



Clinical trial results:

A Phase 2, Randomized, Active Comparator-Controlled, Multicenter, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam (MK-7625A) Plus Metronidazole Versus Meropenem in Pediatric Subjects with Complicated Intra-Abdominal Infection

Summary

EudraCT number	2016-004820-41
Trial protocol	LT ES HU Outside EU/EEA
Global end of trial date	20 January 2021

Results information

Result version number	v1
This version publication date	23 July 2021
First version publication date	23 July 2021

Trial information

Trial identification

Sponsor protocol code	7625A-035
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03217136
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001142-PIP01-11
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	16 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2020
Global end of trial reached?	Yes
Global end of trial date	20 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aims to evaluate the safety and tolerability of MK-7625A (ceftolozane/tazobactam) plus metronidazole, compared with that of meropenem in pediatric participants with complicated intra-abdominal infection (cIAI).

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	03 April 2018
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	Brazil: 1
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Lithuania: 8
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	94
EEA total number of subjects	29

Notes:

Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	2
Children (2-11 years)	69
Adolescents (12-17 years)	23
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study enrolled 94 paediatric participants from 27 sites in 11 countries.

Pre-assignment

Screening details:

Of participants screened, 94 participants were randomized, and 91 received study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Blinding applied only to intravenous (IV) drugs. Participants were not blinded to drugs administered as part of oral step-down therapy.

Arms

Are arms mutually exclusive?	Yes
Arm title	C/T+MTZ

Arm description:

Participants received intravenous (IV) ceftolozane, tazobactam, and metronidazole for 5-14 days. Dosage was based on age and weight. Following IV therapy, participants may have received oral step-down therapy. IV and oral antibiotic therapy could total a maximum of 14 days.

Arm type	Experimental
Investigational medicinal product name	Ceftolozane + tazobactam
Investigational medicinal product code	
Other name	MK-7625A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For participants aged birth to <12 years of age: 20 mg/kg ceftolozane + 10 mg/kg tazobactam, intravenous every 8 hours. Maximum dose was 1 g of ceftolozane and 0.5 g of tazobactam. For participants 12 to <18 years of age: 1 g ceftolozane + 0.5 g tazobactam, intravenous every 8 hours.

Investigational medicinal product name	Metronidazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous metronidazole. For participants >28 days of age: 10 mg/kg, every 8 hours. For participants ≤28 days of age and ≤2 kg: 15 mg/kg loading dose then 7.5 mg/kg every 12 hours. For participants ≤28 days of age and >2 kg 15 mg/kg loading dose then 10 mg/kg every 12 hours. Maximum of 1.5 g per dose.

Investigational medicinal product name	Standard of Care Oral Therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Capsule, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

After receiving at least 9 doses of double-blind, IV study treatment, participants could have switched to

open-label, standard of care, oral step-down antibiotic therapy at the investigator's discretion: β -lactam/ β -lactamase inhibitor combination, Second or third generation cephalosporin in combination with metronidazole, or Quinolone standard of care. If ciprofloxacin or levofloxacin were chosen, they were to be used in combination with metronidazole. Total antibiotic duration (IV only or IV + oral) was a minimum of 5 days to a maximum of 14 days. Optional oral step-down therapy is considered study treatment in this study.

Arm title	MERO
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Arm description:

Participants received IV meropenem and placebo for metronidazole for 5-14 days. Dosage was based on age and weight. Following IV therapy, participants may have received oral step-down therapy. IV and oral antibiotic therapy could total a maximum of 14 days.

Arm type	Active comparator
Investigational medicinal product name	Meropenem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous meropenem, 20 mg/kg every 8 hours. Maximum of 1 g per dose.

Investigational medicinal product name	Placebo for metronidazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous placebo for metronidazole every 8 hours.

Investigational medicinal product name	Standard of Care Oral Therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Capsule, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

After receiving at least 9 doses of double-blind, IV study treatment, participants could have switched to open-label, standard of care, oral step-down antibiotic therapy at the investigator's discretion: β -lactam/ β -lactamase inhibitor combination, Second or third generation cephalosporin in combination with metronidazole, or Quinolone standard of care. If ciprofloxacin or levofloxacin were chosen, they were to be used in combination with metronidazole. Total antibiotic duration (IV only or IV + oral) was a minimum of 5 days to a maximum of 14 days. Optional oral step-down therapy is considered study treatment in this study.

Number of subjects in period 1	C/T+MTZ	MERO
Started	71	23
Treated	70	21
Completed	67	20
Not completed	4	3
Dispensing Error	1	-
Withdrawal by Parent/Guardian	1	-
Site Randomized Participant in Error	-	1

Did Not Meet Criteria after Randomization	-	1
Lost to follow-up	2	1

Baseline characteristics

Reporting groups

Reporting group title	C/T+MTZ
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Reporting group description:

Participants received intravenous (IV) ceftolozane, tazobactam, and metronidazole for 5-14 days. Dosage was based on age and weight. Following IV therapy, participants may have received oral step-down therapy. IV and oral antibiotic therapy could total a maximum of 14 days.

Reporting group title	MERO
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Reporting group description:

Participants received IV meropenem and placebo for metronidazole for 5-14 days. Dosage was based on age and weight. Following IV therapy, participants may have received oral step-down therapy. IV and oral antibiotic therapy could total a maximum of 14 days.

Reporting group values	C/T+MTZ	MERO	Total
Number of subjects	71	23	94
Age Categorical			
Units: Participants			
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)	2	0	2
Children (2-11 years)	52	17	69
Adolescents (12-17 years)	17	6	23
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender Categorical			
Units: Participants			
Female	23	15	38
Male	48	8	56
Race			
Units: Subjects			
Asian	3	2	5
Black Or African American	6	1	7
More than one race	1	0	1
White	61	20	81
Ethnicity			
Units: Subjects			
Hispanic or Latino	18	7	25
Not Hispanic or Latino	50	16	66
Unknown or Not Reported	3	0	3

End points

End points reporting groups

Reporting group title	C/T+MTZ
Reporting group description: Participants received intravenous (IV) ceftolozane, tazobactam, and metronidazole for 5-14 days. Dosage was based on age and weight. Following IV therapy, participants may have received oral step-down therapy. IV and oral antibiotic therapy could total a maximum of 14 days.	
Reporting group title	MERO
Reporting group description: Participants received IV meropenem and placebo for metronidazole for 5-14 days. Dosage was based on age and weight. Following IV therapy, participants may have received oral step-down therapy. IV and oral antibiotic therapy could total a maximum of 14 days.	

Primary: Number of Participants Experiencing ≥ 1 Adverse Events (AEs)

End point title	Number of Participants Experiencing ≥ 1 Adverse Events (AEs)
End point description: An AE was defined as any untoward medical occurrence in a participant administered study treatment and which did not necessarily have to have a causal relationship with this treatment. The number of participants who experienced an AE is presented. The analysis population consisted of all randomized participants who received any amount of study treatment.	
End point type	Primary
End point timeframe: Up to approximately 75 days	

End point values	C/T+MTZ	MERO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	21		
Units: Participants	56	13		

Statistical analyses

Statistical analysis title	Difference in Percentage (C/T+MTZ minus MERO)
Statistical analysis description: The Miettinen & Nurminen method was used.	
Comparison groups	MERO v C/T+MTZ
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentage
Point estimate	18.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	41.1

Primary: Number of Participants Who Discontinued Study Therapy Due to AE(s)

End point title	Number of Participants Who Discontinued Study Therapy Due to AE(s)
End point description: An AE was defined as any untoward medical occurrence in a participant administered study treatment and which did not necessarily have to have a causal relationship with this treatment. The number of participants who discontinued study treatment due to an AE is presented. The analysis population consisted of all randomized participants who received any amount of study treatment.	
End point type	Primary
End point timeframe: Up to approximately 18 days	

End point values	C/T+MTZ	MERO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	21		
Units: Participants	2	0		

Statistical analyses

Statistical analysis title	Difference in Percentage (C/T+MTZ minus MERO)
Statistical analysis description: The Miettinen & Nurminen method was used.	
Comparison groups	C/T+MTZ v MERO
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentage
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.9
upper limit	9.9

Secondary: Percentage of Participants with a Clinical Response of "Cure" at the End of Treatment (EOT) Visit

End point title	Percentage of Participants with a Clinical Response of "Cure" at the End of Treatment (EOT) Visit
End point description:	
The percentage of participants who had a clinical outcome of "cure" at the time of the EOT visit is presented. The "cure" clinical outcome was defined as complete resolution or marked improvement in signs and symptoms of the complicated intra-abdominal infection (cIAI) or return to preinfection signs and symptoms such that no further antibiotic therapy (intravenous or oral) or surgical or drainage procedure is required for treatment of the cIAI. Participants who were missing clinical response data were considered treatment failures. The analysis population consisted of all randomized participants who received any amount of study treatment. Participants were included in the IV study treatment group to which they were randomized, irrespective of what treatment they actually received.	
End point type	Secondary
End point timeframe:	
Up to approximately 27 days	

End point values	C/T+MTZ	MERO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	21		
Units: Percentage of Participants				
number (confidence interval 95%)	80.0 (69.18 to 87.70)	95.2 (77.33 to 99.15)		

Statistical analyses

Statistical analysis title	Difference in Percentage (C/T+MTZ minus MERO)
Statistical analysis description:	
The Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights was used. If there was a zero count in any class of the stratum, the groups with the lower count were pooled with its near age group stratum in the model.	
Comparison groups	C/T+MTZ v MERO
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentage
Point estimate	-14.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.67
upper limit	4.93

Secondary: Percentage of Participants with a Clinical Response of "Cure" at the Test of Cure (TOC) Visit

End point title	Percentage of Participants with a Clinical Response of "Cure" at the Test of Cure (TOC) Visit
End point description:	
The percentage of participants who had a clinical outcome of "cure" at the time of the TOC visit is	

presented. The "cure" clinical outcome was defined as complete resolution or marked improvement in signs and symptoms of the complicated intra-abdominal infection (cIAI) or return to preinfection signs and symptoms such that no further antibiotic therapy (intravenous or oral) or surgical or drainage procedure is required for treatment of the cIAI. Participants who were missing clinical response data were considered treatment failures. The analysis population consisted of all randomized participants who received any amount of study treatment. Participants were included in the IV study treatment group to which they were randomized, irrespective of what treatment they actually received.

End point type	Secondary
End point timeframe:	
Up to approximately 39 days	

End point values	C/T+MTZ	MERO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	21		
Units: Percentage of Participants				
number (confidence interval 95%)	80.0 (69.18 to 87.70)	100.0 (84.54 to 100.0)		

Statistical analyses

Statistical analysis title	Difference in Percentage (C/T+MTZ minus MERO)
Statistical analysis description:	
The Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights was used. If there was a zero count in any class of the stratum, the groups with the lower count were pooled with its near age group stratum in the model.	
Comparison groups	C/T+MTZ v MERO
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentage
Point estimate	-19.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.18
upper limit	-2.89

Secondary: Per-Participant Microbiological Eradication at the End of Treatment (EOT) Visit

End point title	Per-Participant Microbiological Eradication at the End of Treatment (EOT) Visit
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End point description:

The percentage of participants who achieved either eradication or presumed eradication of each baseline infecting pathogen by the time of the EOT visit is presented. Eradication was defined as absence of the baseline pathogen(s) in a postbaseline specimen appropriately obtained from the original site of infection. Presumed eradication was defined as absence of material to culture in a participant who is assessed as having partial improvement, or clinical cure. In the event of multiple baseline pathogens, the least favorable microbiological response from all possible baseline pathogens was used. The analysis

population consisted of all randomized participants who received any amount of study treatment and had at least 1 pathogen identified from the baseline intra-abdominal culture, regardless of susceptibility to study treatment. Participants were included in the IV study treatment group to which they were randomized, irrespective of what treatment they actually received.

End point type	Secondary
End point timeframe:	
Up to approximately 27 days	

End point values	C/T+MTZ	MERO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	19		
Units: Percentage of Participants				
number (confidence interval 95%)	84.1 (73.19 to 91.14)	94.7 (75.36 to 99.06)		

Statistical analyses

Statistical analysis title	Difference in Percentage (C/T+MTZ minus MERO)
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Statistical analysis description:

The Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights was used. If there was a zero count in any class of the stratum, the groups with the lower count were pooled with its near age group stratum in the model.

Comparison groups	C/T+MTZ v MERO
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentage
Point estimate	-11.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.66
upper limit	9.61

Secondary: Per-Participant Microbiological Eradication at the Test of Cure (TOC) Visit

End point title	Per-Participant Microbiological Eradication at the Test of Cure (TOC) Visit
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End point description:

The percentage of participants who achieved either eradication or presumed eradication of each baseline infecting pathogen by the time of the TOC visit is presented. Eradication was defined as absence of the baseline pathogen(s) in a postbaseline specimen appropriately obtained from the original site of infection. Presumed eradication was defined as absence of material to culture in a participant who is assessed as having partial improvement, or clinical cure. In the event of multiple baseline pathogens, the least favorable microbiological response from all possible baseline pathogens was used. The analysis population consisted of all randomized participants who received any amount of study treatment and had at least 1 pathogen identified from the baseline intra-abdominal culture, regardless of susceptibility to study treatment. Participants were included in the IV study treatment group to which they were

randomized, irrespective of what treatment they actually received.

End point type	Secondary
End point timeframe:	
Up to approximately 39 days	

End point values	C/T+MTZ	MERO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	19		
Units: Percentage of Participants				
number (confidence interval 95%)	84.1 (73.19 to 91.14)	100 (83.18 to 100.00)		

Statistical analyses

Statistical analysis title	Difference in Percentage (C/T+MTZ minus MERO)
Statistical analysis description:	
The Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights was used. If there was a zero count in any class of the stratum, the groups with the lower count were pooled with its near age group stratum in the model.	
Comparison groups	C/T+MTZ v MERO
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentage
Point estimate	-16.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.59
upper limit	1.39

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 75 days

Adverse event reporting additional description:

Deaths are counted in the population of all randomized participants. Serious adverse events and non-serious adverse events are reported for all randomized participants who received any amount of study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	C/T + MTZ
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Reporting group description:

Participants received intravenous (IV) ceftolozane, tazobactam, and metronidazole for 5-14 days. Dosage was based on age and weight. Following IV therapy, participants may have received oral step-down therapy. IV and oral antibiotic therapy could total a maximum of 14 days.

Reporting group title	MERO
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Reporting group description:

Participants received IV meropenem and placebo for metronidazole for 5-14 days. Dosage was based on age and weight. Following IV therapy, participants may have received oral step-down therapy. IV and oral antibiotic therapy could total a maximum of 14 days.

Serious adverse events	C/T + MTZ	MERO	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 70 (11.43%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
White blood cell count increased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 70 (1.43%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			

subjects affected / exposed	1 / 70 (1.43%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 70 (1.43%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal fluid collection			
subjects affected / exposed	1 / 70 (1.43%)	0 / 21 (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			
Abdominal sepsis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 70 (1.43%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 70 (1.43%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 70 (2.86%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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	C/T + MTZ	MERO	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 70 (65.71%)	10 / 21 (47.62%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 70 (5.71%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 70 (7.14%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Platelet count increased			
subjects affected / exposed	5 / 70 (7.14%)	2 / 21 (9.52%)	
occurrences (all)	5	2	
Injury, poisoning and procedural complications			
Incision site pain			
subjects affected / exposed	7 / 70 (10.00%)	1 / 21 (4.76%)	
occurrences (all)	7	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 70 (5.71%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	5 / 70 (7.14%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 70 (5.71%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Thrombocytosis			
subjects affected / exposed	6 / 70 (8.57%)	1 / 21 (4.76%)	
occurrences (all)	6	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 70 (12.86%)	3 / 21 (14.29%)	
occurrences (all)	10	7	
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	7 / 70 (10.00%) 8	0 / 21 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	13 / 70 (18.57%) 14	5 / 21 (23.81%) 5	
Vomiting subjects affected / exposed occurrences (all)	7 / 70 (10.00%) 8	1 / 21 (4.76%) 1	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 70 (4.29%) 3	3 / 21 (14.29%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2019	Amendment 2: Enrollment targets for participants aged birth to <6 years of age were applied.
23 September 2020	Amendment 3: Due to enrollment challenges, enrollment targets for participants aged birth to <6 years of age were adjusted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported