Clinical trial results:
A Phase 1 Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in Human Immunodeficiency Virus-1 (HIV-1)-Exposed Neonates at High Risk of Acquiring HIV-1 Infection

Summary

EudraCT number	2016-003248-34
Trial protocol	Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1
This version publication date	25 August 2017
First version publication date	25 August 2017

Trial information

Trial identification

Sponsor protocol code	0518-080

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01780831
WHO universal trial number (UTN)	-
Other trial identifiers	Protocol number: IMPAACT P1110

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000279-PIP01-08
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	06 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study were to evaluate the safety and tolerability through 6 weeks of age of raltegravir oral granules for suspension (GFS) when administered during the first 6 weeks of age with standard prevention of mother-to-child transmission (PMTCT) antiretroviral prophylaxis to human immunodeficiency virus Type 1 (HIV-1)-exposed infants assessed at high risk of HIV-1 infection, to evaluate the pharmacokinetics (PK) of raltegravir GFS during the first 6 weeks of age along with standard PMTCT antiretroviral therapy prophylaxis, and to determine an appropriate dose of raltegravir GFS for use in neonates and infants during the first 6 weeks of 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. At the end of the study, HIV infected infants (if any) who continue to receive raltegravir as part of their combination antiretroviral therapy (cART) regimen will have access to raltegravir through Merck Pediatric Compassionate Use program.

Background therapy:

All enrolled neonates also received standard of care antiretroviral (ARV) for PMTCT prophylaxis. Choice of the ARV regimen will be left to the discretion of the site investigator.

Evidence for comparator: -

Actual start date of recruitment	04 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 21
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	United States: 17
Worldwide total number of subjects	42
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	42
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Mother/infant pairs were enrolled. Mother was known to be HIV-1 infected. Infants were HIV-1 exposed full-term neonates aged ≤48 hours who may have received up to 48 hours of standard of care ARV prophylaxis before enrollment and either had been exposed to raltegravir in utero or not exposed to raltegravir in utero.

Pre-assignment

Screening details:

Neonates enrolled in Cohort I received 3 mg/kg raltegravir GFS as a single dose within 48 hours of birth. Assessment of the PK and safety data from the 1st 6 enrolled raltegravir-unexposed neonates resulted in lowering of the first dose to 2 mg/kg for subsequent enrolled Cohort I neonates and the 2nd dose remained unchanged.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Raltegravir Exposed

Arm description:

Raltegravir granules for suspension (GFS) 3 mg/kg as a single dose within 48 hours of birth in addition to standard of care antiretroviral therapy for PMTCT prophylaxis. A second dose of raltegravir 3 mg/kg administered at 7 to 10 days of age.

Arm type	Experimental
Investigational medicinal product name	Raltegravir
Investigational medicinal product code	
Other name	MK-0518, Isentress
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Raltegravir granules for suspension (GFS) 1.5 mg/kg as a single dose within 48 hours of birth in addition to standard of care antiretroviral therapy for PMTCT prophylaxis. A second dose of raltegravir 3 mg/kg administered at 7 to 10 days of age.

Arm title	Cohort 1: Raltegravir Unexposed

Arm description:

Raltegravir granules for suspension (GFS) 3 mg/kg as a single dose within 48 hours of birth in addition to standard of care antiretroviral therapy for PMTCT prophylaxis. A second dose of raltegravir 3 mg/kg administered at 7 to 10 days of age.

Arm type	Experimental
Investigational medicinal product name	Raltegravir
Investigational medicinal product code	
Other name	MK-0518, Isentress
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Raltegravir granules for suspension (GFS) 2 or 3 mg/kg as a single dose within 48 hours of birth in addition to standard of care antiretroviral therapy for PMTCT prophylaxis. A second dose of raltegravir 3 mg/kg administered at 7 to 10 days of age.

Arm title	Cohort 2: Raltegravir Unexposed

Arm description:

Raltegravir GFS in addition to standard of care antiretroviral therapy for PMTCT prophylaxis. Participants received Raltegravir 1.5 mg/kg once daily during Days 1 to 7 of age (Week 1), Raltegravir 3 mg/kg twice daily (BID) during Days 8 to 28 of age (Weeks 2 to 4) and Raltegravir 6 mg/kg twice daily during Days 29 to 42 of age (Weeks 5 and 6)

Arm type	Experimental
Investigational medicinal product name	Raltegravir
Investigational medicinal product code	
Other name	MK-0518, Isentress
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Raltegravir 1.5 mg/kg once daily during Days 1 to 7 of age (Week 1), Raltegravir 3 mg/kg twice daily during Days 8 to 28 of age (Weeks 2 to 4) and Raltegravir 6 mg/kg twice daily during Days 29 to 42 of age (Weeks 5 and 6). All doses administered in addition to standard of care antiretroviral therapy for PMTCT prophylaxis.

Number of subjects in period 1	Cohort 1: Raltegravir Exposed	Cohort 1: Raltegravir Unexposed	Cohort 2: Raltegravir Unexposed
Started	6	10	26
Completed Study Treatment	6	10	23
Completed	6	10	22
Not completed	0	0	4
Consent withdrawn by subject	-	-	4

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Raltegravir Exposed
Reporting group description:	
Raltegravir granules for suspension (GFS) 3 mg/kg as a single dose within 48 hours of birth in addition to standard of care antiretroviral therapy for PMTCT prophylaxis. A second dose of raltegravir 3 mg/kg administered at 7 to 10 days of age.	
Reporting group title	Cohort 1: Raltegravir Unexposed
Reporting group description:	
Raltegravir granules for suspension (GFS) 3 mg/kg as a single dose within 48 hours of birth in addition to standard of care antiretroviral therapy for PMTCT prophylaxis. A second dose of raltegravir 3 mg/kg administered at 7 to 10 days of age.	
Reporting group title	Cohort 2: Raltegravir Unexposed
Reporting group description:	
Raltegravir GFS in addition to standard of care antiretroviral therapy for PMTCT prophylaxis. Participants received Raltegravir 1.5 mg/kg once daily during Days 1 to 7 of age (Week 1), Raltegravir 3 mg/kg twice daily (BID) during Days 8 to 28 of age (Weeks 2 to 4) and Raltegravir 6 mg/kg twice daily during Days 29 to 42 of age (Weeks 5 and 6)	

Reporting group values	Cohort 1: Raltegravir Exposed	Cohort 1: Raltegravir Unexposed	Cohort 2: Raltegravir Unexposed
Number of subjects	6	10	26
Age Categorical Units: Subjects			
Age Continuous			
Age reported is the age of the first dose was administered.			
Units: days			
arithmetic mean	1.7	0.8	1.5
standard deviation	± 0.5	± 0.6	± 0.6
Gender Categorical Units: Subjects			
Female	2	6	12
Male	4	4	14

Reporting group values	Total		
Number of subjects	42		
Age Categorical Units: Subjects			
Age Continuous			
Age reported is the age of the first dose was administered.			
Units: days			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	20		
Male	22		

End points

End points reporting groups

Reporting group title	Cohort 1: Raltegravir Exposed

Reporting group description:

Raltegravir granules for suspension (GFS) 3 mg/kg as a single dose within 48 hours of birth in addition to standard of care antiretroviral therapy for PMTCT prophylaxis. A second dose of raltegravir 3 mg/kg administered at 7 to 10 days of age.

Reporting group title	Cohort 1: Raltegravir Unexposed

Reporting group description:

Raltegravir granules for suspension (GFS) 3 mg/kg as a single dose within 48 hours of birth in addition to standard of care antiretroviral therapy for PMTCT prophylaxis. A second dose of raltegravir 3 mg/kg administered at 7 to 10 days of age.

Reporting group title	Cohort 2: Raltegravir Unexposed

Reporting group description:

Raltegravir GFS in addition to standard of care antiretroviral therapy for PMTCT prophylaxis. Participants received Raltegravir 1.5 mg/kg once daily during Days 1 to 7 of age (Week 1), Raltegravir 3 mg/kg twice daily (BID) during Days 8 to 28 of age (Weeks 2 to 4) and Raltegravir 6 mg/kg twice daily during Days 29 to 42 of age (Weeks 5 and 6)

Subject analysis set title	Cohort 1: Raltegravir Exposed - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants previously exposed to Raltegravir who received 1.5 mg/kg of Raltegravir in Cohort 1. A second dose of Raltegravir 3 mg/kg administered at 7 to 10 days of age. Study drug administered in addition to standard of care antiretroviral therapy for PMTCT prophylaxis.

Subject analysis set title	Cohort 1: Raltegravir Unexposed - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants not previously exposed to Raltegravir who received either 2.0 or 3.0 mg/kg of Raltegravir in Cohort 1. A second dose of Raltegravir 3 mg/kg administered at 7 to 10 days of age. Study drug administered in addition to standard of care antiretroviral therapy for PMTCT prophylaxis.

Subject analysis set title	Cohort 2: Raltegravir Unexposed - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Participant not previously exposed to Raltegravir who received Raltegravir 1.5 mg/kg once daily during Days 1 to 7 of age (Week 1), Raltegravir 3 mg/kg twice daily during Days 8 to 28 of age (Weeks 2 to 4) and Raltegravir 6 mg/kg twice daily during Days 29 to 42 of age (Weeks 5 and 6). Study drug administered in addition to standard of care antiretroviral therapy for PMTCT prophylaxis.

Subject analysis set title	Cohort 1: Raltegravir Unexposed - 2 mg/kg - PK
Subject analysis set type	Per protocol

Subject analysis set description:

Participants not previously exposed to Raltegravir who received 2.0 mg/kg of Raltegravir in Cohort 1. Study drug administered in addition to standard of care antiretroviral therapy for PMTCT prophylaxis.

Subject analysis set title	Cohort 1: Raltegravir Unexposed - 3 mg/kg - PK
Subject analysis set type	Per protocol

Subject analysis set description:

Participants not previously exposed to Raltegravir who received 3.0 mg/kg of Raltegravir in Cohort 1. Study drug administered in addition to standard of care antiretroviral therapy for PMTCT prophylaxis.

Subject analysis set title	Cohort 2: Raltegravir Unexposed - PK
Subject analysis set type	Per protocol

Subject analysis set description:

Participants not previously exposed to Raltegravir who received Raltegravir 1.5 mg/kg once daily during Days 1 to 7 of age (Week 1), Raltegravir 3 mg/kg twice daily during Days 8 to 28 of age (Weeks 2 to 4) and Raltegravir 6 mg/kg twice daily during Days 29 to 42 of age (Weeks 5 and 6). Study drug administered in addition to standard of care antiretroviral therapy for PMTCT prophylaxis.

Subject analysis set title	Cohort 1: Raltegravir - Exposed- 1.5 mg/kg - PK

Subject analysis set type	Per protocol

Subject analysis set description:

Participants previously exposed to Raltegravir who received 1.5 mg/kg of Raltegravir in Cohort 1. Study drug administered in addition to standard of care antiretroviral therapy for PMTCT prophylaxis.

Primary: Percentage of Participants Who Experience 1 or More Grade 3 or 4 Adverse Event: Week 6 - Cohorts 1 and 2

End point title	Percentage of Participants Who Experience 1 or More Grade 3 or 4 Adverse Event: Week 6 - Cohorts 1 and 2[1]

End point description:

An adverse event (AE) was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study drug, whether or not considered related to the use of the product. Adverse events were graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table). Participants that experienced AEs that were reported as either Grade 3 or 4 in intensity were summarized.

End point type	Primary

End point timeframe:

up to Week 6 of Cohort 1 and Cohort 2

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: No statistical analysis was planned for the endpoint

End point values	Cohort 1: Raltegravir Exposed - Safety	Cohort 1: Raltegravir Unexposed - Safety	Cohort 2: Raltegravir Unexposed - Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	10	26	
Units: Percentage of Participants				
number (not applicable)	33.3	20	23.1	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Experience a Suspected Adverse Drug Reaction (ADR) of Grade 3 or 4: Week 6 - Cohorts 1 and 2

End point title	Percentage of Participants Who Experience a Suspected Adverse Drug Reaction (ADR) of Grade 3 or 4: Week 6 - Cohorts 1 and 2[2]

End point description:

An AE was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study drug, whether or not considered related to the use of the product. Adverse events were graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table). Suspected Adverse Drug Reaction (ADR) was an AE that was an AE that was reported as possibly, probably or definitely related to the study drug. Participants that experienced suspected ADR that were reported as either Grade 3 or 4 in intensity were summarized.

End point type	Primary

End point timeframe:

up to Week 6 of Cohort 1 and Cohort 2

Notes:

[2] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 1: Raltegravir Exposed - Safety	Cohort 1: Raltegravir Unexposed - Safety	Cohort 2: Raltegravir Unexposed - Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	10	26	
Units: Percentage of Participants				
number (not applicable)	0	10	0	

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Terminal Half-life (t1/2) of Raltegravir – Single Dose: Cohort 1

End point title	Apparent Terminal Half-life (t1/2) of Raltegravir – Single Dose: Cohort 1[3]

End point description:

Blood samples taken at Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours postdose, and 24 (±1) hours post-dose on day of 1st dose to determine the t1/2 of Raltegravir. One participant who received 3 mg/kg was excluded from pharmacokinetic analyses. Another participant was scheduled to receive 2 mg/kg but was administered a 3 mg/kg dose in error and thus is included in the 3 mg/kg arm.

End point type	Primary

End point timeframe:

Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours post-dose, and 24 (±1) hours postdose on day of 1st dose, which was to administered within 48 hours after birth

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: No statistical analysis was planned for the endpoint

End point values	Cohort 1: Raltegravir Unexposed - 2 mg/kg - PK	Cohort 1: Raltegravir Unexposed - 3 mg/kg - PK	Cohort 1: Raltegravir - Exposed- 1.5 mg/kg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	6	
Units: hours				
geometric mean (geometric coefficient of variation)	17.15 (± 63.92)	11.82 (± 25.5)	12.6 (± 39.86)	

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Concentration (Cmax) of Raltegravir – Single Dose: Cohort 1

End point title	Maximum Concentration (Cmax) of Raltegravir – Single Dose: Cohort 1[4]

End point description:

Blood samples taken at Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours postdose, and 24 (±1) hours postdose on day of 1st dose to determine the Cmax of Raltegravir. One participant who received 3 mg/kg was excluded from pharmacokinetic analyses. Another participant was scheduled to receive 2 mg/kg but was administered a 3 mg/kg dose in error and thus is included in the 3 mg/kg arm.

End point type	Primary

End point timeframe:

Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours post-dose, and 24 (±1) hours postdose on day of 1st dose which was to administered within 48 hours after birth

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for the endpoint

End point values	Cohort 1: Raltegravir Unexposed - 2 mg/kg - PK	Cohort 1: Raltegravir Unexposed - 3 mg/kg - PK	Cohort 1: Raltegravir - Exposed- 1.5 mg/kg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	6	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	3405.24 (± 32.41)	3360.89 (± 33.33)	2188.82 (± 49.5)	

Statistical analyses

No statistical analyses for this end point

Primary: Time to Maximum Concentration (Tmax) of Raltegravir – Single Dose: Cohort 1

End point title	Time to Maximum Concentration (Tmax) of Raltegravir – Single Dose: Cohort 1[5]

End point description:

Blood samples taken at Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours postdose, and 24 (±1) hours postdose on day of 1st dose to determine the Tmax of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant who received 3 mg/kg was excluded from pharmacokinetic analyses. Another participant was scheduled to receive 2 mg/kg but was administered a 3 mg/kg dose in error and thus is included in the 3 mg/kg arm.

End point type	Primary

End point timeframe:

Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours post-dose, and 24 (±1) hours postdose on day of 1st dose which was to administered within 48 hours after birth

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for the endpoint

End point values	Cohort 1: Raltegravir Unexposed - 2 mg/kg - PK	Cohort 1: Raltegravir Unexposed - 3 mg/kg - PK	Cohort 1: Raltegravir - Exposed- 1.5 mg/kg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	6	
Units: hours				
geometric mean (geometric coefficient of variation)	4.42 (± 4.44)	6.51 (± 93.89)	5.23 (± 69.87)	

Statistical analyses

No statistical analyses for this end point

Primary: Last Observed Quantifiable Concentration (Clast) of Raltegravir – Single Dose: Cohort 1

End point title	Last Observed Quantifiable Concentration (Clast) of Raltegravir – Single Dose: Cohort 1[6]

End point description:

Blood samples taken at Predose, 1 to 2 hours post-dose, 4 to 8 hours postdose, 12 (±1) hours postdose, and 24 (±1) hours postdose on day of 1st dose to determine the Clast of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant who received 3 mg/kg was excluded from pharmacokinetic analyses. Another participant was scheduled to receive 2 mg/kg but was administered a 3 mg/kg dose in error and thus is included in the 3 mg/kg arm.

End point type	Primary

End point timeframe:

Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours post-dose, and 24 (±1) hours postdose on day of 1st dose which was to administered within 48 hours after birth

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: No statistical analysis was planned for the endpoint

End point values	Cohort 1: Raltegravir Unexposed - 2 mg/kg - PK	Cohort 1: Raltegravir Unexposed - 3 mg/kg - PK	Cohort 1: Raltegravir - Exposed- 1.5 mg/kg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	6	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	704.49 (± 92.25)	66.81 (± 122.64)	201.6 (± 98.6)	

Statistical analyses

No statistical analyses for this end point

Primary: Time to Last Observed Quantifiable Concentration (Tlast) of Raltegravir – Single Dose: Cohort 1

End point title	Time to Last Observed Quantifiable Concentration (Tlast) of Raltegravir – Single Dose: Cohort 1[7]

End point description:

Blood samples taken at Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours postdose, and 24 (±1) hours postdose on day of 1st dose to determine the Tlast of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant who received 3 mg/kg was excluded from pharmacokinetic analyses. Another participant was scheduled to receive 2 mg/kg but was administered a 3 mg/kg dose in error and thus is included in the 3 mg/kg arm.

End point type	Primary

End point timeframe:

Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours post-dose, and 24 (±1) hours postdose on day of 1st dose which was to administered within 48 hours after birth

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for the endpoint

End point values	Cohort 1: Raltegravir Unexposed - 2 mg/kg - PK	Cohort 1: Raltegravir Unexposed - 3 mg/kg - PK	Cohort 1: Raltegravir - Exposed- 1.5 mg/kg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	6	
Units: hours				
geometric mean (geometric coefficient of variation)	28.56 (± 0.66)	74.79 (± 40.93)	45.87 (± 37.37)	

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Volume of Distribution During the Terminal Phase (V/F) of Raltegravir – Single Dose: Cohort 1

End point title	Apparent Volume of Distribution During the Terminal Phase (V/F) of Raltegravir – Single Dose: Cohort 1[8]

End point description:

Blood samples taken at Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours postdose, and 24 (±1) hours postdose on day of 1st dose to determine the V/F of Raltegravir in the neonates not exposed to Raltegravir in-utero. V/F is a measure of the amount of the Raltegravir enters circulation. One participant who received 3 mg/kg was excluded from pharmacokinetic analyses. Another participant was scheduled to receive 2 mg/kg but was administered a 3 mg/kg dose in error and thus is included in the 3 mg/kg arm.

End point type	Primary

End point timeframe:

Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours post-dose, and 24 (±1) hours postdose on day of 1st dose which was to administered within 48 hours after birth

Notes:

[8] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 1: Raltegravir Unexposed - 2 mg/kg - PK	Cohort 1: Raltegravir Unexposed - 3 mg/kg - PK	Cohort 1: Raltegravir - Exposed- 1.5 mg/kg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	6	
Units: Liters (L)				
geometric mean (geometric coefficient of variation)	2 (± 57.51)	1.72 (± 37.08)	1.37 (± 83.2)	

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Clearance Following Dosing (CL/F) of Raltegravir – Single Dose: Cohort 1

End point title	Apparent Clearance Following Dosing (CL/F) of Raltegravir – Single Dose: Cohort 1[9]

End point description:

Blood samples taken at Predose, 1 to 2 hours post-dose, 4 to 8 hours postdose, 12 (±1) hours postdose, and 24 (±1) hours postdose on day of 1st dose to determine the Cl/F of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant who received 3 mg/kg was excluded from pharmacokinetic analyses. Another participant was scheduled to receive 2 mg/kg but was administered a 3 mg/kg dose in error and thus is included in the 3 mg/kg arm.

End point type	Primary

End point timeframe:

Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours post-dose, and 24 (±1) hours postdose on day of 1st dose which was to administered within 48 hours after birth

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: No statistical analysis was planned for the endpoint

End point values	Cohort 1: Raltegravir Unexposed - 2 mg/kg - PK	Cohort 1: Raltegravir Unexposed - 3 mg/kg - PK	Cohort 1: Raltegravir - Exposed- 1.5 mg/kg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	6	
Units: Liters/hour				
geometric mean (geometric coefficient of variation)	0.08 (± 98.28)	0.1 (± 28.88)	0.08 (± 139.57)	

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration-time Curve From 0 to 12 Hours (AUC12) of Raltegravir – Single Dose: Cohort 1

End point title	Area Under the Concentration-time Curve From 0 to 12 Hours (AUC12) of Raltegravir – Single Dose: Cohort 1[10]

End point description:

Blood samples taken at Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, and 12 (±1) hours postdose on day of 1st dose to determine the AUC12 of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant who received 3 mg/kg was excluded from pharmacokinetic analyses. Another participant was scheduled to receive 2 mg/kg but was administered a 3 mg/kg dose in error and thus is included in the 3 mg/kg arm.

End point type	Primary

End point timeframe:

Pre-dose, 1 to 2 hours post-dose, 4 to 8 hours postdose, and 12 (±1) hours postdose on day of 1st dose which was to administered within 48 hours after birth

Notes:

[10] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 1: Raltegravir Unexposed - 2 mg/kg - PK	Cohort 1: Raltegravir Unexposed - 3 mg/kg - PK	Cohort 1: Raltegravir - Exposed- 1.5 mg/kg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	6	
Units: hr*mg/L				
geometric mean (geometric coefficient of variation)	28.11 (± 44.2)	29.48 (± 34.98)	20.33 (± 53.06)	

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration-time Curve From 0 to 24 Hours (AUC24) of Raltegravir – Single Dose: Cohort 1

End point title	Area Under the Concentration-time Curve From 0 to 24 Hours (AUC24) of Raltegravir – Single Dose: Cohort 1[11]

End point description:

Blood samples taken at Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours postdose, and 24 (±1) hours postdose on day of 1st dose to determine the AUC24 of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant who received 3 mg/kg was excluded from pharmacokinetic analyses. Another participant was scheduled to receive 2 mg/kg but was administered a 3 mg/kg dose in error and thus is included in the 3 mg/kg arm.

End point type	Primary

End point timeframe:

Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours post-dose, and 24 (±1) hours postdose on day of 1st dose which was to administered within 48 hours after birth

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: No statistical analysis was planned for the endpoint

End point values	Cohort 1: Raltegravir Unexposed - 2 mg/kg - PK	Cohort 1: Raltegravir Unexposed - 3 mg/kg - PK	Cohort 1: Raltegravir - Exposed- 1.5 mg/kg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	6	
Units: hr*mg/L				

geometric mean (geometric coefficient of variation)	44.26 (± 59.17)	53.88 (± 30.96)	37.42 (± 54.63)	

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration-time Curve From 0 to infinity (AUCinf) of Raltegravir – Single Dose: Cohort 1

End point title	Area Under the Concentration-time Curve From 0 to infinity (AUCinf) of Raltegravir – Single Dose: Cohort 1[12]

End point description:

Blood samples taken at Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours postdose, and 24 (±1) hours postdose on day of 1st dose to determine the AUCinf of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant who received 3 mg/kg was excluded from pharmacokinetic analyses. Another participant was scheduled to receive 2 mg/kg but was administered a 3 mg/kg dose in error and thus is included in the 3 mg/kg arm.

End point type	Primary

End point timeframe:

Predose, 1 to 2 hours postdose, 4 to 8 hours postdose, 12 (±1) hours post-dose, and 24 (±1) hours postdose on day of 1st dose which was to administered within 48 hours after birth

Notes:

[12] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 1: Raltegravir Unexposed - 2 mg/kg - PK	Cohort 1: Raltegravir Unexposed - 3 mg/kg - PK	Cohort 1: Raltegravir - Exposed- 1.5 mg/kg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	6	
Units: hr*mg/L				
geometric mean (geometric coefficient of variation)	78.26 (± 73.98)	98.67 (± 33.45)	62.5 (± 62.74)	

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Terminal Half-life (t1/2) of Raltegravir - 1.5 mg/kg Once Daily (QD): Cohort 2

End point title	Apparent Terminal Half-life (t1/2) of Raltegravir - 1.5 mg/kg Once Daily (QD): Cohort 2[13]

End point description:

Blood samples taken within 1 hour pre-dose, and at 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post 1st dose to determine the t1/2 of Raltegravir in the neonates not exposed to Raltegravir in-utero.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose. Dose administered

within 48 hours after birth.

Notes:

[13] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Hours				
geometric mean (geometric coefficient of variation)	15.79 (± 174.79)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Concentration (Cmax) of Raltegravir – 1.5 mg/kg QD: Cohort 2

End point title	Maximum Concentration (Cmax) of Raltegravir – 1.5 mg/kg QD: Cohort 2[14]

End point description:

Blood samples taken within1 hour pre-dose, and at 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-post-dose on day
of 1st dose to determine the Cmax of Raltegravir in the neonates not exposed to Raltegravir in-utero.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose. Dose administered within 48 hours after birth.

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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	2349.91 (± 35.02)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Maximum Concentration (Tmax) of Raltegravir – 1.5 mg/kg QD:

Cohort 2

End point title	Time to Maximum Concentration (Tmax) of Raltegravir – 1.5 mg/kg QD: Cohort 2[15]

End point description:

Blood samples taken within 1 hour pre-dose and at 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose post-dose on day of 1st dose to determine the Tmax of Raltegravir in the neonates not exposed to Raltegravir in-utero.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose. Dose administered within 48 hours after birth.

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: Hours				
geometric mean (geometric coefficient of variation)	5.37 (± 57.49)			

Statistical analyses

No statistical analyses for this end point

Primary: Last Observed Quantifiable Concentration (Clast) of Raltegravir – 1.5 mg/kg QD: Cohort 2

End point title	Last Observed Quantifiable Concentration (Clast) of Raltegravir – 1.5 mg/kg QD: Cohort 2[16]

End point description:

Blood samples taken within 1 hour pre-dose and at 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose, and 24 (±1) hours post-dose on day of 1st dose to determine the Clast of Raltegravir in the neonates not exposed to Raltegravir in-utero.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose. Dose administered within 48 hours after birth.

Notes:

[16] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: ng/mL				

geometric mean (geometric coefficient of variation)	947.9 (± 64.23)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Time-concentration Curve for All Values (AUCall) - 1.5 mg/kg QD: Cohort 2

End point title	Area Under the Time-concentration Curve for All Values (AUCall) - 1.5 mg/kg QD: Cohort 2[17]

End point description:

Blood samples taken within 1 hour pre-dose and at 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose on day of 1st dose to determine the AUCall of Raltegravir in the neonates not exposed to Raltegravir in-utero.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose. Dose administered within 48 hours after birth.

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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: hr*mg/L				
geometric mean (geometric coefficient of variation)	36.74 (± 36.16)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Volume of Distribution During the Terminal Phase (V/F) of Raltegravir- 1.5 mg/kg QD: Cohort 2

End point title	Apparent Volume of Distribution During the Terminal Phase (V/F) of Raltegravir- 1.5 mg/kg QD: Cohort 2[18]

End point description:

Blood samples taken within 1 hour pre-dose and at 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post 1st dose to determine the V/F of Raltegravir in the neonates not exposed to Raltegravir in-utero.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose. Dose administered within 48 hours after birth.

Notes:

[18] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Liters (L)				
geometric mean (geometric coefficient of variation)	1.63 (± 41.22)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Clearance Following Dosing (CL/F) of Raltegravir – 1.5 mg/kg QD: Cohort 2

End point title	Apparent Clearance Following Dosing (CL/F) of Raltegravir – 1.5 mg/kg QD: Cohort 2[19]

End point description:

Blood samples taken within 1 hour pre-dose and at 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose on day of 1st dose to determine the Cl/F of Raltegravir in the neonates not exposed to Raltegravir in-utero.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose. Dose administered within 48 hours after birth.

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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Liters/hour				
geometric mean (geometric coefficient of variation)	0.07 (± 62.39)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration-time Curve From 0 to 24 Hours (AUC24) of

Raltegravir – 1.5 mg/kg QD: Cohort 2

End point title	Area Under the Concentration-time Curve From 0 to 24 Hours (AUC24) of Raltegravir – 1.5 mg/kg QD: Cohort 2[20]

End point description:

Blood samples taken within 1 hour pre-dose and at 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose on day of 1st dose to determine the AUC24 of Raltegravir in the neonates not exposed to Raltegravir in-utero.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1 to 2 hours, 6 to 10 hours, 20 to 24 hours post-dose. Dose administered within 48 hours after birth.

Notes:

[20] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: hr*mg/L				
geometric mean (geometric coefficient of variation)	38.2 (± 38.35)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Terminal Half-life (t1/2) of Raltegravir – 3 mg/kg Twice Daily (BID): Cohort 2

End point title	Apparent Terminal Half-life (t1/2) of Raltegravir – 3 mg/kg Twice Daily (BID): Cohort 2[21]

End point description:

Blood samples taken Within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth) to determine the t1/2 of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant's mother withdrew consent after 1.5 mg QD dosing thus no 3 mg/kg BID PK analyses were performed. Another participant could not have all PK parameters calculated due to issues related to drug concentration increasing.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth)

Notes:

[21] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Hours				
geometric mean (geometric coefficient of variation)	2.45 (± 33.49)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Concentration (Cmax) of Raltegravir – 3 mg/kg BID: Cohort 2

End point title	Maximum Concentration (Cmax) of Raltegravir – 3 mg/kg BID: Cohort 2[22]

End point description:

Blood samples taken within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth) to determine the Cmax of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant's mother withdrew consent after 1.5 mg QD dosing thus no 3 mg/kg BID PK analyses were performed.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth)

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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	2849.48 (± 41.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Maximum Concentration (Tmax) of Raltegravir – 3 mg/kg BID: Cohort 2

End point title	Time to Maximum Concentration (Tmax) of Raltegravir – 3 mg/kg BID: Cohort 2[23]

End point description:

Blood samples taken within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth) to determine the Tmax of Raltegravir in the neonates

not exposed to Raltegravir in-utero. One participant's mother withdrew consent after 1.5 mg QD dosing thus no 3 mg/kg BID PK analyses were performed.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth)

Notes:

[23] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Hours				
geometric mean (geometric coefficient of variation)	2.34 (± 67.12)			

Statistical analyses

No statistical analyses for this end point

Primary: Last Observed Quantifiable Concentration (Clast) of Raltegravir – 3 mg/kg BID: Cohort 2

End point title	Last Observed Quantifiable Concentration (Clast) of Raltegravir – 3 mg/kg BID: Cohort 2[24]

End point description:

Blood samples taken within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth) to determine the Clast of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant's mother withdrew consent after 1.5 mg QD dosing thus no 3 mg/kg BID PK analyses were performed.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth)

Notes:

[24] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	557.99 (± 83.74)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Last Observed Quantifiable Concentration (Tlast) of Raltegravir – 3 mg/kg BID: Cohort 2

End point title	Time to Last Observed Quantifiable Concentration (Tlast) of Raltegravir – 3 mg/kg BID: Cohort 2[25]

End point description:

Blood samples taken within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth) to determine the Tlast of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant's mother withdrew consent after 1.5 mg QD dosing thus no 3 mg/kg BID PK analyses were performed.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth)

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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Hours				
geometric mean (geometric coefficient of variation)	8.42 (± 7.34)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Time-concentration Curve for All Values (AUCall) of Raltegravir - 3 mg/kg BID: Cohort 2

End point title	Area Under the Time-concentration Curve for All Values (AUCall) of Raltegravir - 3 mg/kg BID: Cohort 2[26]

End point description:

Blood samples taken within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth) to determine the AUCall of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant's mother withdrew consent after 1.5 mg QD dosing thus no 3 mg/kg BID PK analyses were performed.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth)

Notes:

[26] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: hr*mg/L				
geometric mean (geometric coefficient of variation)	13.23 (± 42.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Volume of Distribution During the Terminal Phase (V/F) of Raltegravir - 3 mg/kg BID: Cohort 2

End point title	Apparent Volume of Distribution During the Terminal Phase (V/F) of Raltegravir - 3 mg/kg BID: Cohort 2[27]

End point description:

Blood samples taken within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth) to determine the V/F of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant's mother withdrew consent after 1.5 mg QD dosing thus no 3 mg/kg BID PK analyses were performed. Another participant could not have all PK parameters calculated due to issues related to drug concentration increasing.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth)

Notes:

[27] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Liters				
geometric mean (geometric coefficient of variation)	2.32 (± 64.02)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Clearance Following Dosing (CL/F) of Raltegravir - 3 mg/kg BID: Cohort 2

End point title	Apparent Clearance Following Dosing (CL/F) of Raltegravir - 3 mg/kg BID: Cohort 2[28]

End point description:

Blood samples taken within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth) to determine the CL/F of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant's mother withdrew consent after 1.5 mg QD dosing thus no 3 mg/kg BID PK analyses were performed. Another participant could not have all PK parameters calculated due to issues related to drug concentration increasing.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth)

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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Liters/hour				
geometric mean (geometric coefficient of variation)	0.66 (± 54.98)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration-time Curve From 0 to 12 Hours (AUC12) of Raltegravir - 3 mg/kg BID: Cohort 2

End point title	Area Under the Concentration-time Curve From 0 to 12 Hours (AUC12) of Raltegravir - 3 mg/kg BID: Cohort 2[29]

End point description:

Blood samples taken within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth) to determine the AUC12 of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant's mother withdrew consent after 1.5 mg QD dosing thus no 3 mg/kg BID PK analyses were performed. Another participant could not have all PK parameters calculated due to issues related to drug concentration increasing.

End point type	Primary

End point timeframe:

Within 1 hour pre-dose, and 1-2 hours post-dose, 4-6 hours post-dose, and 8-12 hours post-dose on Day 15 (Day 15-18 after birth)

Notes:

[29] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: hr*mg/L				
geometric mean (geometric coefficient of variation)	14.3 (± 43.25)			

Statistical analyses

No statistical analyses for this end point

Primary: Concentration of Raltegravir at Hour 12 (C12) – 3 mg/kg BID: Cohort 2

End point title	Concentration of Raltegravir at Hour 12 (C12) – 3 mg/kg BID: Cohort 2[30]

End point description:

Blood samples 8-12 hours post-dose on Day 15 (Day 15-18 after birth) to estimate the C12 of Raltegravir in the neonates not exposed to Raltegravir in-utero. One participant's mother withdrew consent after 1.5 mg QD dosing thus no 3 mg/kg BID PK analyses were performed. Another participant could not have all PK parameters calculated due to issues related to drug concentration increasing.

End point type	Primary

End point timeframe:

12 hours post-dose on Day 15 (Day 15-18 after birth)

Notes:

[30] - 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: No statistical analysis was planned for the endpoint

End point values	Cohort 2: Raltegravir Unexposed - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	176.11 (± 93.75)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to 28 weeks for both Cohort 1 and Cohort 2	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Cohort 1 RAL Unexposed
Reporting group description: Participants not previously exposed to Raltegravir who received either 2.0 or 3.0 mg/kg of Raltegravir in Cohort 1. A second dose of Raltegravir 3 mg/kg administered at 7 to 10 days of age. Study drug administered in addition to standard of care antiretroviral therapy for PMTCT prophylaxis.	
Reporting group title	Cohort 1 RAL Exposed
Reporting group description: Participants previously exposed to Raltegravir who received 1.5 mg/kg of Raltegravir in Cohort 1. A second dose of Raltegravir 3 mg/kg administered at 7 to 10 days of age. Study drug administered in addition to standard of care antiretroviral therapy for PMTCT prophylaxis.	
Reporting group title	Cohort 2 RAL Unexposed
Reporting group description: Participant not previously exposed to Raltegravir who received Raltegravir 1.5 mg/kg once daily during Days 1 to 7 of age (Week 1), Raltegravir 3 mg/kg twice daily during Days 8 to 28 of age (Weeks 2 to 4) and Raltegravir 6 mg/kg twice daily during Days 29 to 42 of age (Weeks 5 and 6). Study drug administered in addition to standard of care antiretroviral therapy for PMTCT prophylaxis.	

Serious adverse events	Cohort 1 RAL Unexposed	Cohort 1 RAL Exposed	Cohort 2 RAL Unexposed
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	7 / 26 (26.92%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood glucose decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Craniocerebral injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital syphilis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia neonatal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 26 (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
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (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
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 26 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort 1 RAL Unexposed	Cohort 1 RAL Exposed	Cohort 2 RAL Unexposed
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	6 / 6 (100.00%)	24 / 26 (92.31%)
Vascular disorders			
Hypertension neonatal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Pallor			
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	2 / 26 (7.69%)
occurrences (all)	0	4	4
Pregnancy, puerperium and perinatal conditions			
Jaundice neonatal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	4 / 26 (15.38%)
occurrences (all)	0	0	4
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Mucosal discolouration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	7 / 26 (26.92%)
occurrences (all)	1	0	9
Vessel puncture site bruise			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Acquired hydrocele			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Breast induration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Penile erythema			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	8 / 26 (30.77%)
occurrences (all)	2	1	10
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	4
Nasal congestion			
subjects affected / exposed	4 / 10 (40.00%)	0 / 6 (0.00%)	5 / 26 (19.23%)
occurrences (all)	6	0	7
Rales			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	2	0	1
Sneezing			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Snoring			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Blood bilirubin increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	5 / 26 (19.23%)
occurrences (all)	1	1	6
Blood calcium increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	2
Blood creatinine increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	5 / 26 (19.23%)
occurrences (all)	1	0	6
Blood glucose decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Blood potassium increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	3
Blood pressure increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Blood sodium decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Cardiac murmur			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	4 / 10 (40.00%)	5 / 6 (83.33%)	19 / 26 (73.08%)
occurrences (all)	7	11	60
Neutrophil count decreased			
subjects affected / exposed	6 / 10 (60.00%)	4 / 6 (66.67%)	7 / 26 (26.92%)
occurrences (all)	12	5	15
Injury, poisoning and procedural complications			
Scar			

subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Congenital megaureter			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Congenital renal cyst			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Congenital umbilical hernia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	0	3
Craniosynostosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Laryngomalacia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Pulmonary artery stenosis congenital			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Talipes			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Nervous system disorders			
Hypertonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			

Anaemia neonatal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 26 (3.85%)
occurrences (all)	0	4	2
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Eye discharge			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Infantile colic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	2
Infantile vomiting			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Oral mucosal discolouration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Umbilical hernia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Vomiting			

subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	3 / 26 (11.54%)
occurrences (all)	1	1	4
Hepatobiliary disorders			
Hyperbilirubinaemia neonatal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Jaundice			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Dermatitis allergic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Dermatitis atopic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Dermatitis bullous			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Dermatitis diaper			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Eczema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Milia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Neurodermatitis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Papule			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	3 / 26 (11.54%)
occurrences (all)	1	0	3
Scab			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Seborrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	4 / 26 (15.38%)
occurrences (all)	0	0	6
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Body tinea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Bronchiolitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Folliculitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Genital candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2

Impetigo			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	8 / 26 (30.77%)
occurrences (all)	0	1	9
Otitis media acute			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Pneumonia bacterial			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	2
Skin candida			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	5 / 26 (19.23%)
occurrences (all)	0	0	8
Varicella			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	2
Failure to thrive			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Malnutrition			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2014	Amendment 1: Primary reason for amendment was to change the initial dose regimen for Raltegravir-exposed neonates in Cohort 1 to single dose of 1.5 mg/kg. Second dose regimen was not changed.
09 July 2015	Amendment 2: Primary reason for the amendment was to define the 3 doses of MK-0518 for Raltegravir-unexposed neonates in Cohort 2.
26 May 2016	Amendment 3: Primary reason for the amendment was to change inclusion criterion regarding multi-class resistant virus to permit inclusion of mothers with at least one class of resistant HIV.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported