



## 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	20 April 2018

#### Results information

Result version number	v2 (current)
This version publication date	15 October 2020
First version publication date	25 August 2017
Version creation reason	

#### Trial information

##### Trial identification

Sponsor protocol code	0518-080
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##### 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)	EMA-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	Final
Date of interim/final analysis	20 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2017
Global end of trial reached?	Yes
Global end of trial date	20 April 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the safety and pharmacokinetics (PK) of raltegravir (RAL) when given to HIV-1-exposed, normal birth weight newborn infants at risk of acquiring HIV-1 infection. (PK is the study of the time course of absorption, distribution, metabolism, and excretion of drugs in the body.) The primary goal of this study was to determine a dose of RAL that was safe and met the PK targets for infants when administered during the first 6 weeks of life in addition to standard of care antiretroviral (ARV) agents for prevention of perinatal transmission.

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 may have access to raltegravir through Merck Pediatric Compassionate Use program.

Background therapy:

All enrolled neonates also received standard of care antiretroviral (ARV) for prevention of mother-to-child transmission (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	28 January 2014
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: 25
Country: Number of subjects enrolled	South Africa: 5
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Thailand: 4
Worldwide total number of subjects	52
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)	52
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: -

### Pre-assignment

Screening details:

Cohort 1 participants were from 2 sites in Brazil, 1 site in South Africa, and 7 sites in the USA.

Enrollment period was January 2014 - December 2015. Cohort 2 participants were from 3 sites in Brazil, 2 sites in South Africa, 1 site in Thailand, and 4 sites in the USA. Enrollment period was September 2015 - November 2017.

### 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
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<b>Arm title</b>	Cohort 1: Raltegravir-naïve
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Arm description:

Full term Infants not exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single doses of RAL: first dose (3 mg/kg or 2 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7-10 days of life.

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. A second dose of raltegravir 3 mg/kg administered at 7 to 10 days of age.

<b>Arm title</b>	Cohort 1: Raltegravir-exposed
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Arm description:

Full term Infants exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single doses of RAL: first dose (1.5 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7-10 days of life.

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. A second dose of raltegravir 3 mg/kg administered at 7 to 10 days of age.

<b>Arm title</b>	Cohort 2: Raltegravir-naïve
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Arm description:

Full term Infants not exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL through 6 weeks of life starting within 48 hours of birth: 1.5 mg/kg once daily during Days 1-

7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.

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).

<b>Arm title</b>	Cohort 2: Raltegravir-exposed
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Arm description:

Full term Infants exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL through 6 weeks of life starting between 12 and 60 hours of birth: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.

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).

<b>Number of subjects in period 1</b>	Cohort 1: Raltegravir-naïve	Cohort 1: Raltegravir-exposed	Cohort 2: Raltegravir-naïve
Started	10	6	26
Completed	10	6	22
Not completed	0	0	4
Consent withdrawn by parent/guardian	-	-	4
Lost to follow-up	-	-	-

<b>Number of subjects in period 1</b>	Cohort 2: Raltegravir-exposed
Started	10
Completed	9
Not completed	1
Consent withdrawn by parent/guardian	-
Lost to follow-up	1

## Baseline characteristics

### Reporting groups

Reporting group title	Cohort 1: Raltegravir-naïve
Reporting group description:	
Full term Infants not exposed in utero to maternal RAL, $\geq 2000$ grams and $\geq 37$ weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single doses of RAL: first dose (3 mg/kg or 2 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7-10 days of life.	
Reporting group title	Cohort 1: Raltegravir-exposed
Reporting group description:	
Full term Infants exposed in utero to maternal RAL, $\geq 2000$ grams and $\geq 37$ weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single doses of RAL: first dose (1.5 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7-10 days of life.	
Reporting group title	Cohort 2: Raltegravir-naïve
Reporting group description:	
Full term Infants not exposed in utero to maternal RAL, $\geq 2000$ grams and $\geq 37$ weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL through 6 weeks of life starting within 48 hours of birth: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.	
Reporting group title	Cohort 2: Raltegravir-exposed
Reporting group description:	
Full term Infants exposed in utero to maternal RAL, $\geq 2000$ grams and $\geq 37$ weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL through 6 weeks of life starting between 12 and 60 hours of birth: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.	

Reporting group values	Cohort 1: Raltegravir-naïve	Cohort 1: Raltegravir-exposed	Cohort 2: Raltegravir-naïve
Number of subjects	10	6	26
Age Categorical			
Units: Subjects			
<=18 years	10	6	26
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age Continuous			
Gestational age at birth			
Units: weeks			
median	39	38	38
full range (min-max)	38 to 40	37 to 40	37 to 41
Gender Categorical			
Units: Subjects			
Female	6	2	12
Male	4	4	14
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	3	19
Not Hispanic or Latino	7	2	7
Unknown or Not Reported	0	1	0

Birth weight			
Units: Grams			
median	3020	2948	2930
full range (min-max)	2385 to 4200	2320 to 3385	2390 to 3745
Apgar score at 1 minute			
The Apgar score is an evaluation typically done at 1 minute and 5 minutes after birth to describe an infant's health. It ranges from 0 – 10, where 10 is the best possible score. Baseline table includes Apgar Score at 1 minute after birth.			
Units: Score on a scale			
median	8	9	9
full range (min-max)	8 to 9	8 to 9	6 to 10

Reporting group values	Cohort 2: Raltegravir-exposed	Total	
Number of subjects	10	52	
Age Categorical			
Units: Subjects			
<=18 years	10	52	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Age Continuous			
Gestational age at birth			
Units: weeks			
median	39		
full range (min-max)	38 to 41	-	
Gender Categorical			
Units: Subjects			
Female	4	24	
Male	6	28	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	5	30	
Not Hispanic or Latino	4	20	
Unknown or Not Reported	1	2	
Birth weight			
Units: Grams			
median	3085		
full range (min-max)	2090 to 4130	-	
Apgar score at 1 minute			
The Apgar score is an evaluation typically done at 1 minute and 5 minutes after birth to describe an infant's health. It ranges from 0 – 10, where 10 is the best possible score. Baseline table includes Apgar Score at 1 minute after birth.			
Units: Score on a scale			
median	9		
full range (min-max)	8 to 10	-	

## End points

### End points reporting groups

Reporting group title	Cohort 1: Raltegravir-naïve
Reporting group description: Full term Infants not exposed in utero to maternal RAL, $\geq 2000$ grams and $\geq 37$ weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single doses of RAL: first dose (3 mg/kg or 2 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7-10 days of life.	
Reporting group title	Cohort 1: Raltegravir-exposed
Reporting group description: Full term Infants exposed in utero to maternal RAL, $\geq 2000$ grams and $\geq 37$ weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single doses of RAL: first dose (1.5 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7-10 days of life.	
Reporting group title	Cohort 2: Raltegravir-naïve
Reporting group description: Full term Infants not exposed in utero to maternal RAL, $\geq 2000$ grams and $\geq 37$ weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL through 6 weeks of life starting within 48 hours of birth: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.	
Reporting group title	Cohort 2: Raltegravir-exposed
Reporting group description: Full term Infants exposed in utero to maternal RAL, $\geq 2000$ grams and $\geq 37$ weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL through 6 weeks of life starting between 12 and 60 hours of birth: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.	
Subject analysis set title	Cohort 1: Raltegravir-naïve
Subject analysis set type	Safety analysis
Subject analysis set description: Full term Infants not exposed in utero to maternal RAL, $\geq 2000$ grams and $\geq 37$ weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single doses of RAL: first dose (3 mg/kg or 2 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7-10 days of life.	
Subject analysis set title	Cohort 1: Raltegravir-exposed
Subject analysis set type	Safety analysis
Subject analysis set description: Full term Infants exposed in utero to maternal RAL, $\geq 2000$ grams and $\geq 37$ weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single doses of RAL: first dose (1.5 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7-10 days of life.	
Subject analysis set title	Cohort 1 Total
Subject analysis set type	Safety analysis
Subject analysis set description: Full term Infants, $\geq 2000$ grams and $\geq 37$ weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single doses of RAL: first dose (3 mg/kg, 2 mg/kg or 1.5 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7-10 days of life.	
Subject analysis set title	Cohort 2: Raltegravir-naïve
Subject analysis set type	Safety analysis
Subject analysis set description: Full term Infants not exposed in utero to maternal RAL, $\geq 2000$ grams and $\geq 37$ weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL through 6 weeks of life starting within 48 hours of birth: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.	



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

Subject analysis set description:

Full term Infants exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL through 6 weeks of life starting between 12 and 60 hours of birth: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.

Subject analysis set title	Cohort 2 Total
Subject analysis set type	Safety analysis

Subject analysis set description:

Full term Infants,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL through 6 weeks of life starting within 48 hours of birth and between 12 to 60 hours of birth for in utero RAL-naïve and RAL-exposed infants, respectively: 1.5 mg/kg once daily during Days 1- 7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days Go to daily during Days 29-42 of life.

Subject analysis set title	Cohort 1 RAL-naïve: 3 mg/kg for First Dose
Subject analysis set type	Per protocol

Subject analysis set description:

Full term Infants not exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single RAL doses: first dose (3 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7-10 days of life.

Subject analysis set title	Cohort 1 RAL-naïve: 2 mg/kg for First Dose
Subject analysis set type	Per protocol

Subject analysis set description:

Full term Infants not exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single RAL doses: first dose (2 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7-10 days of life.

Subject analysis set title	Cohort 1 RAL-exposed 1.5 mg/kg
Subject analysis set type	Per protocol

Subject analysis set description:

Full term Infants exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single RAL doses: first dose (1.5 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7-10 days of life.

Subject analysis set title	Cohort 2 RAL-naïve: 1.5 mg/kg Once Daily on Days 1-7 of Life
Subject analysis set type	Per protocol

Subject analysis set description:

Full term Infants not exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL dosing through 6 weeks of life starting within 48 hours of birth: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.

Subject analysis set title	Cohort 2 RAL-exposed: 1.5mg/kg Once Daily on Days 1-7 of Life
Subject analysis set type	Per protocol

Subject analysis set description:

Full term Infants exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL dosing through 6 weeks of life starting within 48 hours of birth: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.

Subject analysis set title	Cohort 2 RAL-naïve: 3 mg/kg Twice Daily on Days 8-18 of Life
Subject analysis set type	Per protocol

Subject analysis set description:

Full term Infants not exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL dosing through 6 weeks of life starting within 48 hours of birth: 1.5 mg/kg once daily during

Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.

Subject analysis set title	Cohort 2 RAL-exposed: 3 mg/kg Twice Daily on Days 8-28 of Life
Subject analysis set type	Per protocol
Subject analysis set description: Full term Infants exposed in utero to maternal RAL, ≥2000 grams and ≥37 weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL dosing through 6 weeks of life starting between 12 to 60 hours of birth: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.	
Subject analysis set title	Cohort 1 (TA)5(TA)6
Subject analysis set type	Per protocol
Subject analysis set description: Cohort 1 infants whose UGT1A1 genotype were (TA)5(TA)6.	
Subject analysis set title	Cohort 1 (TA)6(TA)6
Subject analysis set type	Per protocol
Subject analysis set description: Cohort 1 infants whose UGT1A1 genotype were (TA)6(TA)6 (wildtype).	
Subject analysis set title	Cohort 1 (TA)6(TA)7
Subject analysis set type	Per protocol
Subject analysis set description: Cohort 1 infants whose UGT1A1 genotype were (TA)6(TA)7.	
Subject analysis set title	Cohort 2 (TA)6(TA)6 Wildtype
Subject analysis set type	Per protocol
Subject analysis set description: Cohort 2 infants whose UGT1A1 genotype were (TA)6(TA)6 (wildtype).	
Subject analysis set title	Cohort 2 Mutation
Subject analysis set type	Per protocol
Subject analysis set description: Cohort 2 infants whose UGT1A1 genotype were mutation: (TA)5(TA)5, (TA)5(TA)6, (TA)5(TA)7, (TA)6(TA)7, or (TA)7(TA)7.	
Subject analysis set title	Cohort 2 (TA)5(TA)5
Subject analysis set type	Per protocol
Subject analysis set description: Cohort 2 infants whose UGT1A1 genotype were mutation (TA)5(TA)5	
Subject analysis set title	Cohort 2 (TA)5(TA)6
Subject analysis set type	Per protocol
Subject analysis set description: Cohort 2 infants whose UGT1A1 genotype were (TA)5(TA)6.	
Subject analysis set title	Cohort 2 (TA)5(TA)7
Subject analysis set type	Per protocol
Subject analysis set description: Cohort 2 infants whose UGT1A1 genotype were (TA)5(TA)7.	
Subject analysis set title	Cohort 2 (TA)6(TA)7
Subject analysis set type	Per protocol
Subject analysis set description: Cohort 2 infants whose UGT1A1 genotype were (TA)6(TA)7.	
Subject analysis set title	Cohort 2 (TA)7(TA)7
Subject analysis set type	Per protocol
Subject analysis set description: Cohort 2 infants whose UGT1A1 genotype were (TA)7(TA)7.	
Subject analysis set title	Cohort 1 C/C
Subject analysis set type	Per protocol

Subject analysis set description:

Cohort 1 infants whose SLCO1B3 genotype were C/C (wildtype).

Subject analysis set title	Cohort 1 C/T
Subject analysis set type	Per protocol

Subject analysis set description:

Cohort 1 infants whose SLCO1B3 genotype were C/T.

Subject analysis set title	Cohort 1 T/T
Subject analysis set type	Per protocol

Subject analysis set description:

Cohort 1 infants whose SLCO1B3 genotype were T/T.

Subject analysis set title	Cohort 2 C/C
Subject analysis set type	Per protocol

Subject analysis set description:

Cohort 2 infants whose SLCO1B3 genotype were C/C (wildtype).

Subject analysis set title	Cohort 2 C/T
Subject analysis set type	Per protocol

Subject analysis set description:

Cohort 2 infants whose SLCO1B3 genotype were C/T.

Subject analysis set title	Cohort 2 T/T
Subject analysis set type	Per protocol

Subject analysis set description:

Cohort 2 infants whose SLCO1B3 genotype were T/T

### **Primary: Number of Infants Who Died or Had Grade 3/4 Adverse Event Through 6 Weeks of Life**

End point title	Number of Infants Who Died or Had Grade 3/4 Adverse Event Through 6 Weeks of Life <sup>[1]</sup>
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End point description:

Number of infants who died or had adverse events (AEs) of Grade 3 or 4 as defined in Division of AIDS (DAIDS) AE Grading Table. Events with onset dates prior to first RAL dosing and congenital anomalies assessed as baseline by the study team were considered baseline events and not AEs. The population analyzed were all infants who received at least one dose of RAL. Excluded one Cohort 2 RAL-naïve infant who received one dose of RAL at study entry but was off study right after study entry and thus had no post entry safety data.

End point type	Primary
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End point timeframe:

From first dosing of RAL through 6 weeks of life

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: As statistical analyses were performed separately on individual arms, they were not included.

<b>End point values</b>	Cohort 1: Raltegravir- naïve	Cohort 1: Raltegravir- exposed	Cohort 1 Total	Cohort 2: Raltegravir- naïve
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	6	16	25
Units: Participants	2	2	4	7

<b>End point values</b>	Cohort 2: Raltegravir- exposed	Cohort 2 Total		
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Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	35		
Units: Participants	4	11		

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC24 for Cohort 1 RAL Dose #1 (Within 48 Hours of Birth)

End point title	AUC24 for Cohort 1 RAL Dose #1 (Within 48 Hours of Birth) <sup>[2]</sup>
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End point description:

Area Under the Concentration-time Curve at 24-hour interval (AUC24) based on intensive PK sampling around Cohort 1 RAL dose #1 (within 48 hours of birth). The population analyzed were all Cohort 1 infants who received the first RAL dosing within 48 hours of birth and had AUC24 data for the dosing. AUC24 was missing for one Cohort 1 RAL-naïve infant whose PK samples were possibly switched.

End point type	Primary
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End point timeframe:

Cohort 1 RAL dose #1 (within 48 hours of birth) intensive PK sampling: within 30 min pre-dose; and 1-2, 4-8, 12 ( $\pm 1$ ), 24 ( $\pm 1$ ) hours post-dose.

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: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	Cohort 1 RAL-naïve: 3 mg/kg for First Dose	Cohort 1 RAL-naïve: 2 mg/kg for First Dose	Cohort 1 RAL-exposed 1.5 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	3	6	
Units: mg*h/L				
geometric mean (geometric coefficient of variation)	53.88 ( $\pm$ 34.6)	44.26 ( $\pm$ 71.9)	37.42 ( $\pm$ 92.7)	

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax for Cohort 1 RAL Dose #1 (Within 48 Hours of Birth)

End point title	Cmax for Cohort 1 RAL Dose #1 (Within 48 Hours of Birth) <sup>[3]</sup>
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End point description:

Maximum concentration (Cmax) for Cohort 1 dose #1 (within 48 hours of birth). The population analyzed were all Cohort 1 infants who received the first RAL dosing within 48 hours of birth and had Cmax data for the dosing. Cmax was missing for one Cohort 1 RAL-naïve infant whose PK samples were possibly switched.

End point type	Primary
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End point timeframe:

Cohort 1 dose #1 (within 48 hours of birth) intensive PK sampling: within 30 min pre-dose; and 1-2, 4-8, 12 ( $\pm 1$ ), 24 ( $\pm 1$ ) hours postdose.

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 nor performed for this primary endpoint.

End point values	Cohort 1 RAL-naive: 3 mg/kg for First Dose	Cohort 1 RAL-naive: 2 mg/kg for First Dose	Cohort 1 RAL-exposed 1.5 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	3	6	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	3360.89 ( $\pm$ 35.5)	3405.24 ( $\pm$ 38.1)	2188.82 ( $\pm$ 73.3)	

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC24 for Cohort 2 Initial RAL Dose (Within 48 and 12-60 Hours of Birth for RAL-naive and RAL-exposed Groups, Respectively)

End point title	AUC24 for Cohort 2 Initial RAL Dose (Within 48 and 12-60 Hours of Birth for RAL-naive and RAL-exposed Groups, Respectively) <sup>[4]</sup>
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End point description:

Area Under the Concentration-time Curve at the 24-hour interval (AUC24) for Cohort 2 initial RAL dose (within 48 and between 12-60 hours of birth for RAL-naive and RAL-exposed, respectively). The population analyzed were all Cohort 2 infants who had AUC24 data for the initial RAL dosing. AUC24 were missing for 2 Cohort 2 RAL-naive infants: one was off-study right after study entry and had incomplete PK specimen collection; and one whose AUC24 could not be estimated due to possible administration of next dose before the 24 hr sample was collected.

End point type	Primary
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End point timeframe:

Cohort 2 initial dose (within 48 and between 12-60 hours of birth for RAL-naive and RAL-exposed, respectively) intensive PK sampling: within 1 hour pre-dose; and 1-2, 6-10, 20-24 hours post-dose.

Notes:

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

Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	Cohort 2 RAL-naive: 1.5 mg/kg Once Daily on Days 1-7 of Life	Cohort 2 RAL-exposed: 1.5mg/kg Once Daily on Days 1-7 of Life		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	10		
Units: mg*h/L				
geometric mean (geometric coefficient of variation)	38.2 ( $\pm$ 42)	42.89 ( $\pm$ 25.3)		

## Statistical analyses

**Primary: Clast for Cohort 2 Initial RAL Dose (Within 48 and Between 12-60 Hours of Birth for RAL-naïve and RAL-exposed Groups, Respectively)**

End point title	Clast for Cohort 2 Initial RAL Dose (Within 48 and Between 12-60 Hours of Birth for RAL-naïve and RAL-exposed Groups, Respectively) <sup>[5]</sup>
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## End point description:

Last concentration of the drug (Clast) at 24 hour interval post dosing for the Cohort 2 initial RAL dose (within 48 and at 12-60 hours of birth for RAL-naïve and RAL-exposed, respectively). This is the plasma RAL concentration from a sample collected at or close to 24 hours post dose. The population analyzed were all Cohort 2 infants who had Clast data for the initial RAL dosing. Clast was missing for one Cohort 2 RAL-naïve infant who was off-study right after study entry and had incomplete PK specimen collection.

End point type	Primary
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## End point timeframe:

Cohort 2 initial dose (within 48 and between 12-60 hours of birth for RAL-naïve and RAL-exposed groups, respectively) intensive PK sampling: within 1 hour pre-dose; and 1-2, 6-10, 20-24 hours post-dose.

## 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: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

<b>End point values</b>	Cohort 2 RAL-naïve: 1.5 mg/kg Once Daily on Days 1-7 of Life	Cohort 2 RAL-exposed: 1.5mg/kg Once Daily on Days 1-7 of Life		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	10		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	947.90 (± 84)	946.24 (± 74)		

**Statistical analyses**

No statistical analyses for this end point

**Primary: RAL AUC12 for Cohort 2 at 15-18 Days of Life**

End point title	RAL AUC12 for Cohort 2 at 15-18 Days of Life <sup>[6]</sup>
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## End point description:

Area Under the Concentration-time Curve at 12-hour interval (AUC12) of RAL for Cohort 2 at 15-18 days of life. The population analyzed were all infants who continued to receive RAL at or beyond Day 15-18 study visit and had AUC12 for the dosing. AUC12 were missing for 2 RAL-naïve infants taken off study prior to Day 15-18 visit; 1 RAL-naïve infant with delayed absorption for whom AUC12 could not be estimated; and 1 RAL-exposed infant who had incomplete PK sample collection.

End point type	Primary
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## End point timeframe:

Intensive PK sampling for Cohort 2 at 15-18 days of life: within 1 hour pre-dose; and 1-2, 4-6, 8-12 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 nor performed for this primary endpoint.

<b>End point values</b>	Cohort 2 RAL-naive: 3 mg/kg Twice Daily on Days 8-18 of Life	Cohort 2 RAL-exposed: 3 mg/kg Twice Daily on Days 8-28 of Life		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	9		
Units: mg*h/L				
geometric mean (geometric coefficient of variation)	14.3 (± 49.5)	18.25 (± 62.8)		

## Statistical analyses

No statistical analyses for this end point

### Primary: RAL C12 for Cohort 2 at 15-18 Days of Life

End point title	RAL C12 for Cohort 2 at 15-18 Days of Life <sup>[7]</sup>
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End point description:

RAL concentration at 12 hours (C12) for Cohort 2 at 15-18 days of life. The population analyzed were all infants who continued to receive RAL at or beyond Day 15-18 study visit and had C12 for the dosing. C12 were missing for 2 RAL-naive infants taken off study prior to Day 15-18 visit; 1 RAL-naive infant with delayed absorption for whom C12 could not be estimated; and 1 RAL-exposed infant who had incomplete PK sample collection.

End point type	Primary
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End point timeframe:

Intensive PK sampling for Cohort 2 at 15-18 days of life: within 1 hour pre-dose; and 1-2, 4-6, 8-12 hours post-dose.

Notes:

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

Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

<b>End point values</b>	Cohort 2 RAL-naive: 3 mg/kg Twice Daily on Days 8-18 of Life	Cohort 2 RAL-exposed: 3 mg/kg Twice Daily on Days 8-28 of Life		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	9		
Units: mg*h/L				
geometric mean (geometric coefficient of variation)	176.11 (± 162.1)	273.59 (± 176.4)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Infants Who Died or Had Grade 3/4 Adverse Event Through 24 Weeks of Life

End point title	Number of Infants Who Died or Had Grade 3/4 Adverse Event Through 24 Weeks of Life
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End point description:

Number of infants who died or had adverse events (AEs) of Grade 3 or 4 as defined in DAIDS AE Grading Table. Events with onset dates prior to first RAL dosing and congenital anomalies assessed as baseline by the study team were considered baseline events and not AEs. The population analyzed were all infants who received at least one dose of RAL. Excluded was one Cohort 2 RAL-naïve infant who received one dose of RAL at study entry but was off study right after study entry and thus had no post entry safety data.

End point type	Secondary
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End point timeframe:

From first RAL dose through 24 weeks of life

End point values	Cohort 1: Raltegravir- naïve	Cohort 1: Raltegravir- exposed	Cohort 1 Total	Cohort 2: Raltegravir- naïve
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	6	16	25
Units: Participants	2	2	4	11

End point values	Cohort 2: Raltegravir- exposed	Cohort 2 Total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	35		
Units: Participants	4	15		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Infants Who Died or Had SADR of Grade 3 or 4 Through 6 Weeks of Life

End point title	Number of Infants Who Died or Had SADR of Grade 3 or 4 Through 6 Weeks of Life
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End point description:

Number of infants who died or had Suspected Adverse Drug Reaction (SADR) of Grade 3 or 4 as defined in DAIDS AE Grading Table. Events with onset dates prior to the first RAL dosing and congenital anomalies assessed as baseline by the study team were considered baseline events and not AEs. SADRs are AEs assessed as definitely related, probably related or possibly related to RAL. The population analyzed were all infants who received at least one dose of RAL. Excluded was one Cohort 2 RAL-naïve infant who received one dose of RAL at study entry but was off study right after study entry and thus had no post entry safety data.

End point type	Secondary
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End point timeframe:

From first RAL dose through 6 weeks of life



End point values	Cohort 1: Raltegravir- naïve	Cohort 1: Raltegravir- exposed	Cohort 1 Total	Cohort 2: Raltegravir- naïve
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	6	16	25
Units: Participants	1	0	1	0

End point values	Cohort 2: Raltegravir- exposed	Cohort 2 Total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	35		
Units: Participants	0	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Infants Who Died or Had SADR of Grade 3 or 4 Through 24 Weeks of Life

End point title	Number of Infants Who Died or Had SADR of Grade 3 or 4 Through 24 Weeks of Life
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End point description:

Number of infants who died or had Suspected Adverse Drug Reaction (SADR) of Grade 3 or 4 as defined in DAIDS AE Grading Table. Events with onset dates prior to the first RAL dosing and congenital anomalies assessed as baseline by the study team were considered baseline events and not AEs. SADRs are AEs assessed as definitely related, probably related or possibly related to RAL. The population analyzed were all infants who received at least one dose of RAL. Excluded was one Cohort 2 RAL-naïve infant who received one dose of RAL at study entry but was off study right after study entry and thus had no post entry safety data.

End point type	Secondary
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End point timeframe:

From first RAL dose through 24 weeks of life

End point values	Cohort 1: Raltegravir- naïve	Cohort 1: Raltegravir- exposed	Cohort 1 Total	Cohort 2: Raltegravir- naïve
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	6	16	25
Units: Participants	1	0	1	0

End point values	Cohort 2: Raltegravir- exposed	Cohort 2 Total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	35		

Units: Participants	0	0		
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## Statistical analyses

No statistical analyses for this end point

## Secondary: Cohort 1 Dose #1 Neonatal RAL Elimination (CL/F) by UGT1A1 Genotype Group

End point title	Cohort 1 Dose #1 Neonatal RAL Elimination (CL/F) by UGT1A1 Genotype Group
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End point description:

Cohort 1 Dose #1 neonatal RAL elimination was represented by Clearance (CL/F), which is the volume of plasma cleared of the drug per unit time. Genotyping for polymorphisms of UGT1A1 were performed on infants who were eligible for PK sampling and were consented by their mothers/guardians (i.e. genotyping was optional). The population analyzed were all Cohort 1 infants with data on CL/F (for dose #1) and UGT1A1 genotype. Excluded were: 1 Cohort 1 RAL-naïve infant with missing CL/F due to possible PK specimen switch; 2 Cohort 1 RAL-naïve infants with no specimen for genotype testing; 1 Cohort 1 RAL-exposed infant with CL/F and genotype data but was the only infant with (TA)5(TA)6 genotype.

End point type	Secondary
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End point timeframe:

Cohort 1 Dose #1 Intensive PK sampling: within 30 min pre-dose; and 1-2, 4-8, 12, 24 hours post-dose. Samples for UGT1A1 genotype testing were collected at study entry.

End point values	Cohort 1 (TA)6(TA)6	Cohort 1 (TA)6(TA)7		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: L/hr				
median (inter-quartile range (Q1-Q3))	0.11 (0.10 to 0.13)	0.06 (0.04 to 0.15)		

## Statistical analyses

Statistical analysis title	Wild type vs Mutation
Comparison groups	Cohort 1 (TA)6(TA)6 v Cohort 1 (TA)6(TA)7
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.298
Method	Wilcoxon (Mann-Whitney)

## Secondary: Cohort 2 Initial Dose Neonatal RAL Elimination (CL/F) by UGT1A1

## Genotype Group

End point title	Cohort 2 Initial Dose Neonatal RAL Elimination (CL/F) by UGT1A1 Genotype Group
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### End point description:

Cohort 2 initial dose neonatal RAL elimination was represented by Clearance (CL/F), which is defined as the volume of plasma cleared of the drug per unit time. Genotyping for polymorphisms of UGT1A1 were performed on infants who were eligible for PK sampling and were consented by their mothers/guardians (i.e. genotyping was optional). The population analyzed were all Cohort 2 infants with data on initial dose CL/F and UGT1A1 genotype. Exclusions: 1 RAL-naïve infant who was off-study right after entry w/ incomplete PK specimens; 1 RAL-naïve infant's CL/F can't be estimated due to possible administration of next dose before 24 hr sample collection; 3 RAL-naïve and 4 exposed infants without genotype specimen.

End point type	Secondary
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### End point timeframe:

Intensive PK sampling for Cohort 2 initial dose: within 1 hour pre-dose; and 1-2, 6-10, 20-24 hours post-dose. Samples for UGT1A1 genotype testing were collected at study entry.

End point values	Cohort 2 (TA)6(TA)6	Cohort 2 Mutation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	12		
Units: L/hr				
median (inter-quartile range (Q1-Q3))	0.1 (0.1 to 0.2)	0.1 (0.1 to 0.1)		

## Statistical analyses

Statistical analysis title	Wild type vs Mutation
Comparison groups	Cohort 2 (TA)6(TA)6 Wildtype v Cohort 2 Mutation
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.37
Method	Wilcoxon (Mann-Whitney)

## Secondary: Cohort 2 Neonatal RAL Elimination (CL/F) at 15-18 Days of Life by UGT1A1 Genotype Group

End point title	Cohort 2 Neonatal RAL Elimination (CL/F) at 15-18 Days of Life by UGT1A1 Genotype Group
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### End point description:

Cohort 2 15-18 days of life dose neonatal RAL elimination was represented by Clearance (CL/F), which is defined as the volume of plasma cleared of the drug per unit time at 15-18 days of life when RAL dosing would have been 3 mg/kg twice daily. Genotyping for polymorphisms of UGT1A1 were performed on infants who were eligible for PK sampling and were consented by their mothers/guardians (i.e. genotyping was optional). The population analyzed were all Cohort 2 infants with data on CL/F for Day 15-18 visit and UGT1A1 genotype. Exclusions: 1 RAL-naïve infant off-study right after entry w/ incomplete PK specimens; consent withdrawn for 1 RAL-naïve infant; 1 RAL-naïve infant stopped RAL after wk 4; 1 RAL-exposed infant w/ incomplete PK specimens; 3 RAL-naïve and 4 exposed infants w/o genotype specimen.

End point type	Secondary
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End point timeframe:

Intensive PK sampling for Cohort 2 at 15-18 days of life: within 1 hour pre-dose; and 1-2 hours post-dose, 4-6, 8-12 hours post-dose. Samples for UGT1A1 genotype testing were collected at study entry.

End point values	Cohort 2 (TA)6(TA)6	Cohort 2 Mutation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	11		
Units: L/hr				
median (inter-quartile range (Q1-Q3))	0.5 (0.4 to 1)	0.5 (0.4 to 0.8)		

### Statistical analyses

Statistical analysis title	Wild type vs Mutation
Comparison groups	Cohort 2 (TA)6(TA)6 Wildtype v Cohort 2 Mutation
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.98
Method	Wilcoxon (Mann-Whitney)

### Secondary: Number of Cohort 1 Infants With Hyperbilirubinemia by UGT1A1 Genotype

End point title	Number of Cohort 1 Infants With Hyperbilirubinemia by UGT1A1 Genotype
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End point description:

The intent of this endpoint was to investigate the association between UGT1A1 genotypes with hyperbilirubinemia. Hyperbilirubinemia was defined as total bilirubin exceeding 16.0 mg/dL or receipt of phototherapy, or transfusion therapy, or other therapies for hyperbilirubinemia or elevated bilirubin.

End point type	Secondary
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End point timeframe:

Specimens for bilirubin testing were collected at study entry; Days 3-4, 7-10 of life; and Weeks 2, 6, 24 of life for Cohort 1. Specimen for genotype testing was collected at entry.

End point values	Cohort 1 (TA)5(TA)6	Cohort 1 (TA)6(TA)6	Cohort 1 (TA)6(TA)7	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0 <sup>[8]</sup>	0 <sup>[9]</sup>	0 <sup>[10]</sup>	
Units: Participants				

Notes:

[8] - No infants had hyperbilirubinemia.

[9] - No infants had hyperbilirubinemia.

[10] - No infants had hyperbilirubinemia.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Cohort 2 Infants With Hyperbilirubinemia by UGT1A1 Genotype

End point title	Number of Cohort 2 Infants With Hyperbilirubinemia by UGT1A1 Genotype
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End point description:

The intent of this endpoint was to investigate the association between UGT1A1 genotypes with hyperbilirubinemia. Hyperbilirubinemia was defined as total bilirubin exceeding 16.0 mg/dL or receipt of phototherapy, or transfusion therapy, or other therapies for hyperbilirubinemia or elevated bilirubin.

End point type	Secondary
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End point timeframe:

Specimens for bilirubin testing were collected at study entry; after 2nd dose; Days 6-9, 15-18, 28-32 of life; and Weeks 5-6, 8-10, 24 of life for Cohort 2. Specimen for genotype testing was collected at study entry.

End point values	Cohort 2 (TA)6(TA)6	Cohort 2 (TA)5(TA)5	Cohort 2 (TA)5(TA)6	Cohort 2 (TA)5(TA)7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0 <sup>[11]</sup>	0 <sup>[12]</sup>	0 <sup>[13]</sup>	0 <sup>[14]</sup>
Units: Participants				

Notes:

[11] - No infants had hyperbilirubinemia.

[12] - No infants had hyperbilirubinemia

[13] - No infants had hyperbilirubinemia

[14] - No infants had hyperbilirubinemia

End point values	Cohort 2 (TA)6(TA)7	Cohort 2 (TA)7(TA)7		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 <sup>[15]</sup>	0 <sup>[16]</sup>		
Units: Participants				

Notes:

[15] - No infants had hyperbilirubinemia

[16] - No infants had hyperbilirubinemia

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Cohort 1 Infants With Hyperbilirubinemia by SLC01B3 Genotype

End point title	Number of Cohort 1 Infants With Hyperbilirubinemia by
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## End point description:

The intent of this Outcome Measure was to investigate the association between SLCO1B3 genotypes with hyperbilirubinemia. Hyperbilirubinemia was defined as total bilirubin exceeding 16.0 mg/dL or receipt of phototherapy, or transfusion therapy, or other therapies for hyperbilirubinemia or elevated bilirubin.

## End point type

Secondary

## End point timeframe:

Specimens for bilirubin test were collected at study entry; Days 3-4, 7-10 of life; and Weeks 2, 6, 24 of life for Cohort 1. Specimen for genotype testing was collected at study entry.

End point values	Cohort 1 C/C	Cohort 1 C/T	Cohort 1 T/T	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0 <sup>[17]</sup>	0 <sup>[18]</sup>	0 <sup>[19]</sup>	
Units: Participants				

## Notes:

[17] - No infants had hyperbilirubinemia.

[18] - No infants had hyperbilirubinemia.

[19] - No infants had hyperbilirubinemia.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Cohort 2 Infants With Hyperbilirubinemia by SLCO1B3 Genotype

## End point title

Number of Cohort 2 Infants With Hyperbilirubinemia by SLCO1B3 Genotype

## End point description:

The intent of this endpoint was to investigate the association between SLCO1B3 genotypes with hyperbilirubinemia. Hyperbilirubinemia was defined as total bilirubin exceeding 16.0 mg/dL or receipt of phototherapy, or transfusion therapy, or other therapies for hyperbilirubinemia or elevated bilirubin.

## End point type

Secondary

## End point timeframe:

Specimens for bilirubin testing were collected at study entry; after 2nd dose; Days 6-9, 15-18, 28-32 of life; and Weeks 5-6, 8-10, 24 of life for Cohort 2. Specimen for genotype testing was collected at study entry.

End point values	Cohort 2 C/C	Cohort 2 C/T	Cohort 2 T/T	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0 <sup>[20]</sup>	0 <sup>[21]</sup>	0 <sup>[22]</sup>	
Units: Participants				

## Notes:

[20] - No infants had hyperbilirubinemia.

[21] - No infants had hyperbilirubinemia.

[22] - No infants had hyperbilirubinemia.

## Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first RAL dose through 24 weeks of life.

Adverse event reporting additional description:

All Adverse Events (AEs) including diagnoses, signs/symptoms and abnormal laboratory test results. Events with onset dates prior to first RAL dose and congenital anomalies assessed as baseline by the study team were considered baseline events and not AEs.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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### Reporting groups

Reporting group title	Cohort 1 RAL-naïve
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Reporting group description:

Full term Infants not exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single RAL doses: first dose (3 mg/kg or 2 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7- 10 days of life.

Reporting group title	Cohort 1 RAL-exposed
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Reporting group description:

Full term Infants exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: RAL was given as oral granules for suspension. Two single RAL doses: first dose (1.5 mg/kg) within 48 hours of birth and second dose (3 mg/kg) at 7- 10 days of life.

Reporting group title	Cohort 2 RAL-naïve
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Reporting group description:

Full term Infants not exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL dosing through 6 weeks of life starting within 48 hours of birth: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.

Reporting group title	Cohort 2 RAL-exposed
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Reporting group description:

Full term Infants exposed in utero to maternal RAL,  $\geq 2000$  grams and  $\geq 37$  weeks gestational age at birth, born to women living with HIV-1 infection and at risk of acquiring HIV-1 infection. Raltegravir: Daily RAL dosing through 6 weeks of life starting between 12 to 60 hours of birth: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.

Serious adverse events	Cohort 1 RAL-naïve	Cohort 1 RAL-exposed	Cohort 2 RAL-naïve
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)	1 / 6 (16.67%)	7 / 25 (28.00%)
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 / 25 (4.00%)
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 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematocrit decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 25 (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
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 25 (4.00%)
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%)	0 / 6 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension neonatal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 25 (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
Blood and lymphatic system disorders			
Anaemia neonatal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 25 (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 / 25 (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%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 / 25 (4.00%)
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 bacterial			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 25 (4.00%)
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 syncytial virus bronchiolitis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Cohort 2 RAL-exposed		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Blood glucose decreased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematocrit decreased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Congenital syphilis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension neonatal			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia neonatal			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Cohort 1 RAL-naive	Cohort 1 RAL-exposed	Cohort 2 RAL-naive
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	6 / 6 (100.00%)	24 / 25 (96.00%)
Vascular disorders			
Pallor			
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	2 / 25 (8.00%)
occurrences (all)	0	2	2
Pregnancy, puerperium and perinatal conditions			
Jaundice neonatal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	4 / 25 (16.00%)
occurrences (all)	0	0	4
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	7 / 25 (28.00%)
occurrences (all)	1	0	7
Vessel puncture site bruise			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 25 (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 / 25 (0.00%)
occurrences (all)	1	0	0
Breast induration			

subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Penile erythema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	9 / 25 (36.00%)
occurrences (all)	2	1	9
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Nasal congestion			
subjects affected / exposed	4 / 10 (40.00%)	0 / 6 (0.00%)	5 / 25 (20.00%)
occurrences (all)	4	0	5
Rhinorrhoea			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	1 / 25 (4.00%)
occurrences (all)	2	0	1
Cyanosis neonatal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal plaque			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	2 / 25 (8.00%)
occurrences (all)	2	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Blood bilirubin increased			

subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	4 / 25 (16.00%)
occurrences (all)	1	1	4
Blood creatinine increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	6 / 25 (24.00%)
occurrences (all)	1	0	6
Blood glucose decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Blood potassium increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Blood pressure increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Blood sodium decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Cardiac murmur			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	4 / 10 (40.00%)	5 / 6 (83.33%)	20 / 25 (80.00%)
occurrences (all)	4	5	20
Neutrophil count decreased			
subjects affected / exposed	5 / 10 (50.00%)	4 / 6 (66.67%)	10 / 25 (40.00%)
occurrences (all)	5	4	10
Blood albumin decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Congenital umbilical hernia			

subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	3 / 25 (12.00%)
occurrences (all)	0	0	3
Craniosynostosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Laryngomalacia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Pulmonary artery stenosis congenital			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Hypertonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Fontanelle bulging			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye discharge			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	2 / 25 (8.00%)
occurrences (all)	1	0	2
Infantile vomiting			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Oral mucosal discolouration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Umbilical hernia			



subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 6 (0.00%) 0	1 / 25 (4.00%) 1
Vomiting subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 6 (16.67%) 1	3 / 25 (12.00%) 3
Infantile spitting up subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 6 (0.00%) 0	0 / 25 (0.00%) 0
Hepatobiliary disorders Hyperbilirubinaemia neonatal subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 6 (0.00%) 0	0 / 25 (0.00%) 0
Jaundice subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 6 (0.00%) 0	2 / 25 (8.00%) 2
Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 6 (0.00%) 0	1 / 25 (4.00%) 1
Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 6 (0.00%) 0	2 / 25 (8.00%) 2
Dermatitis diaper subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 6 (16.67%) 1	0 / 25 (0.00%) 0
Eczema subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 6 (0.00%) 0	0 / 25 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 6 (16.67%) 1	1 / 25 (4.00%) 1
Papule subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 6 (0.00%) 0	0 / 25 (0.00%) 0
Rash			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	3 / 25 (12.00%)
occurrences (all)	1	0	3
Seborrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	4 / 25 (16.00%)
occurrences (all)	0	0	4
Rash erythematous			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Rash generalised			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Folliculitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Genital candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	3 / 25 (12.00%)
occurrences (all)	0	0	3
Oral candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	8 / 25 (32.00%)
occurrences (all)	0	1	8
Otitis media acute			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Skin candida			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	5 / 25 (20.00%)
occurrences (all)	0	0	5
Tinea versicolour			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0

<b>Non-serious adverse events</b>	Cohort 2 RAL-exposed		
Total subjects affected by non-serious adverse events subjects affected / exposed	9 / 10 (90.00%)		
Vascular disorders Pallor subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Pregnancy, puerperium and perinatal conditions Jaundice neonatal subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)  Vessel puncture site bruise subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1  0 / 10 (0.00%) 0		
Reproductive system and breast disorders Acquired hydrocele subjects affected / exposed occurrences (all)  Breast induration subjects affected / exposed occurrences (all)  Penile erythema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0  0 / 10 (0.00%) 0  0 / 10 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Dyspnoea subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1  0 / 10 (0.00%) 0		

Nasal congestion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Cyanosis neonatal			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Oropharyngeal plaque			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Blood creatinine increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood glucose decreased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Blood potassium increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Blood pressure increased			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Blood sodium decreased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Cardiac murmur			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	7 / 10 (70.00%)		
occurrences (all)	7		
Neutrophil count decreased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood albumin decreased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Congenital umbilical hernia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Craniosynostosis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Laryngomalacia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pulmonary artery stenosis congenital			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Hypertonia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Fontanelle bulging subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Eye disorders Eye discharge subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3		
Infantile vomiting subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Oral mucosal discolouration subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Umbilical hernia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Vomiting subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Infantile spitting up subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Hepatobiliary disorders Hyperbilirubinaemia neonatal subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Jaundice			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dermatitis allergic			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dermatitis diaper			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Papule			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Seborrhoea			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Rash erythematous			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rash generalised			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

Infections and infestations Folliculitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Genital candidiasis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Oral candidiasis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Otitis media acute subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Skin candida subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Tinea versicolour subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported