# 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 |

### 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 | 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 |
| **Arm title** | Cohort 1: Raltegravir-naive |

Arm description:

Full term Infants not 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: 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.

| | |
|---|---|
| **Arm title** | Cohort 1: Raltegravir-exposed |

Arm 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: 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.

| | |
|---|---|
| **Arm title** | Cohort 2: Raltegravir-naive |

Arm description:

Full term Infants not 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 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).

| | |
|---|---|
| **Arm title** | Cohort 2: Raltegravir-exposed |

Arm 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 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).

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| Consent withdrawn by parent/guardian | - | - | 4 |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

| **Number of subjects in period 1** | 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-naive |
| Reporting group description: | |
| Full term Infants not 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: 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, ≥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: 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-naive |
| Reporting group description: | |
| Full term Infants not 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 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, ≥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 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-naive | Cohort 1: Raltegravir-exposed | Cohort 2: Raltegravir-naive |
|---|---|---|---|
| Number of subjects | 10 | 6 | 26 |
| Age Categorical<br>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<br>Units: Subjects | | | |
| Female | 6 | 2 | 12 |
| Male | 4 | 4 | 14 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 3 | 3 | 19 |
| Not Hispanic or Latino | 7 | 2 | 7 |
| Unknown or Not Reported | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Birth weight<br>Units: Grams<br>median<br>full range (min-max) | <br><br>3020<br>2385 to 4200 | <br><br>2948<br>2320 to 3385 | <br><br>2930<br>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<br>median<br>full range (min-max) | <br>8<br>8 to 9 | <br>9<br>8 to 9 | <br>9<br>6 to 10 |

| **Reporting group values** | Cohort 2: Raltegravir-exposed | Total | |
|---|---|---|---|
| Number of subjects | 10 | 52 | |
| Age Categorical<br>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<br>median<br>full range (min-max) | <br>39<br>38 to 41 | <br><br>- | |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 4 | 24 | |
| Male | 6 | 28 | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 5 | 30 | |
| Not Hispanic or Latino | 4 | 20 | |
| Unknown or Not Reported | 1 | 2 | |
| Birth weight<br>Units: Grams<br>median<br>full range (min-max) | <br><br>3085<br>2090 to 4130 | <br><br><br>- | <br><br><br> |
| 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<br>median<br>full range (min-max) | <br>9<br>8 to 10 | <br><br>- | <br><br> |

## End points

### End points reporting groups

| Reporting group title | Cohort 1: Raltegravir-naive |
|---|---|

Reporting group description:

Full term Infants not 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: 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, ≥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: 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-naive |
|---|---|

Reporting group description:

Full term Infants not 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 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, ≥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 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-naive |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Full term Infants not 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: 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, ≥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: 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, ≥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: 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-naive |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Full term Infants not 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 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, ≥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 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, ≥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 through 6 weeks of life starting within 48 hours of birth and between 12 to 60 hours of birth for in utero RAL-naive 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-naive: 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, ≥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: 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-naive: 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, ≥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: 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, ≥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: 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-naive: 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, ≥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 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, ≥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 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-naive: 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, ≥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 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[1] |
|---|---|

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-naive 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 |
|---|---|

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.

| **End point values** | Cohort 1: Raltegravir-naive | Cohort 1: Raltegravir-exposed | Cohort 1 Total | Cohort 2: Raltegravir-naive |
|---|---|---|---|---|
| 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 |

| **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 | 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)[2] |
|---|---|

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-naive infant whose PK samples were possibly switched.

| End point type | Primary |
|---|---|

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 (±1), 24 (±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-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: mg*h/L | | | | |
| geometric mean (geometric coefficient of variation) | 53.88 (± 34.6) | 44.26 (± 71.9) | 37.42 (± 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)[3] |
|---|---|

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-naive infant whose PK samples were possibly switched.

| End point type | Primary |
|---|---|

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 (±1), 24 (±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 (± 35.5) | 3405.24 (± 38.1) | 2188.82 (± 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)[4] |
|---|---|

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 |
|---|---|

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 (± 42) | 42.89 (± 25.3) | | |

## Statistical analyses

No statistical analyses for this end point

## 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)[5] |
|---|---|

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-naive 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-naive infant who was off-study right after study entry and had incomplete PK specimen collection.

| End point type | Primary |
|---|---|

End point timeframe:

Cohort 2 initial dose (within 48 and between 12-60 hours of birth for RAL-naive 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.

| **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 | 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[6] |
|---|---|

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-naive infants taken off study prior to Day 15-18 visit; 1 RAL-naive 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 |
|---|---|

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.

| End point values | 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[7] |
|---|---|

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 |
|---|---|

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.

| End point values | 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 |
|---|---|

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-naive 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 |
|---|---|

End point timeframe:

From first RAL dose through 24 weeks of life

| **End point values** | Cohort 1: Raltegravir-naive | Cohort 1: Raltegravir-exposed | Cohort 1 Total | Cohort 2: Raltegravir-naive |
|---|---|---|---|---|
| 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 |
|---|---|

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-naive 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 |
|---|---|

End point timeframe:

From first RAL dose through 6 weeks of life

| End point values | Cohort 1: Raltegravir-naive | Cohort 1: Raltegravir-exposed | Cohort 1 Total | Cohort 2: Raltegravir-naive |
|---|---|---|---|---|
| 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 |
|---|---|

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-naive 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 |
|---|---|

End point timeframe:

From first RAL dose through 24 weeks of life

| End point values | Cohort 1: Raltegravir-naive | Cohort 1: Raltegravir-exposed | Cohort 1 Total | Cohort 2: Raltegravir-naive |
|---|---|---|---|---|
| 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: 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 |

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-naive infant with missing CL/F due to possible PK specimen switch; 2 Cohort 1 RAL-naive 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 |

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 |

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-naive infant who was off-study right after entry w/ incomplete PK specimens; 1 RAL-naive infant's CL/F can't be estimated due to possible administration of next dose before 24 hr sample collection; 3 RAL-naive and 4 exposed infants without genotype specimen.

| End point type | Secondary |
|---|---|

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 |

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-naive infant off-study right after entry w/ incomplete PK specimens; consent withdrawn for 1 RAL-naive infant; 1 RAL-naive infant stopped RAL after wk 4; 1 RAL-exposed infant w/ incomplete PK specimens; 3 RAL-naive and 4 exposed infants w/o genotype specimen.

| End point type | Secondary |
|---|---|

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 |
|---|---|

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 |
|---|---|

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[8] | 0[9] | 0[10] | |
| 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 |
|---|---|

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 |
|---|---|

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[11] | 0[12] | 0[13] | 0[14] |
| 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[15] | 0[16] | | |
| 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 SLCO1B3 Genotype

| End point title | Number of Cohort 1 Infants With Hyperbilirubinemia by |
|---|---|

| | |
|---|---|
| | SLCO1B3 Genotype |

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[17] | 0[18] | 0[19] | |
| 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[20] | 0[21] | 0[22] | |
| Units: Participants | | | | |

Notes:

[20] - No infants had hyperbilirubinemia.

[21] - No infants had hyperbilirubinemia.

[22] - No infants had hyperbilirubinemia.

### Statistical analyses

No statistical analyses for this end point

## 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1 RAL-naive |

Reporting group description:

Full term Infants not 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-1infection. 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 |

Reporting group 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-1infection. 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-naive |

Reporting group description:

Full term Infants not 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 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 |

Reporting group 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.

| Serious adverse events | Cohort 1 RAL-naive | Cohort 1 RAL-exposed | Cohort 2 RAL-naive |
|---|---|---|---|
| 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 |

| **Serious adverse events** | 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 %

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

| **Non-serious adverse events** | 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 | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Jaundice neonatal | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Vessel puncture site bruise | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Reproductive system and breast disorders | | | |
| Acquired hydrocele | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Breast induration | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Penile erythema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 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<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0 | | |
| Fontanelle bulging<br>subjects affected / exposed<br>occurrences (all) | 1 / 10 (10.00%)<br>1 | | |
| Eye disorders<br>Eye discharge<br>subjects affected / exposed<br>occurrences (all) | 1 / 10 (10.00%)<br>1 | | |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0 | | |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all) | 3 / 10 (30.00%)<br>3 | | |
| Infantile vomiting<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0 | | |
| Oral mucosal discolouration<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0 | | |
| Umbilical hernia<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0 | | |
| Vomiting<br>subjects affected / exposed<br>occurrences (all) | 1 / 10 (10.00%)<br>1 | | |
| Infantile spitting up<br>subjects affected / exposed<br>occurrences (all) | 2 / 10 (20.00%)<br>2 | | |
| Hepatobiliary disorders<br>Hyperbilirubinaemia neonatal<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>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 | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Genital candidiasis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Otitis media acute | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin candida | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Tinea versicolour | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 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