Clinical trial results:
A Phase 2b open-label, single-arm study to evaluate pharmacokinetics, efficacy, safety and tolerability of letermovir in pediatric participants from birth to less than 18 years of age at risk of developing CMV infection and/or disease following allogeneic haematopoietic stem cell transplantation (HSCT)

Summary

EudraCT number	2018-001326-25
Trial protocol	DE ES Outside EU/EEA FR PL
Global end of trial date	25 August 2023

Results information

Result version number	v1 (current)
This version publication date	15 February 2024
First version publication date	15 February 2024

Trial information

Trial identification

Sponsor protocol code	8228-030

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03940586
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-001631-PIP01-14
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	Interim
Date of interim/final analysis	04 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2023
Global end of trial reached?	Yes
Global end of trial date	25 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the pharmacokinetics (PK) of letermovir (LET) in pediatric participants. Participants were enrolled in the following 3 age groups: Age Group 1: From 12 to <18 years of age (adolescents); Age Group 2: From 2 to <12 years of age (children); and Age Group 3: From birth to <2 years of age (neonates, infants and toddlers). All participants received open label LET for 14 weeks (~100 days) post-transplant, with doses based on body weight and age.

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	08 August 2019
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	Australia: 7
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Türkiye: 6
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	65
EEA total number of subjects	19

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)	8
Children (2-11 years)	29
Adolescents (12-17 years)	28
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 and female recipients of a first allogeneic hematopoietic stem cell transplant (HSCT), between the ages of birth and <18 years of age, who were at risk for cytomegalovirus (CMV) infection and/or disease, and who had undetectable CMV deoxyribonucleic acid (DNA) collected within 5 days before enrollment. were enrolled in this study.

Period 1

Period 1 title	Randomized
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	12 - <18 Years

Arm description:

Letermovir (LET) 480 mg without cyclosporin (CsA), or 240 mg with CsA, administered either orally as tablets or in granular form, or by intravenous (IV) infusion, once daily (QD) through week 14 (~ 100 days) post-transplant.

Arm type	Experimental
Investigational medicinal product name	Letermovir oral granules
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Granules administered orally based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Investigational medicinal product name	Letermovir intravenous
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Letermovir administered intravenously based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Investigational medicinal product name	Letermovir tablet
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet administered orally based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Arm title	2 - <12 Years

Arm description:

Participants ≥30 kg body weight (BW): LET 480 mg orally without CsA, or 240 mg with CsA, in granular form, or 240 mg IV with or without CsA; 18 to <30 kg BW: LET 240 mg orally without CsA, or 120 mg with CsA, either in granular form, or 120 mg IV with or without CsA; 10 to <18 kg BW: LET 120 mg orally without CsA, or 60 mg with CsA, in granular form, or 60 mg IV with or without CsA, all QD through week 14 (~ 100 days) post-transplant.

Arm type	Experimental
Investigational medicinal product name	Letermovir intravenous
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Letermovir administered intravenously based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Investigational medicinal product name	Letermovir oral granules
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Granules administered orally based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Arm title	Birth - <2 Years

Arm description:

10 to ≤15 kg BW: LET 120 mg orally without CsA, or 60 mg with CsA, in granular form, or 60 mg IV with or without CsA; 7.5 to <10 kg BW: LET 80 mg orally without CsA, or 40 mg with CsA, either in granular form, or 40 mg IV with or without CsA; 5.0 to <7.5 kg BW: LET 40 mg orally without CsA, or 20 mg with CsA, in granular form, or 20 mg IV with or without CsA; 2.5 to <5.0 kg BW: LET 20 mg orally without CsA, or 10 mg with CsA, in granular form, or 10 mg IV with or without CsA, all QD through week 14 (~ 100 days) post-transplant.

Arm type	Experimental
Investigational medicinal product name	Letermovir intravenous
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Letermovir administered intravenously based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Investigational medicinal product name	Letermovir oral granules
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Granules administered orally based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Number of subjects in period 1	12 - <18 Years	2 - <12 Years	Birth - <2 Years
Started	28	29	8
Completed	28	27	8
Not completed	0	2	0
Not Treated	-	2	-

Period 2

Period 2 title	Treated
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	12 - <18 Years

Arm description:

Letermovir (LET) 480 mg without cyclosporin (CsA), or 240 mg with CsA, administered either orally as tablets or in granular form, or by intravenous (IV) infusion, once daily (QD) through week 14 (~ 100 days) post-transplant.

Arm type	Experimental
Investigational medicinal product name	Letermovir oral granules
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Granules administered orally based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Investigational medicinal product name	Letermovir intravenous
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Letermovir administered intravenously based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Investigational medicinal product name	Letermovir tablet
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet administered orally based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Arm title	2 - <12 Years

Arm description:

Participants ≥30 kg body weight (BW): LET 480 mg orally without CsA, or 240 mg with CsA, in granular form, or 240 mg IV with or without CsA; 18 to <30 kg BW: LET 240 mg orally without CsA, or 120 mg with CsA, either in granular form, or 120 mg IV with or without CsA; 10 to <18 kg BW: LET 120 mg orally without CsA, or 60 mg with CsA, in granular form, or 60 mg IV with or without CsA, all QD through week 14 (~ 100 days) post-transplant.

Arm type	Experimental
Investigational medicinal product name	Letermovir intravenous
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Letermovir administered intravenously based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Investigational medicinal product name	Letermovir oral granules
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Granules administered orally based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Arm title	Birth - <2 Years

Arm description:

10 to ≤15 kg BW: LET 120 mg orally without CsA, or 60 mg with CsA, in granular form, or 60 mg IV with or without CsA; 7.5 to <10 kg BW: LET 80 mg orally without CsA, or 40 mg with CsA, either in granular form, or 40 mg IV with or without CsA; 5.0 to <7.5 kg BW: LET 40 mg orally without CsA, or 20 mg with CsA, in granular form, or 20 mg IV with or without CsA; 2.5 to <5.0 kg BW: LET 20 mg orally without CsA, or 10 mg with CsA, in granular form, or 10 mg IV with or without CsA, all QD through week 14 (~ 100 days) post-transplant.

Arm type	Experimental
Investigational medicinal product name	Letermovir oral granules
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Granules administered orally based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Investigational medicinal product name	Letermovir intravenous
Investigational medicinal product code	
Other name	MK-8228 AIC246 AIC001
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Letermovir administered intravenously based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1, the number of participants randomized, is not the baseline period. Rather Period

2, the number of participants treated is the baseline period.

Number of subjects in period 2[2]	12 - <18 Years	2 - <12 Years	Birth - <2 Years
Started	28	27	8
Completed	21	21	6
Not completed	7	6	2
Adverse event, serious fatal	3	2	-
Physician decision	1	-	1
Withdrawal By Parent/Guardian	3	4	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of participants reported to in the baseline period are not the same as the worldwide number enrolled in the trial because the number of participants in the baseline period are instead the number of participants treated.

Baseline characteristics

Reporting groups	
Reporting group title	12 - <18 Years
Reporting group description:	
Letermovir (LET) 480 mg without cyclosporin (CsA), or 240 mg with CsA, administered either orally as tablets or in granular form, or by intravenous (IV) infusion, once daily (QD) through week 14 (~ 100 days) post-transplant.	
Reporting group title	2 - <12 Years
Reporting group description:	
Participants ≥30 kg body weight (BW): LET 480 mg orally without CsA, or 240 mg with CsA, in granular form, or 240 mg IV with or without CsA; 18 to <30 kg BW: LET 240 mg orally without CsA, or 120 mg with CsA, either in granular form, or 120 mg IV with or without CsA; 10 to <18 kg BW: LET 120 mg orally without CsA, or 60 mg with CsA, in granular form, or 60 mg IV with or without CsA, all QD through week 14 (~ 100 days) post-transplant.	
Reporting group title	Birth - <2 Years
Reporting group description:	
10 to ≤15 kg BW: LET 120 mg orally without CsA, or 60 mg with CsA, in granular form, or 60 mg IV with or without CsA; 7.5 to <10 kg BW: LET 80 mg orally without CsA, or 40 mg with CsA, either in granular form, or 40 mg IV with or without CsA; 5.0 to <7.5 kg BW: LET 40 mg orally without CsA, or 20 mg with CsA, in granular form, or 20 mg IV with or without CsA; 2.5 to <5.0 kg BW: LET 20 mg orally without CsA, or 10 mg with CsA, in granular form, or 10 mg IV with or without CsA, all QD through week 14 (~ 100 days) post-transplant.	

Reporting group values	12 - <18 Years	2 - <12 Years	Birth - <2 Years
Number of subjects	28	27	8
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	8
Children (2-11 years)	0	27	0
Adolescents (12-17 years)	28	0	0
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	14.1	6.6	0.7
standard deviation	± 1.5	± 3.2	± 0.3
Sex: Female, Male Units:			
Female	13	5	1
Male	15	22	7
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	6	3	0
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	3	0	0
White	15	22	7
More than one race	4	2	1
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	9	4	1
Not Hispanic or Latino	14	21	6
Unknown or Not Reported	5	2	1

Reporting group values	Total		
Number of subjects	63		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	8		
Children (2-11 years)	27		
Adolescents (12-17 years)	28		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units:			
Female	19		
Male	44		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	9		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	3		
White	44		
More than one race	7		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	14		
Not Hispanic or Latino	41		
Unknown or Not Reported	8		

End points

End points reporting groups

Reporting group title	12 - <18 Years
Reporting group description:	
Letermovir (LET) 480 mg without cyclosporin (CsA), or 240 mg with CsA, administered either orally as tablets or in granular form, or by intravenous (IV) infusion, once daily (QD) through week 14 (~ 100 days) post-transplant.	
Reporting group title	2 - <12 Years
Reporting group description:	
Participants ≥30 kg body weight (BW): LET 480 mg orally without CsA, or 240 mg with CsA, in granular form, or 240 mg IV with or without CsA; 18 to <30 kg BW: LET 240 mg orally without CsA, or 120 mg with CsA, either in granular form, or 120 mg IV with or without CsA; 10 to <18 kg BW: LET 120 mg orally without CsA, or 60 mg with CsA, in granular form, or 60 mg IV with or without CsA, all QD through week 14 (~ 100 days) post-transplant.	
Reporting group title	Birth - <2 Years
Reporting group description:	
10 to ≤15 kg BW: LET 120 mg orally without CsA, or 60 mg with CsA, in granular form, or 60 mg IV with or without CsA; 7.5 to <10 kg BW: LET 80 mg orally without CsA, or 40 mg with CsA, either in granular form, or 40 mg IV with or without CsA; 5.0 to <7.5 kg BW: LET 40 mg orally without CsA, or 20 mg with CsA, in granular form, or 20 mg IV with or without CsA; 2.5 to <5.0 kg BW: LET 20 mg orally without CsA, or 10 mg with CsA, in granular form, or 10 mg IV with or without CsA, all QD through week 14 (~ 100 days) post-transplant.	
Reporting group title	12 - <18 Years
Reporting group description:	
Letermovir (LET) 480 mg without cyclosporin (CsA), or 240 mg with CsA, administered either orally as tablets or in granular form, or by intravenous (IV) infusion, once daily (QD) through week 14 (~ 100 days) post-transplant.	
Reporting group title	2 - <12 Years
Reporting group description:	
Participants ≥30 kg body weight (BW): LET 480 mg orally without CsA, or 240 mg with CsA, in granular form, or 240 mg IV with or without CsA; 18 to <30 kg BW: LET 240 mg orally without CsA, or 120 mg with CsA, either in granular form, or 120 mg IV with or without CsA; 10 to <18 kg BW: LET 120 mg orally without CsA, or 60 mg with CsA, in granular form, or 60 mg IV with or without CsA, all QD through week 14 (~ 100 days) post-transplant.	
Reporting group title	Birth - <2 Years
Reporting group description:	
10 to ≤15 kg BW: LET 120 mg orally without CsA, or 60 mg with CsA, in granular form, or 60 mg IV with or without CsA; 7.5 to <10 kg BW: LET 80 mg orally without CsA, or 40 mg with CsA, either in granular form, or 40 mg IV with or without CsA; 5.0 to <7.5 kg BW: LET 40 mg orally without CsA, or 20 mg with CsA, in granular form, or 20 mg IV with or without CsA; 2.5 to <5.0 kg BW: LET 20 mg orally without CsA, or 10 mg with CsA, in granular form, or 10 mg IV with or without CsA, all QD through week 14 (~ 100 days) post-transplant.	
Subject analysis set title	12 - <18 Years
Subject analysis set type	Per protocol
Subject analysis set description:	
LET 480 mg without CsA as tablets or in granular form, was administered orally, QD through week 14 (~ 100 days) post-transplant.	
Subject analysis set title	2 - <12 Years
Subject analysis set type	Per protocol
Subject analysis set description:	
LET administered orally in granular form without CsA within 28 days post-transplant, QD through week 14 (approximately 100 days). Dosing varied based on weight.	
Subject analysis set title	Birth - <2 Years
Subject analysis set type	Per protocol
Subject analysis set description:	
LET administered orally in granular form without CsA within 28 days post-transplant, QD through week 14 (approximately 100 days). Dosing varied based on weight.	

Subject analysis set title	2 - <12 Years, 18 to <30 kg BW
Subject analysis set type	Per protocol

Subject analysis set description:

Participants 18 to <30 kg BW)received LET 240 mg without CsA orally in granular form QD through week 14 (~ 100 days) post-transplant.

Subject analysis set title	Birth - <2 Years, 5 to <7.5 kg BW
Subject analysis set type	Per protocol

Subject analysis set description:

Participants 5 to <7.5 kg BW received LET 60 mg orally without CsA, in granular form, QD through week 14 (~ 100 days) post-transplant.

Subject analysis set title	2 - <12 Years, 10 to <18 kg BW
Subject analysis set type	Per protocol

Subject analysis set description:

Participants 10 to <18 kg BW received LET 120 mg without CsA orally in granular form QD through week 14 (~ 100 days) post-transplant.

Subject analysis set title	Birth - <2 Years, 7.5 to <10 kg BW
Subject analysis set type	Per protocol

Subject analysis set description:

Participants 7.5 to <10 kg BW received LET 40 mg orally without CsA, in granular form, QD through week 14 (~ 100 days) post-transplant.

Subject analysis set title	Birth - <2 Years, 5 to <7.5 kg BW
Subject analysis set type	Per protocol

Subject analysis set description:

Participants 5 to <7.5 kg BW received LET 60 mg orally without CsA, in granular form, QD through week 14 (~ 100 days) post-transplant.

Subject analysis set title	12 - <18 Years
Subject analysis set type	Per protocol

Subject analysis set description:

LET 480 mg without CsA was administered by IV, QD through week 14 (~ 100 days) post-transplant.

Subject analysis set title	2 - <12 Years, ≥30 kg BW
Subject analysis set type	Per protocol

Subject analysis set description:

Participants ≥30 kg BW received LET 240 mg without CsA orally by IV QD through week 14 (~ 100 days) post-transplant.

Subject analysis set title	2 - <12 Years, 18 to <30 kg BW
Subject analysis set type	Per protocol

Subject analysis set description:

Participants 18 to <30 kg BW received LET 120 mg without CsA, by IV QD through week 14 (~ 100 days) post-transplant.

Subject analysis set title	2 - <12 Years, 18 to <30 kg BW
Subject analysis set type	Per protocol

Subject analysis set description:

Participants 18 to <30 kg BW received LET 240 mg without CsA by IV QD through week 14 (~ 100 days) post-transplant.

Subject analysis set title	2 - <12 Years, 10 to <18 kg BW
Subject analysis set type	Per protocol

Subject analysis set description:

Participants 10 to <18 kg BW received LET 60 mg without CsA by IV QD through week 14 (~ 100 days) post-transplant.

Subject analysis set title	Birth - <2 Years, 5 to <7.5 kg BW
Subject analysis set type	Per protocol

Subject analysis set description:

Participants 5.0 to <7.5 kg BW received LET 40 mg without CsA, by IV QD through week 14 (~ 100 days) post-transplant.

Subject analysis set title	Birth - <2 Years, 7.5 to <10 kg BW

Subject analysis set type	Per protocol

Subject analysis set description:

Participants 7.5 to <10 kg BW received LET 40 mg without CsA, by IV, QD through week 14 (~ 100 days) post-transplant.

Subject analysis set title	2 - <12 Years
Subject analysis set type	Per protocol

Subject analysis set description:

LET administered by IV within 28 days post-transplant, QD without CsA through week 14 (approximately 100 days). Dosing varied based on weight.

Subject analysis set title	Birth - <2 Years
Subject analysis set type	Per protocol

Subject analysis set description:

LET administered by IV without CsA within 28 days post-transplant, QD through week 14 (approximately 100 days). Dosing varied based on weight.

Primary: Area under the concentration-time curve from time 0 to 24 hours post-dose (AUC0-24) of plasma letermovir taken as oral formulation by ages 2 - <18 years

End point title	Area under the concentration-time curve from time 0 to 24 hours post-dose (AUC0-24) of plasma letermovir taken as oral formulation by ages 2 - <18 years[1]

End point description:

Blood was collected on treatment Day 7 from participants aged 2 - <18 years in order to determine the AUC0-24 of plasma letermovir for participants receiving oral formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 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: Statistical comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 18 to <30 kg BW	Birth - <2 Years, 5 to <7.5 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5	4	0[2]	
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	80300 (± 74.9)	62900 (± 37.4)	()	

Notes:

[2] - Data analysis resulted in a different measure type and method of dispersion.

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-24 of plasma letermovir taken as oral formulation by ages 2 to <12 years

End point title	AUC0-24 of plasma letermovir taken as oral formulation by

	ages 2 to <12 years[3]

End point description:

Blood was collected on treatment Day 7 from participants aged 2 to <12 years in order to determine the AUC0-24 of plasma letermovir for participants receiving oral formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	Birth - <2 Years, 5 to <7.5 kg BW	2 - <12 Years, 10 to <18 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[4]	0[5]	2	
Units: hr*ng/mL				
geometric mean (full range (min-max))	(to)	(to)	39500 (23900 to 65200)	

Notes:

[4] - data analysis resulted in a different measure type and method of dispersion.

[5] - Data analysis resulted in a different measure type and method of dispersion.

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-24 of plasma letermovir taken as oral formulation by ages <2 years

End point title	AUC0-24 of plasma letermovir taken as oral formulation by ages <2 years[6]

End point description:

Blood was collected on treatment Day 7 from participants aged <2 years in order to determine the AUC0-24 of plasma letermovir for participants receiving oral formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. The measure of dispersion is not determined when N <2. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[6] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 18 to <30 kg BW	Birth - <2 Years, 5 to <7.5 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[7]	0[8]	1	
Units: hr*ng/mL				
number (not applicable)			26200	

Notes:

[7] - Data analysis resulted in a different measure type and method of dispersion.

[8] - Data analysis resulted in a different measure type and method of dispersion.

Statistical analyses

No statistical analyses for this end point

Primary: Maximal concentration (Cmax) of plasma letermovir taken as oral formulation by ages 2 - <18 years

End point title	Maximal concentration (Cmax) of plasma letermovir taken as oral formulation by ages 2 - <18 years[9]

End point description:

Blood was collected on treatment Day 7 from participants aged 2 - <18 years in order to determine the Cmax of plasma letermovir for participants receiving oral formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. The measure type is geometric least squares mean. Participants aged < 2 years were not presented as their data analysis resulted in a different measure type and method of dispersion. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 18 to <30 kg BW	Birth - <2 Years, 7.5 to <10 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5	4	0[10]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	7410 (± 70.1)	10800 (± 17.4)	()	

Notes:

[10] - Data analysis resulted in a different measure type and method of dispersion.

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of plasma letermovir taken as oral formulation by ages 2 to <12 years

End point title	Cmax of plasma letermovir taken as oral formulation by ages 2

	to <12 years[11]

End point description:

Blood was collected on treatment Day 7 from participants aged 2 to <12 years in order to determine Cmax of plasma letermovir for participants receiving oral formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. Participants aged <2 and >12 years were not presented as their data analysis resulted in a different measure type and method of dispersion. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 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: Statistical comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 10 to <18 kg BW	Birth - <2 Years, 5 to <7.5 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[12]	2	0[13]	
Units: ng/mL				
geometric mean (full range (min-max))	(to)	5500 (5430 to 5580)	(to)	

Notes:

[12] - Data analysis resulted in a different measure type and method of dispersion.

[13] - Data analysis resulted in a different measure type and method of dispersion.

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of plasma letermovir taken as oral formulation by ages < 2 years

End point title	Cmax of plasma letermovir taken as oral formulation by ages < 2 years[14]

End point description:

Blood was collected on treatment Day 7 from participants aged <2 years in order to determine the Cmax of plasma letermovir for participants receiving oral formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. Participants aged 2 - <18 years were not presented as their data analysis resulted in a different measure type and method of dispersion. The measure of dispersion is not determined when N <2. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[14] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 18 to <30 kg BW	Birth - <2 Years, 5 to <7.5 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[15]	0[16]	1	
Units: ng/mL				
number (not applicable)			2950	

Notes:

[15] - Data analysis resulted in a different measure type and method of dispersion.

[16] - Data analysis resulted in a different measure type and method of dispersion.

Statistical analyses

No statistical analyses for this end point

Primary: Minimum concentration of plasma letermovir observed before next dose (Ctrough) taken as oral formulation by ages 2 - <18 years

End point title	Minimum concentration of plasma letermovir observed before next dose (Ctrough) taken as oral formulation by ages 2 - <18 years[17]

End point description:

Blood was collected on treatment Day 7 from participants aged 2 - <18 years in order to determine the Ctrough of plasma letermovir for participants receiving oral formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. Participants aged < 2 years were not presented as their data analysis resulted in a different measure type and method of dispersion. The measure type is geometric least squares mean. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: 24 hours post-dose

Notes:

[17] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 18 to <30 kg BW	Birth - <2 Years, 7.5 to <10 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5	4	0[18]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	845 (± 107.5)	171 (± 2046.8)	()	

Notes:

[18] - Data analysis resulted in a different measure type and method of dispersion.

Statistical analyses

No statistical analyses for this end point

Primary: Ctrough of plasma letermovir taken as oral formulation by ages 2 to <12 years

End point title	Ctrough of plasma letermovir taken as oral formulation by ages 2 to <12 years[19]

End point description:

Blood was collected on treatment Day 7 from participants aged 2 to <12 years in order to determine Ctrough of plasma letermovir for participants receiving oral formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. Participants aged <2 and >12 years were not presented as their data analysis resulted in a different measure type and method of dispersion. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[19] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 10 to <18 kg BW	Birth - <2 Years, 5 to <7.5 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[20]	2	0[21]	
Units: ng/mL				
geometric mean (full range (min-max))	(to)	481 (207 to 1120)	(to)	

Notes:

[20] - Data analysis resulted in a different measure type and method of dispersion.

[21] - Data analysis resulted in a different measure type and method of dispersion.

Statistical analyses

No statistical analyses for this end point

Primary: Ctrough of plasma letermovir taken as oral formulation by ages < 2 years

End point title	Ctrough of plasma letermovir taken as oral formulation by ages < 2 years[22]

End point description:

Blood was collected on treatment Day 7 from participants aged <2 years in order to determine the Ctrough of plasma letermovir for participants receiving oral formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. Participants aged 2 - <18 years were not presented as their data analysis resulted in a different measure type and method of dispersion. The measure of dispersion is not determined when N <2. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: 24 hours post-dose

Notes:

[22] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 18 to <30 kg BW	Birth - <2 Years, 5 to <7.5 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[23]	0[24]	1	
Units: ng/mL				
number (not applicable)			61.7	

Notes:

[23] - Data analysis resulted in a different measure type and method of dispersion.

[24] - Data analysis resulted in a different measure type and method of dispersion.

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-24 of plasma letermovir taken as intravenous (IV) formulation by ages 12 - <18 years

End point title	AUC0-24 of plasma letermovir taken as intravenous (IV) formulation by ages 12 - <18 years[25]

End point description:

Blood was collected on treatment Day 7 from participants aged 12 - <18 years in order to determine the AUC0-24 of plasma letermovir for participants receiving IV formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[25] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 18 to <30 kg BW	Birth - <2 Years, 7.5 to <10 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	0[26]	0[27]	
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	114000 (± 37.8)	()	()	

Notes:

[26] - Data analysis resulted in a different measure type and method of dispersion

[27] - Data analysis resulted in a different measure type and method of dispersion

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-24 of plasma letermovir taken as IV formulation by ages 2 to <12 years

End point title	AUC0-24 of plasma letermovir taken as IV formulation by ages 2 to <12 years[28]

End point description:

Blood was collected on treatment Day 7 from participants aged 2 to <12 years in order to determine the AUC0-24 of plasma letermovir for participants receiving IV formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[28] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, ≥30 kg BW	2 - <12 Years, 18 to <30 kg BW	Birth - <2 Years, 5 to <7.5 kg BW
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[29]	2	2	0[30]
Units: hr*ng/mL				
geometric mean (full range (min-max))	(to)	36200 (21000 to 62100)	31500 (20300 to 48900)	(to)

Notes:

[29] - Data analysis resulted in a different measure type and method of dispersion

[30] - Data analysis resulted in a different measure type and method of dispersion

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-24 of plasma letermovir taken as IV formulation by ages 2 to <12 years

End point title	AUC0-24 of plasma letermovir taken as IV formulation by ages 2 to <12 years[31]

End point description:

Blood was collected on treatment Day 7 from participants aged 2 to <12 years in order to determine the AUC0-24 of plasma letermovir for participants receiving IV formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. The measure of dispersion is not determined when N <2. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[31] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 10 to <18 kg BW	Birth - <2 Years, 5 to <7.5 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[32]	1	0[33]	
Units: hr*ng/mL				
number (not applicable)		25300		

Notes:

[32] - Data analysis resulted in a different measure type and method of dispersion

[33] - Data analysis resulted in a different measure type and method of dispersion

Statistical analyses

No statistical analyses for this end point

Primary: Concentration at the end of infusion (Ceoi) of plasma letermovir taken as IV formulation by ages 12 - <18 years

End point title	Concentration at the end of infusion (Ceoi) of plasma letermovir taken as IV formulation by ages 12 - <18 years[34]

End point description:

Blood was collected on treatment Day 7 from participants aged 12 - <18 years in order to determine the Ceoi of plasma letermovir for participants receiving IV formulation. As samples were collected outside the collection window Ceoi for these samples were predicted by using a log linear model .The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[34] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 18 to <30 kg BW	Birth - <2 Years, 7.5 to <10 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	0[35]	0[36]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	30600 (± 16.4)	()	()	

Notes:

[35] - Data analysis resulted in a different measure type and method of dispersion

[36] - Data analysis resulted in a different measure type and method of dispersion

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-24 of plasma letermovir taken as IV formulation by ages <2 years

End point title	AUC0-24 of plasma letermovir taken as IV formulation by ages <2 years[37]

End point description:

Blood was collected on treatment Day 7 from participants aged <2 years in order to determine the

AUC0-24 of plasma letermovir for participants receiving IV formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. The measure of dispersion is not determined when N <2. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[37] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, ≥30 kg BW	Birth - <2 Years, 5 to <7.5 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[38]	0[39]	1	
Units: hr*ng/mL				
number (not applicable)			37300	

Notes:

[38] - Data analysis resulted in a different measure type and method of dispersion

[39] - Data analysis resulted in a different measure type and method of dispersion

Statistical analyses

No statistical analyses for this end point

Primary: Ceoi of plasma letermovir taken as IV formulation by ages 2 to <12 years

End point title	Ceoi of plasma letermovir taken as IV formulation by ages 2 to <12 years[40]

End point description:

Blood was collected on treatment Day 7 from participants aged 2 to <12 years in order to determine the Ceoi of plasma letermovir for participants receiving IV formulation. As samples were collected outside the collection window Ceoi for these samples were predicted by using a log linear model. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[40] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, ≥30 kg BW	2 - <12 Years, 18 to <30 kg BW	Birth - <2 Years, 7.5 to <10 kg BW
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[41]	2	2	0[42]
Units: ng/mL				
geometric mean (full range (min-max))	(to)	16800 (14900 to 19000)	8200 (7580 to 8870)	(to)

Notes:

[41] - Data analysis resulted in a different measure type and method of dispersion

[42] - Data analysis resulted in a different measure type and method of dispersion

Statistical analyses

No statistical analyses for this end point

Primary: Ceoi of plasma letermovir taken as IV formulation by ages s 2 to <12 years

End point title	Ceoi of plasma letermovir taken as IV formulation by ages s 2 to <12 years[43]

End point description:

Blood was collected on treatment Day 7 from participants aged 2 to <12 years in order to determine the Ceoi of plasma letermovir for participants receiving IV formulation. As samples were collected outside the collection window Ceoi for these samples were predicted by using a log linear model. A measure of dispersion is not determined when N <2. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[43] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 10 to <18 kg BW	Birth - <2 Years, 5 to <7.5 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[44]	1	0[45]	
Units: ng/mL				
number (not applicable)		8630		

Notes:

[44] - Data analysis resulted in a different measure type and method of dispersion

[45] - Data analysis resulted in a different measure type and method of dispersion

Statistical analyses

No statistical analyses for this end point

Primary: Ceoi of plasma letermovir taken as IV formulation by ages <2 years

End point title	Ceoi of plasma letermovir taken as IV formulation by ages <2 years[46]

End point description:

Blood was collected on treatment Day 7 from participants aged <2 years in order to determine the Ceoi of plasma letermovir for participants receiving IV formulation. As samples were collected outside the collection window Ceoi for these samples were predicted by using a log linear modelA measure of dispersion is not determined when N <2. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important

protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[46] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, ≥30 kg BW	Birth - <2 Years, 5 to <7.5 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[47]	0[48]	1	
Units: ng/mL				
number (not applicable)			11700	

Notes:

[47] - Data analysis resulted in a different measure type and method of dispersion

[48] - Data analysis resulted in a different measure type and method of dispersion

Statistical analyses

No statistical analyses for this end point

Primary: Ctrough of plasma letermovir taken as IV formulation by ages 2 to <12 years

End point title	Ctrough of plasma letermovir taken as IV formulation by ages 2 to <12 years[49]

End point description:

Blood was collected on treatment Day 7 from participants aged 2 to <12 years in order to determine the Ctrough of plasma letermovir for participants receiving IV formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: 24 hours post-dose

Notes:

[49] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, ≥30 kg BW	2 - <12 Years, 18 to <30 kg BW	Birth - <2 Years, 7.5 to <10 kg BW
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[50]	2	2	0[51]
Units: ng/mL				
geometric mean (full range (min-max))	(to)	71.6 (12.9 to 397)	318 (134 to 754)	(to)

Notes:

[50] - Data analysis resulted in a different measure type and method of dispersion

[51] - Data analysis resulted in a different measure type and method of dispersion

Statistical analyses

No statistical analyses for this end point

Primary: Ctrough of plasma letermovir taken as IV formulation by ages 12 - <18 years

End point title	Ctrough of plasma letermovir taken as IV formulation by ages 12 - <18 years[52]

End point description:

Blood was collected on treatment Day 7 from participants aged 12 - <18 years in order to determine the Ctrough of plasma letermovir for participants receiving IV formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: 24 hours post-dose

Notes:

[52] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 18 to <30 kg BW	Birth - <2 Years, 7.5 to <10 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	0[53]	0[54]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	709 (± 256.8)	()	()	

Notes:

[53] - Data analysis resulted in a different measure type and method of dispersion

[54] - Data analysis resulted in a different measure type and method of dispersion

Statistical analyses

No statistical analyses for this end point

Primary: Ctrough of plasma letermovir taken as IV formulation by ages 2 to <12 years

End point title	Ctrough of plasma letermovir taken as IV formulation by ages 2 to <12 years[55]

End point description:

Blood was collected on treatment Day 7 from participants aged <2 years in order to determine the Ctrough of plasma letermovir for participants receiving IV formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. The measure of dispersion is not determined when N <2.

The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[55] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, 10 to <18 kg BW	Birth - <2 Years, 5 to <7.5 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[56]	1	0[57]	
Units: ng/mL				
number (not applicable)		216		

Notes:

[56] - Data analysis resulted in a different measure type and method of dispersion

[57] - Data analysis resulted in a different measure type and method of dispersion

Statistical analyses

No statistical analyses for this end point

Primary: Ctrough of plasma letermovir taken as IV formulation by ages <2 years

End point title	Ctrough of plasma letermovir taken as IV formulation by ages <2 years[58]

End point description:

Blood was collected on treatment Day 7 from participants aged <2 years in order to determine the Ctrough of plasma letermovir for participants receiving IV formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant. The measure type is Geometric Mean, and a measure of dispersion is not determined when N <2. The population analyzed was all participants with at least one measurable PK sample who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations.

End point type	Primary

End point timeframe:

Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose

Notes:

[58] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years, ≥30 kg BW	Birth - <2 Years, 5 to <7.5 kg BW	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[59]	0[60]	1	
Units: ng/mL				
number (not applicable)			98.3	

Notes:

[59] - Data analysis resulted in a different measure type and method of dispersion

[60] - Data analysis resulted in a different measure type and method of dispersion

Statistical analyses

No statistical analyses for this end point

Primary: Ctrough of plasma letermovir taken during sparse PK for oral formulation

End point title	Ctrough of plasma letermovir taken during sparse PK for oral formulation[61]

End point description:

Blood was collected on treatment Day 7 in order to determine the Ctrough of plasma letermovir during sparse PK for participants receiving oral formulation. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant.

End point type	Primary

End point timeframe:

Day 7: 24 hours post-dose

Notes:

[61] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years	Birth - <2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[62]	0[63]	0[64]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()	()	()	

Notes:

[62] - As sparse PK data were instead used in population PK model development, they were not summarized

[63] - As sparse PK data were instead used in population PK model development, they were not summarized

[64] - As sparse PK data were instead used in population PK model development, they were not summarized

Statistical analyses

No statistical analyses for this end point

Primary: Ctrough of plasma letermovir taken during sparse PK as IV formulation

End point title	Ctrough of plasma letermovir taken during sparse PK as IV formulation[65]

End point description:

Blood was collected on treatment Day 7 in order to determine the Ctrough of plasma letermovir for participants receiving IV formulation during sparse PK. Individual values were natural log transformed and evaluated separately with a linear mixed effects model containing a fixed effect for treatment and a random effect for participant.

End point type	Primary

End point timeframe:

Day 7: 24 hours post-dose

Notes:

[65] - 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 comparisons between treatment groups were neither planned or performed for this primary endpoint.

End point values	12 - <18 Years	2 - <12 Years	Birth - <2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[66]	0[67]	0[68]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()	()	()	

Notes:

[66] - As sparse PK data were instead used in population PK model development, they were not summarized
[67] - As sparse PK data were instead used in population PK model development, they were not summarized
[68] - As sparse PK data were instead used in population PK model development, they were not summarized

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with one or more adverse event (AE)

End point title	Percentage of participants with one or more adverse event (AE)

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. The 95% confidence interval (CI) is based on the exact binomial method proposed by Clopper and Pearson. The population analyzed was all participants who received ≥1 dose of study intervention.

End point type	Secondary

End point timeframe:

Up to Week 48 post-transplant (up to 52 weeks)

End point values	12 - <18 Years	2 - <12 Years	Birth - <2 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	8	
Units: Percentage of participants				
number (confidence interval 95%)	100.0 (87.7 to 100.0)	100.0 (87.7 to 100.0)	100.0 (63.1 to 100.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who discontinued study medication due to an AE.

End point title	Percentage of participants who discontinued study medication due to an AE.

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. The 95% CI is based on the exact binomial method proposed by Clopper and Pearson. The population analyzed was all participants who received ≥1 dose of study intervention.

End point type	Secondary

End point timeframe:

Up to Week 14 post-transplant (up to 18 weeks)

End point values	12 - <18 Years	2 - <12 Years	Birth - <2 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	8	
Units: Percentage of participants				
number (confidence interval 95%)	17.9 (6.1 to 36.9)	7.4 (0.9 to 24.3)	12.5 (0.3 to 52.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with clinically significant CMV infection through Week 14 post-transplant

End point title	Percentage of participants with clinically significant CMV infection through Week 14 post-transplant

End point description:

Clinically significant cytomegalovirus (CMV) infection is defined as CMV end organ disease (proven or probable) or initiation of pre-emptive therapy (PET) based on documented CMV viremia and the clinical condition of the participant. The 95% confidence interval (CI) was based on the exact binomial method proposed by Clopper and Pearson. Missing values: were handled by the Non-Completer=Failure (NC=F) approach. where failure was defined as all participants who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through week 14 post-transplant visit window. The population analyzed was participants who received ≥1 dose of study intervention, had no detectable CMV viral DNA on the day study intervention was initiated, had not prematurely discontinued from the study and had an outcome through week 14 post-transplant.

End point type	Secondary

End point timeframe:

Up to Week 14 post-transplant (up to 18 weeks)

End point values	12 - <18 Years	2 - <12 Years	Birth - <2 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	24	7	
Units: Percentage of participants				
number (confidence interval 95%)	20.0 (6.8 to 40.7)	16.7 (4.7 to 37.4)	28.5 (3.7 to 71.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with clinically significant CMV infection through Week 24 post-transplant

End point title	Percentage of participants with clinically significant CMV infection through Week 24 post-transplant

End point description:

Clinically significant CMV infection is defined as CMV end organ disease (proven or probable) or initiation of PET based on documented CMV viremia and the clinical condition of the participant. The 95% confidence interval (CI) was based on the exact binomial method proposed by Clopper and Pearson. Missing values: were handled by the Non-Completer=Failure (NC=F) approach. where failure was defined as all participants who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through week 24 post-transplant visit window. The population analyzed was participants who received ≥1 dose of study intervention, had no detectable CMV viral DNA on the day study intervention was initiated, had not prematurely discontinued from the study and had an outcome through week 14 post-transplant.

End point type	Secondary

End point timeframe:

Up to Week 24 post-transplant (up to 28 weeks)

End point values	12 - <18 Years	2 - <12 Years	Birth - <2 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	24	7	
Units: Percentage of participants				
number (confidence interval 95%)	24.0 (9.4 to 45.1)	25.0 (9.8 to 46.7)	28.6 (3.7 to 71.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants receiving oral granules with palatability response, based on taste of medication on the first day of administration of oral formulation

End point title	Number of participants receiving oral granules with palatability response, based on taste of medication on the first day of administration of oral formulation

End point description:

Palatability was measured by response to a questionnaire on the taste of medication , with responses from very good, good, neither good nor bad, bad or very bad. The population analyzed was participants who received ≥1 dose of study intervention, and completed palatability questionnaire.

End point type	Secondary

End point timeframe:

Day 1 of administration of oral formulation up to Week 14 post-transplant (up to 18 weeks)

End point values	12 - <18 Years	2 - <12 Years	Birth - <2 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	27	7	
Units: Participants				
Very good	0	3	0	
Good	1	5	3	
Neither good nor bad	1	8	1	
Bad	1	8	3	
Very bad	1	3	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants receiving oral granules with palatability response, based on taste of medication on the eighth day of administration of oral formulation

End point title	Number of participants receiving oral granules with palatability response, based on taste of medication on the eighth day of administration of oral formulation

End point description:

Palatability was measured by response to a questionnaire on the taste of medication , with responses from very good, good, neither good nor bad, bad or very bad. The population analyzed was participants who received ≥1 dose of study intervention, and completed palatability questionnaire.

End point type	Secondary

End point timeframe:

Day 8 of administration of oral formulation up to Week 14 post-transplant (up to 18 weeks)

End point values	12 - <18 Years	2 - <12 Years	Birth - <2 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	23	7	
Units: Participants				
Very good	0	3	0	
Good	1	4	3	
Neither good nor bad	1	8	4	
Bad	0	5	0	

Very bad	0	3	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 allocation/randomization (i.e. prior to treatment) up to Week 48 post-transplant (up to 52 weeks). AEs: From first treatment up to Week 48 post-transplant (up to 52 weeks)

Adverse event reporting additional description:

ACMs: the population analyzed was all allocated/randomized participants.
AEs: the population analyzed was all allocated/randomized participants who received ≥1 dose of study intervention.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	12 - <18 Years

Reporting group description:

LET 480 mg without CsA, or 240 mg with CsA, administered either orally as tablets or in granular form, or by iIV infusion, QD through week 14 (~ 100 days) post-transplant.

Reporting group title	<2 Years

Reporting group description:

10 to ≤15 kg BW: LET 120 mg orally without CsA, or 60 mg with CsA, in granular form, or 60 mg IV with or without CsA; 7.5 to <10 kg BW: LET 80 mg orally without CsA, or 40 mg with CsA, either in granular form, or 40 mg IV with or without CsA; 5.0 to <7.5 kg BW: LET 40 mg orally without CsA, or 20 mg with CsA, in granular form, or 20 mg IV with or without CsA; 2.5 to <5.0 kg BW: LET 20 mg orally without CsA, or 10 mg with CsA, in granular form, or 10 mg IV with or without CsA, all QD through week 14 (~ 100 days) post-transplant.

Reporting group title	2 - <12 Years

Reporting group description:

Participants ≥30 kg BW: LET 480 mg orally without CsA, or 240 mg with CsA, in granular form, or 240 mg IV with or without CsA; 18 to <30 kg BW: LET 240 mg orally without CsA, or 120 mg with CsA, either in granular form, or 120 mg IV with or without CsA; 10 to <18 kg BW: LET 120 mg orally without CsA, or 60 mg with CsA, in granular form, or 60 mg IV with or without CsA, all QD through week 14 (~ 100 days) post-transplant.

Serious adverse events	12 - <18 Years	<2 Years	2 - <12 Years
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 28 (42.86%)	6 / 8 (75.00%)	17 / 27 (62.96%)
number of deaths (all causes)	4	0	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Post transplant lymphoproliferative disorder			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute myeloid leukaemia recurrent			

subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Venoocclusive disease			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 28 (10.71%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Immune system disorders			
Transplant rejection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Graft versus host disease			
subjects affected / exposed	1 / 28 (3.57%)	1 / 8 (12.50%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute graft versus host disease			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophagocytic lymphohistiocytosis			

subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Respiratory distress			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Epstein-Barr virus test positive			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Transfusion reaction			

subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Humerus fracture			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Engraft failure			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transplant failure			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Nervous system disorders			
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Polyneuropathy			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurotoxicity			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Endocrine disorders			
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Candida infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cystitis viral			

subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection reactivation			
subjects affected / exposed	1 / 28 (3.57%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis bacterial			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Bronchitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BK virus infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Epstein-Barr virus infection reactivation			

subjects affected / exposed	0 / 28 (0.00%)	2 / 8 (25.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Septic shock			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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
Klebsiella bacteraemia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Human herpesvirus 6 infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatosplenic candidiasis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastroenteritis clostridial			

subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	0 / 27 (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: 5 %

Non-serious adverse events	12 - <18 Years	<2 Years	2 - <12 Years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 28 (96.43%)	8 / 8 (100.00%)	27 / 27 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 28 (10.71%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	3	0	3
Flushing			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	7 / 28 (25.00%)	0 / 8 (0.00%)	9 / 27 (33.33%)
occurrences (all)	8	0	13
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	3	0	4
Catheter site erythema			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2

Fatigue			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	2	0	3
Face oedema			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Mucosal inflammation			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	4 / 27 (14.81%)
occurrences (all)	0	1	4
Pyrexia			
subjects affected / exposed	10 / 28 (35.71%)	4 / 8 (50.00%)	12 / 27 (44.44%)
occurrences (all)	17	4	21
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	1	0	3
Engraftment syndrome			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Graft versus host disease			
subjects affected / exposed	10 / 28 (35.71%)	2 / 8 (25.00%)	10 / 27 (37.04%)
occurrences (all)	13	2	13
Graft versus host disease in skin			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	3 / 28 (10.71%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	3	0	0
Pulmonary mass			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	5 / 28 (17.86%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	5	0	4
Hypoxia			

subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Epistaxis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	1	0	5
Dyspnoea			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Cough			
subjects affected / exposed	4 / 28 (14.29%)	0 / 8 (0.00%)	4 / 27 (14.81%)
occurrences (all)	4	0	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 28 (17.86%)	1 / 8 (12.50%)	3 / 27 (11.11%)
occurrences (all)	6	1	3
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 28 (14.29%)	1 / 8 (12.50%)	1 / 27 (3.70%)
occurrences (all)	5	1	1
BK polyomavirus test positive			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	2	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Cytomegalovirus test positive			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Gamma-glutamyltransferase increased			

subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Immunosuppressant drug level increased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	7
Oxygen saturation decreased			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	1
Weight decreased			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	3	0	3
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Contusion			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	4 / 28 (14.29%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	4	0	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	1
Headache			
subjects affected / exposed	6 / 28 (21.43%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	8	0	4
Tremor			
subjects affected / exposed	4 / 28 (14.29%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	4	0	0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	4	0	6

Anaemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	6 / 27 (22.22%)
occurrences (all)	4	0	15
Lymphopenia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	2	0	3
Leukopenia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	3	0	2
Thrombocytopenia			
subjects affected / exposed	5 / 28 (17.86%)	0 / 8 (0.00%)	9 / 27 (33.33%)
occurrences (all)	8	0	9
Neutropenia			
subjects affected / exposed	2 / 28 (7.14%)	1 / 8 (12.50%)	8 / 27 (29.63%)
occurrences (all)	4	2	11
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 28 (39.29%)	1 / 8 (12.50%)	6 / 27 (22.22%)
occurrences (all)	14	1	10
Abdominal pain upper			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	2	0	7
Anal fissure			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	2
Constipation			
subjects affected / exposed	4 / 28 (14.29%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	4	0	4
Diarrhoea			
subjects affected / exposed	12 / 28 (42.86%)	1 / 8 (12.50%)	12 / 27 (44.44%)
occurrences (all)	16	1	15
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Gastrointestinal inflammation			

subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Haematochezia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	2	0	2
Nausea			
subjects affected / exposed	12 / 28 (42.86%)	0 / 8 (0.00%)	6 / 27 (22.22%)
occurrences (all)	23	0	7
Oesophagitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	3
Stomatitis			
subjects affected / exposed	7 / 28 (25.00%)	0 / 8 (0.00%)	9 / 27 (33.33%)
occurrences (all)	7	0	9
Vomiting			
subjects affected / exposed	13 / 28 (46.43%)	3 / 8 (37.50%)	20 / 27 (74.07%)
occurrences (all)	41	5	48
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	3	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	1	0	3
Nail pigmentation			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Macule			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hypertrichosis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Erythema			

subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	1	0	5
Eczema			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	1 / 27 (3.70%)
occurrences (all)	0	1	2
Dry skin			
subjects affected / exposed	1 / 28 (3.57%)	1 / 8 (12.50%)	2 / 27 (7.41%)
occurrences (all)	1	1	2
Rash macular			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Rash erythematous			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	4 / 28 (14.29%)	0 / 8 (0.00%)	4 / 27 (14.81%)
occurrences (all)	4	0	6
Pruritus			
subjects affected / exposed	6 / 28 (21.43%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	7	0	3
Palmar erythema			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	3 / 28 (10.71%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	3	0	3
Hypercalciuria			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Haematuria			
subjects affected / exposed	4 / 28 (14.29%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	4	0	2
Dysuria			
subjects affected / exposed	6 / 28 (21.43%)	0 / 8 (0.00%)	3 / 27 (11.11%)
occurrences (all)	6	0	3

Acute kidney injury			
subjects affected / exposed	3 / 28 (10.71%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	3	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 28 (3.57%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Adrenal insufficiency			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	3	0	0
Pain in extremity			
subjects affected / exposed	3 / 28 (10.71%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences (all)	3	0	1
Infections and infestations			
Streptococcal infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Adenovirus infection			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	1
BK virus infection			
subjects affected / exposed	3 / 28 (10.71%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	3	0	0
Bacteraemia			
subjects affected / exposed	3 / 28 (10.71%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences (all)	3	0	1
Cytomegalovirus infection			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Device related bacteraemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0

Device related infection			
subjects affected / exposed	1 / 28 (3.57%)	1 / 8 (12.50%)	3 / 27 (11.11%)
occurrences (all)	1	1	3
Epstein-Barr virus infection reactivation			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Febrile infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 28 (3.57%)	1 / 8 (12.50%)	2 / 27 (7.41%)
occurrences (all)	1	1	2
Pneumonia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Polyomavirus viraemia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Sepsis			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Rhinitis			
subjects affected / exposed	2 / 28 (7.14%)	1 / 8 (12.50%)	2 / 27 (7.41%)
occurrences (all)	3	1	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 28 (10.71%)	0 / 8 (0.00%)	8 / 27 (29.63%)
occurrences (all)	4	0	10
Hypercholesterolaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Hypervolaemia			

subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	1
Hypoalbuminaemia			
subjects affected / exposed	3 / 28 (10.71%)	0 / 8 (0.00%)	5 / 27 (18.52%)
occurrences (all)	7	0	8
Hypokalaemia			
subjects affected / exposed	4 / 28 (14.29%)	1 / 8 (12.50%)	4 / 27 (14.81%)
occurrences (all)	5	1	5
Hypomagnesaemia			
subjects affected / exposed	4 / 28 (14.29%)	1 / 8 (12.50%)	3 / 27 (11.11%)
occurrences (all)	6	1	4
Hypophosphataemia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	3	0	3
Malnutrition			
subjects affected / exposed	1 / 28 (3.57%)	0 / 8 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Neonatal diabetes mellitus			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Sodium retention			
subjects affected / exposed	0 / 28 (0.00%)	1 / 8 (12.50%)	0 / 27 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2019	Amendment 01: Testicular toxicity testing was removed, and creatinine clearance monitoring every 2 weeks was added to the protocol.
03 April 2019	Amendment 02: The description of the coating of the oral granule formulation to be used in this study provided in Section 2.2.4 was incorrect in the original protocol. This amendment provides the correct description of the coating of the oral granule formulation being used (Opadry coating without Surelease) and provides the rationale for selection of this oral granule formulation. Additional minor changes have been made to incorporate changes communicated in prior protocol clarification letters.
27 September 2019	Amendment 03: To add the requirement that the IV formulation of LET supplied by the Sponsor to sites as study medication must be administered through a sterile 0.2-micron or 0.22-micron polyethersulfone (PES) in-line filter and using diethylhexyl phthalate (DEHP)-free IV bags and infusion set materials. This requirement is being added to prevent the possible administration of product-related particulate matter. The presence of visible product-related particulate matter is an expected characteristic of new clinical supplies of the IV formulation of LET. This requirement is being implemented to allow for the release of new clinical supplies of IV LET, and, as a precaution, it must be applied regardless of whether the clinical site considers its current clinical supply to be impacted.
01 October 2021	Amendment 07: To provide the initial dose of oral and IV LET for Age Group 3, which has been determined by interim pharmacokinetics (PK) analyses using data from participants in Age Group 1 and Age Group 2 of this study. To add a requirement for PK sampling of hydroxypropyl-beta-cyclodextrin (HPCD), an excipient in the IV LET formulation, for Age Group 3 participants receiving the IV formulation for at least 4 consecutive days. In addition, the 10-mg oral capsule of LET is now available for use in Spain.
21 October 2022	Amendment 08:The primary reason was Sponsor underwent entity name change and update to the address.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported