Clinical trial results:
A Phase 2, Open-Label, Non-Comparative Clinical Trial to Study the Safety and Efficacy of Posaconazole (POS, MK-5592) in Pediatric Participants Aged 2 to Less Than 18 Years With Invasive Aspergillosis

Summary

EudraCT number	2019-002267-10
Trial protocol	HU Outside EU/EEA GR BE IT
Global end of trial date	18 December 2023

Results information

Result version number	v1
This version publication date	15 June 2024
First version publication date	15 June 2024

Trial information

Trial identification

Sponsor protocol code	5592-104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04218851
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, Rahway, NJ, United States, P.O. Box 2000
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000468-PIP01-12
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	18 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2023
Global end of trial reached?	Yes
Global end of trial date	18 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the safety, efficacy, and pharmacokinetics of posaconazole (POS) intravenous (IV) and oral formulations in pediatric participants 2 to <18 years of age with invasive aspergillosis (IA).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review,
informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Peru: 2
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	31
EEA total number of subjects	9

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)	14
Adolescents (12-17 years)	17
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:

Male or female participants with a diagnosis of possible, probable, or proven invasive aspergillosis (IA) aged 2 to <18 years were enrolled in this study.

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	Age Cohort 1 (2 -< 12 years old)

Arm description:

On Day 1 participants receive 2 administrations of posaconazole (POS) 6 mg/kg body weight by intravenous (IV) infusion. On Days 2 through 7, participants receive POS 6 mg/kg body weight once daily by IV infusion. Beginning at Day 8 up to Day 84, participants may transition to receiving an oral formulation, or they may remain on the IV formulation.

Arm type	Experimental
Investigational medicinal product name	Posaconazole intravenous (IV)
Investigational medicinal product code	
Other name	MK-5592 SCH 056592 Noxafil®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Posaconazole (POS) 6 mg/kg body weight by IV infusion.

Investigational medicinal product name	Posaconazole tablet
Investigational medicinal product code	
Other name	MK-5592 SCH 056592 Noxafil®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

POS tablet 300 mg taken orally. Administered to participants >40 kg.

Investigational medicinal product name	Posaconazole gastro-resistant powder and solvent for oral suspension formulation (PFS)
Investigational medicinal product code	
Other name	MK-5592 SCH 056592 Noxafil®
Pharmaceutical forms	Oral suspension
Routes of administration	Intravenous use

Dosage and administration details:

Dosing based on weight-band. Administered to participants ≤40 kg.

Arm title	Age Cohort 2 (12 -< 18 years old)

Arm description:

On Day 1 participants receive 2 administrations of posaconazole (POS) 6 mg/kg body weight by intravenous (IV) infusion. On Days 2 through 7, participants receive POS 6 mg/kg body weight once daily by IV infusion. Beginning at Day 8 up to Day 84, participants may transition to receiving an oral formulation, or they may remain on the IV formulation.

Arm type	Experimental

Investigational medicinal product name	Posaconazole IV
Investigational medicinal product code	
Other name	MK-5592 SCH 056592 Noxafil®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

POS 6 mg/kg body weight by IV infusion.

Investigational medicinal product name	Posaconazole tablet
Investigational medicinal product code	
Other name	MK-5592 SCH 056592 Noxafil®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

POS tablet 300 mg taken orally. Administered to participants >40 kg

Investigational medicinal product name	Posaconazole PFS
Investigational medicinal product code	
Other name	MK-5592 SCH 056592 Noxafil®
Pharmaceutical forms	Oral suspension
Routes of administration	Intravenous use

Dosage and administration details:

Dosing based on weight-band. Administered to participants ≤40 kg.

Number of subjects in period 1	Age Cohort 1 (2 -< 12 years old)	Age Cohort 2 (12 -< 18 years old)
Started	14	17
Completed	13	14
Not completed	1	3
Adverse event, serious fatal	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Age Cohort 1 (2 -< 12 years old)
Reporting group description:	
On Day 1 participants receive 2 administrations of posaconazole (POS) 6 mg/kg body weight by intravenous (IV) infusion. On Days 2 through 7, participants receive POS 6 mg/kg body weight once daily by IV infusion. Beginning at Day 8 up to Day 84, participants may transition to receiving an oral formulation, or they may remain on the IV formulation.	
Reporting group title	Age Cohort 2 (12 -< 18 years old)
Reporting group description:	
On Day 1 participants receive 2 administrations of posaconazole (POS) 6 mg/kg body weight by intravenous (IV) infusion. On Days 2 through 7, participants receive POS 6 mg/kg body weight once daily by IV infusion. Beginning at Day 8 up to Day 84, participants may transition to receiving an oral formulation, or they may remain on the IV formulation.	

Reporting group values	Age Cohort 1 (2 -< 12 years old)	Age Cohort 2 (12 -< 18 years old)	Total
Number of subjects	14	17	31
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	14	0	14
Adolescents (12-17 years)	0	17	17
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	6.9	14.5	
standard deviation	± 2.7	± 1.7	-
Gender Categorical Units: Subjects			
Female	7	1	8
Male	7	16	23
Race Units: Subjects			
Asian	3	5	8
Multiple	2	4	6
White	9	8	17
Ethnicity Units: Subjects			
Hispanic Or Latino	2	5	7
Not Hispanic Or Latino	12	12	24

End points

End points reporting groups

Reporting group title	Age Cohort 1 (2 -< 12 years old)

Reporting group description:

On Day 1 participants receive 2 administrations of posaconazole (POS) 6 mg/kg body weight by intravenous (IV) infusion. On Days 2 through 7, participants receive POS 6 mg/kg body weight once daily by IV infusion. Beginning at Day 8 up to Day 84, participants may transition to receiving an oral formulation, or they may remain on the IV formulation.

Reporting group title	Age Cohort 2 (12 -< 18 years old)

Reporting group description:

On Day 1 participants receive 2 administrations of posaconazole (POS) 6 mg/kg body weight by intravenous (IV) infusion. On Days 2 through 7, participants receive POS 6 mg/kg body weight once daily by IV infusion. Beginning at Day 8 up to Day 84, participants may transition to receiving an oral formulation, or they may remain on the IV formulation.

Subject analysis set title	All participants (Ages 2 - < 18 years old)
Subject analysis set type	Full analysis

Subject analysis set description:

On Day 1 participants receive 2 administrations of posaconazole (POS) 6 mg/kg body weight by intravenous (IV) infusion. On Days 2 through 7, participants receive POS 6 mg/kg body weight once daily by IV infusion. Beginning at Day 8 up to Day 84, participants may transition to receiving an oral formulation, or they may remain on the IV formulation.

Primary: Percentage of participants who experience one or more treatment-related adverse events (AEs)

End point title	Percentage of participants who experience one or more treatment-related adverse events (AEs)[1]

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. Treatment-related AEs were determined by the investigator to be related to the drug. The 95% confidence interval (CI) was based on the exact binomial method by Clopper- Pearson. The population analyzed consisted of all enrolled participants who received at least 1 dose of study treatment, regardless of their IA classification.

End point type	Primary

End point timeframe:

Up to 14 days after treatment (up to Day 102)

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: Statistical analyses between treatment groups were neither planned nor performed for this primary end point.

End point values	Age Cohort 1 (2 -< 12 years old)	Age Cohort 2 (12 -< 18 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	17		
Units: Percentage of participants				
number (confidence interval 95%)	14.3 (1.8 to 42.8)	29.4 (10.3 to 56.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who have a favorable global clinical response

End point title	Percentage of participants who have a favorable global clinical response

End point description:

A global clinical response is assessed by the investigator as favorable if the participant is alive and has a complete or partial response. The population analyzed was participants who have possible, probable, or proven IA; receive at least 1 dose of study treatment; have at least 1 post-allocation observation subsequent to at least 1 dose of study treatment; and have baseline data for those analyses that require baseline data.

End point type	Secondary

End point timeframe:

Up to End of Trial (EOT) visit (up to Day 88)

End point values	Age Cohort 1 (2 -< 12 years old)	Age Cohort 2 (12 -< 18 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	17		
Units: Percentage of participants				
number (not applicable)				
Success, Complete Response Through Week 6	42.9	17.6		
Success, Partial Response Through Week 6	21.4	52.9		
Success, Complete Response Through Week 12	57.1	41.2		
Success, Partial Response Through Week 12	21.4	35.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who have a relapse of invasive aspergillosis (IA) at any point after achieving favorable global clinical response

End point title	Percentage of participants who have a relapse of invasive aspergillosis (IA) at any point after achieving favorable global clinical response

End point description:

In participants who achieved favorable global clinical response relapse of IA is defined as the re-emergence of clinical, radiographic, or other relevant abnormalities indicating IA. The population analyzed was participants who have possible, probable, or proven IA; receive at least 1 dose of study treatment; have at least 1 post-allocation observation subsequent to at least 1 dose of study treatment; have baseline data for those analyses that require baseline data; and who have achieved a favorable global clinical response at the end of study treatment.

End point type	Secondary

End point timeframe:

Up to 28 days post-treatment (up to Day 116)

End point values	Age Cohort 1 (2 -< 12 years old)	Age Cohort 2 (12 -< 18 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: Percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Average plasma concentration (Cavg) of POS

End point title	Average plasma concentration (Cavg) of POS

End point description:

Blood samples were collected from pre-dose up to Week 12 in order to determine Cavg. The population analyzed was all treated participants who had at least 1 postdose plasma concentration obtained after receiving at least 5 days of treatment with any POS formulation. Per protocol, results were not analyzed because they will be estimated in the future based on population pharmacokinetic (PK) models developed from prior pediatric and adult PK data

End point type	Secondary

End point timeframe:

Pre-dose, Day 1, Weeks 1, 2, 4, 6, 9 and 12

End point values	Age Cohort 1 (2 -< 12 years old)	Age Cohort 2 (12 -< 18 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[2] - Results were not analyzed because they will be based on future pharmacokinetic (PK) analysis .

[3] - Results were not analyzed because they will be based on future PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve (AUC) of POS

End point title	Area under the concentration-time curve (AUC) of POS

End point description:

Blood samples were collected from pre-dose up to Week 12 in order to determine AUC. The population analyzed was all treated participants who had at least 1 postdose plasma concentration obtained after receiving at least 5 days of treatment with any POS formulation. Per protocol, results were not analyzed

because they will be estimated in the future based on population PK models developed from prior pediatric and adult PK data.

End point type	Secondary

End point timeframe:

Pre-dose, Day 1, Weeks 1, 2, 4, 6, 9 and 12

End point values	Age Cohort 1 (2 -< 12 years old)	Age Cohort 2 (12 -< 18 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[4] - Results were not analyzed because they will be based on future PK analysis.

[5] - Results were not analyzed because they will be based on future PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach Cmax (Tmax) of POS

End point title	Time to reach Cmax (Tmax) of POS

End point description:

Blood samples were collected from pre-dose up to Week 12 in order to determine Tmax. The population analyzed was all treated participants who had at least 1 postdose plasma concentration obtained after receiving at least 5 days of treatment with any POS formulation. Per protocol, results were not analyzed because they will be estimated in the future based on population PK models developed from prior pediatric and adult PK data.

End point type	Secondary

End point timeframe:

Pre-dose, Day 1, Weeks 1, 2, 4, 6, 9 and 12

End point values	Age Cohort 1 (2 -< 12 years old)	Age Cohort 2 (12 -< 18 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: hr				
median (full range (min-max))	(to)	(to)		

Notes:

[6] - Results were not analyzed because they will be based on future PK analysis.

[7] - Results were not analyzed because they will be based on future PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum plasma concentration (Cmin) of POS

End point title	Minimum plasma concentration (Cmin) of POS

End point description:

Blood samples were collected from pre-dose up to Week 12 in order to determine Cmin. The population analyzed was all treated participants who had at least 1 postdose plasma concentration obtained after receiving at least 5 days of treatment with any POS formulation. Per protocol, results were not analyzed because they will be estimated in the future based on population PK models developed from prior pediatric and adult PK data.

End point type	Secondary

End point timeframe:

Pre-dose, Day 1, Weeks 1, 2, 4, 6, 9 and 12

End point values	Age Cohort 1 (2 -< 12 years old)	Age Cohort 2 (12 -< 18 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[8] - Results were not analyzed because they will be based on future PK analysis.

[9] - Results were not analyzed because they will be based on future PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum plasma concentration (Cmax) of POS

End point title	Maximum plasma concentration (Cmax) of POS

End point description:

Blood samples were collected from pre-dose up to Week 12 in order to determine Cmax. The population analyzed was all treated participants who had at least 1 postdose plasma concentration obtained after receiving at least 5 days of treatment with any POS formulation. Per protocol, results were not analyzed because they will be estimated in the future based on population PK models developed from prior pediatric and adult PK data.

End point type	Secondary

End point timeframe:

Pre-dose, Day 1, Weeks 1, 2, 4, 6, 9 and 12

End point values	Age Cohort 1 (2 -< 12 years old)	Age Cohort 2 (12 -< 18 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[10] - Results were not analyzed because they will be based on future PK analysis.

[11] - Results were not analyzed because they will be based on future PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with different categories of palatability after treatment with the POS PFS formulation

End point title	Percentage of participants with different categories of palatability after treatment with the POS PFS formulation

End point description:

Palatability was categorized on the first (Day 8) and last (up to Day 84) days on PFS based on responses by participants to a palatability questionnaire. Palatability categories for taste are as follows: Very good; Good; Very bad; Neither good nor bad. The population analyzed was participants who completed the palatability questionnaire. Per protocol participants were pooled into a single treatment group.

End point type	Secondary

End point timeframe:

First day of PFS treatment (Day 8) and last day of PFS treatment (Day 85)

End point values	All participants (Ages 2 - < 18 years old)			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: Percentage of participants				
number (not applicable)				
Very good First Day on PFS	20.0			
Good First Day on PFS	40.0			
Very bad First Day on PFS	10.0			
Neither good nor bad First Day on PFS	30.0			
Very good Last Day on PFS	10.0			
Good Last Day on PFS	40.0			
Very bad Last Day on PFS	10.0			
Neither good nor bad Last Day on PFS	40.0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality (ACM): from enrollment up to 14 days after treatment (up to Day 100), and included those reported beyond the final Day 114 study visit. Adverse events (AEs); from treatment up to 14 days after treatment (up to Day 102).

Adverse event reporting additional description:

ACM population analyzed was all enrolled participants. AE population analyzed was all enrolled participants who received at least 1 dose of study treatment, regardless of their IA classification.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Age Cohort 2 (12 -< 18 years old)

Reporting group description:

On Day 1 participants receive 2 administrations of posaconazole (POS) 6 mg/kg body weight by intravenous (IV) infusion. On Days 2 through 7, participants receive POS 6 mg/kg body weight once daily by IV infusion. Beginning at Day 8 up to Day 84, participants may transition to receiving an oral formulation, or they may remain on the IV formulation.

Reporting group title	Age Cohort 1 (2 -< 12 years old)

Reporting group description:

On Day 1 participants receive 2 administrations of posaconazole (POS) 6 mg/kg body weight by intravenous (IV) infusion. On Days 2 through 7, participants receive POS 6 mg/kg body weight once daily by IV infusion. Beginning at Day 8 up to Day 84, participants may transition to receiving an oral formulation, or they may remain on the IV formulation.

Serious adverse events	Age Cohort 2 (12 -< 18 years old)	Age Cohort 1 (2 -< 12 years old)	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 17 (47.06%)	4 / 14 (28.57%)	
number of deaths (all causes)	4	2	
number of deaths resulting from adverse events	3	1	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemic infiltration extramedullary			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Administration site extravasation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Urinary bladder haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (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			
Sepsis			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis bacterial			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			

subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral sepsis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (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: 5 %

Non-serious adverse events	Age Cohort 2 (12 -< 18 years old)	Age Cohort 1 (2 -< 12 years old)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 17 (82.35%)	12 / 14 (85.71%)	
Vascular disorders			
Vena cava thrombosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	5 / 17 (29.41%)	3 / 14 (21.43%)	
occurrences (all)	5	5	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Drug withdrawal syndrome			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Fatigue			

subjects affected / exposed	3 / 17 (17.65%)	1 / 14 (7.14%)	
occurrences (all)	3	1	
Feeling hot			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Hypothermia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Infusion site thrombosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	6 / 17 (35.29%)	3 / 14 (21.43%)	
occurrences (all)	6	14	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Hypogammaglobulinaemia			

subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Genital pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Testicular pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 17 (5.88%)	2 / 14 (14.29%)	
occurrences (all)	1	4	
Haemoptysis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Hyperventilation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Pulmonary hypertension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Pulmonary oedema			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Wheezing			

subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Delirium			
subjects affected / exposed	2 / 17 (11.76%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Depressed mood			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 17 (23.53%)	0 / 14 (0.00%)	
occurrences (all)	7	0	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 17 (23.53%)	0 / 14 (0.00%)	
occurrences (all)	7	0	
Blood bilirubin unconjugated increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 17 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	3	
Gamma-glutamyltransferase increased			

subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Liver function test increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Weight increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Infusion related reaction			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Spinal compression fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			

Aplasia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Sinus bradycardia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Tachycardia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Neuralgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	4 / 17 (23.53%)	0 / 14 (0.00%)	
occurrences (all)	5	0	
Dysgeusia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 14 (0.00%)	
occurrences (all)	3	0	
Myelosuppression			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Lymphocytosis			

subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Febrile neutropenia			
subjects affected / exposed	2 / 17 (11.76%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Neutropenia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Eye disorders			
Eyelid oedema			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Oculogyric crisis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 17 (11.76%)	3 / 14 (21.43%)	
occurrences (all)	2	3	
Abdominal pain			
subjects affected / exposed	2 / 17 (11.76%)	4 / 14 (28.57%)	
occurrences (all)	2	7	
Abdominal pain lower			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	2 / 17 (11.76%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Anal fissure			

subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Colitis			
subjects affected / exposed	2 / 17 (11.76%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	1 / 17 (5.88%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Haematemesis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Lip dry			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Mouth haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	4 / 17 (23.53%)	1 / 14 (7.14%)	
occurrences (all)	5	2	
Neutropenic colitis			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	1	2	
Rectal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	2 / 17 (11.76%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	7 / 17 (41.18%)	3 / 14 (21.43%)	
occurrences (all)	12	3	
Haematochezia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			

Cholestasis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hepatotoxicity			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Dermatitis acneiform			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Dermatitis contact			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Skin ulcer			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Rash papular			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 17 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Hyperhidrosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 17 (11.76%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Bladder spasm			

subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	2 / 17 (11.76%)	0 / 14 (0.00%)	
occurrences (all)	3	0	
Haematuria			
subjects affected / exposed	3 / 17 (17.65%)	0 / 14 (0.00%)	
occurrences (all)	3	0	
Hydronephrosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Kidney enlargement			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Renal tubular disorder			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Renal haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Pyelocaliectasis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Nephropathy toxic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Urinary retention			

subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Flank pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	4 / 17 (23.53%)	0 / 14 (0.00%)	
occurrences (all)	6	0	
Pain in extremity			
subjects affected / exposed	3 / 17 (17.65%)	0 / 14 (0.00%)	
occurrences (all)	3	0	
Myalgia			
subjects affected / exposed	3 / 17 (17.65%)	1 / 14 (7.14%)	
occurrences (all)	3	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Viruria			
subjects affected / exposed	2 / 17 (11.76%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Adenovirus interstitial nephritis			

subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)		
occurrences (all)	1	0		
BK virus infection				
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)		
occurrences (all)	1	0		
Conjunctivitis				
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)		
occurrences (all)	1	0		
Cytomegalovirus urinary tract infection				
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)		
occurrences (all)	1	0		
Device related infection				
subjects affected / exposed	2 / 17 (11.76%)	0 / 14 (0.00%)		
occurrences (all)	3	0		
Herpes zoster				
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)		
occurrences (all)	1	0		
Infectious disease carrier				
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)		
occurrences (all)	1	0		
Lower respiratory tract infection				
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)		
occurrences (all)	1	0		
Nail infection				
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)		
occurrences (all)	0	1		
Paronychia				
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)		
occurrences (all)	1	0		
Pharyngitis				
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)		
occurrences (all)	1	0		
Pneumonia				
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)		
occurrences (all)	1	1		

Rhinitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Sepsis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Staphylococcal sepsis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Urinary tract infection viral			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Viraemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Viral haemorrhagic cystitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Adenovirus infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 17 (17.65%)	2 / 14 (14.29%)	
occurrences (all)	3	2	
Hyperglycaemia			

subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Hypoalbuminaemia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Hypocalcaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 17 (5.88%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Hypomagnesaemia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Hypoproteinaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hypophosphataemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2020	Amendment 01: To remove the device-related adverse event reporting language and the Future Biomedical Research (FBR) substudy from the protocol
21 January 2021	Amendment 02: To provide details for IV dosing requirements; to clarify procedures (ie, ECG and diagnostic imaging) in the Schedule of Activities; to clarify maximum blood volume and method for calculating creatinine clearance; to remove pregnancy exclusion to avoid potential confusion with the pregnancy criteria in the list of inclusions; and to update informed consent text to align with current informed consent/assent procedures.
10 November 2022	Amendment 04: To revise exclusion criteria to include the specific K values used in the modified Schwartz formula for males of different ages.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported