before, 0.5, 0.75, 1, 2, 3, 4, 8, 12, 24, 36, 48 hours after start of infusion

End point values	Tigecycline 0.75 mg/kg, 1 mg/kg, 1.25 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	0[17]			
Units: liters per hour				
arithmetic mean (standard error)	()			

Notes:

[17] - Separate population pharmacokinetic analysis results were not available for the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Population Pharmacokinetic (PK) Model: Effect of Weight

End point title	Population Pharmacokinetic (PK) Model: Effect of Weight

End point description:

Two compartment model with linear clearance and effect of weight on clearance using pooled PK data from 2 pediatric studies. All concentration-time data were combined and analyzed using population PK methods to investigate potential influence of age, weight, and height (dose, tigecycline concentrations, times, subject weight, height, age, body surface area, serum creatinine, estimated creatinine clearance, serum bilirubin. Separate population pharmacokinetic analysis results were not available for the current study as more than 1 study was involved in this analysis based on pooled data from pediatric studies 3074A1-110 and 3074K4-2207.

End point type	Secondary

End point timeframe:

3074K4-2207: Day 3 just before and immediately after infusion, 0.75, 2, 6 hours post-dose; 3074A1-110: just before, 0.5, 0.75, 1, 2, 3, 4, 8, 12, 24, 36, 48 hours after start of infusion

End point values	Tigecycline 0.75 mg/kg, 1 mg/kg, 1.25 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	0[18]			
Units: units on a scale				
arithmetic mean (standard error)	()			

Notes:

[18] - Separate population pharmacokinetic analysis results were not available for the study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 21 days after the last dose of study drug

Adverse event reporting additional description:

mITT population. An Adverse Event(AE) term may be reported as both a serious and a non-serious AE, but are distinct events. AE may be serious for one subject and non-serious for another subject or subject may have experienced both a serious and non-serious episode of the same event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Tigecycline 0.75 mg/kg

Reporting group description:

0.75 milligram per kilogram (mg/kg) intravenous (IV) infusion every 12 hours

Reporting group title	Tigecycline 1.25 mg/kg

Reporting group description:

1.25 milligram per kilogram (mg/kg) IV infusion every 12 hours

Reporting group title	Tigecycline 1 mg/kg

Reporting group description:

1 milligram per kilogram (mg/kg) IV infusion every 12 hours

Serious adverse events	Tigecycline 0.75 mg/kg	Tigecycline 1.25 mg/kg	Tigecycline 1 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 17 (5.88%)	1 / 20 (5.00%)	1 / 21 (4.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Postoperative wound infection			

subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Tigecycline 0.75 mg/kg	Tigecycline 1.25 mg/kg	Tigecycline 1 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 17 (64.71%)	17 / 20 (85.00%)	16 / 21 (76.19%)
Vascular disorders			
Bloody discharge			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Phlebitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Catheter site related reaction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Crepitations			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			

subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Upper respiratory tract congestion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Alanine aminotransferase increased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Blood bilirubin increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Amylase increased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 20 (5.00%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Fungal test positive			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood phosphorus increased			

subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Blood urea increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Blood calcium decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Blood uric acid increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Platelet count increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Lipase increased			
subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Prothrombin time prolonged			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			

Procedural pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Skin abrasion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Medical device pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Wound dehiscence			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Wolff-Parkinson-White syndrome			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Dysgeusia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Thrombocytosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 20 (5.00%)	1 / 21 (4.76%)
occurrences (all)	1	1	1

Abdominal pain upper			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Chapped lips			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Haematochezia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	2 / 17 (11.76%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Lip dry			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	5 / 17 (29.41%)	11 / 20 (55.00%)	11 / 21 (52.38%)
occurrences (all)	6	20	21
Ileus			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	3 / 17 (17.65%)	12 / 20 (60.00%)	13 / 21 (61.90%)
occurrences (all)	3	18	19
Pancreatitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Skin exfoliation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Decubitus ulcer			

subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Bladder discomfort			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Osteopenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Postoperative wound infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	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