# IMPAACT P1110: RALTEGRAVIR PHARMACOKINETICS AND SAFETY IN HIV-1 EXPOSED NEONATES: DOSE-FINDING STUDY

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## Objectives

- To evaluate the PK, safety and tolerability of RAL oral granules for suspension when administered to HIV-1 exposed infants

## Background

- While antiretroviral drugs (ARVs) are used in neonates for prophylaxis of perinatal transmission or early intensive treatment of neonates with HIV infection, safety and dosing information in neonates are limited
- Raltegravir (RAL) first INSTI to be available in formulation suitable for use in young infants
  - RAL has good safety and tolerability
  - RAL is primarily metabolized by UGT1A1 enzyme
  - UGT1A1 activity low at birth and increases exponentially over the first weeks to months of life[1,2]
  - In vitro study suggests that RAL plasma concentrations may displace unconjugated bilirubin from albumin, increasing neonatal risk of kernicterus, at plasma concentrations 50-100 X greater than typical peak concentrations (~ 5000 ng/mL)[3]
- Raltegravir elimination in neonates following maternal dosing was highly variable and is reflective of low neonatal UGT1A1 enzyme activity at birth [4]
- PK and safety data from an initial cohort of 15 infants receiving 2 single doses of RAL during the first week of life has been previously reported[5]
- A population PK model using NONMEM was developed incorporating PK data from the first 6 infants from initial cohort and from 24 infants and children ages 4 weeks to < 2 years enrolled in IMPAACT P1066, a Phase I/II, multi-center, open-label, non-comparative intensive PK study of RAL in infants and children.[6,7] Model included maturation of:
  - Absorption rate from 16% of max at birth to 90% at 2 weeks
  - Clearance from almost nil to a max at ~ 6 months of age
- Model used to perform simulations of possible daily dosing regimens for new cohort of infants[8]

| Regimen | 1-7 (wk-1) | 8-14 (wk-2) | 15-21 (wk-3) | 22-28 (wk-4) | 29-35 (wk-5) | 36-42 (wk-6) | Trough | Cmax | AUC24 (QD) | AUC12 (BID) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 QD | 3 BID | | | | | Day42 | | Day2+3 | |
| 2 | 3 QD | 3 BID | | | 4 BID | | Day42 | | Day2+3 | |
| 3 | 2 QD | 2 BID | | | 6 BID | | Day28 | | Day2+3 | |
| 4 | 2 QD | 2 BID | 6 BID | | | | | | Day2+3 | Day14-16 |
| 5 | 3 QD | | 3 BID | | 6 BID | | Day 14 | | Day2+3 | |
| 6 | 2 QD | 4 QD | 6 BID | | | | | | Day2+3 | Day14-16 |
| 7 | 2 QD | 3 BID | | | 6 BID | | | | Day2+3 | |
| 8 | 2 QD | 6 QD | | | 6 BID | | Day 28 | | Day2+3 | |
| 9 | 3 QD | 3 BID | | | 6 BID | | | | Day2+3 | |
| 10 | 1.5 QD | 3 BID | | | 6 BID | | | | | |

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## Materials and Methods

- Infants born to HIV infected mothers and at high risk of mother to child HIV transmission were enrolled
- Inclusion Criteria:
  - Full-term infant aged ≤ 48 hours of age
  - Gestational age at birth at least 37 weeks & weight ≥ 2 kg
- Exclusion criteria:
  - Mother did not receive RAL during pregnancy
  - Elevated bilirubin requiring phototherapy
  - Receipt of disallowed medications - phenytoin, phenobarbital, rifampin
- Raltegravir Dosing Table:

| | Oral granules for suspension | Frequency |
|---|---|---|
| Day 1 to 7 of life | 1.5 mg/kg | Once daily |
| Day 8 to 28 of life | 3.0 mg/kg | Twice daily |
| After 4 weeks of age | 6.0 mg/kg | Twice daily |

- Sampling Schedule:
  - First dose: Pre-dose, 1-2 hours post-dose, 6-10 hour post-dose, and 20-24 hours post-dose;
  - Second dose: 3-6 hours post-dose
  - Day 6-9 of life: pre-dose
  - Day 15-18 of life: Pre-dose, 1-2 hours post-dose, 4-6 hours post-dose, 8-12 hours post-dose
  - Day 28-32 of life: pre-dose
  - Week 5-6 of life: pre-dose, 3-6 hours
  - PK samples were analyzed for RAL concentrations using a validated HPLC-MS-MS method LLOQ=10 ng/mL
- Protocol exposure targets for each subject are $AUC_{24}$ 12-40mg*h/L, $AUC_{12}$ 6-20 mg*h/L, $C_{12}$ or $C_{24}$ > 33ng/mL, and $C_{max}$ < 8724 ng/mL
- Safety was assessed based on clinical and laboratory evaluations
  - Hematology including CBC and platelet count
  - Chemistries including AST, ALT, creatinine, total and direct bilirubin
  - HIV nucleic acid test (HIV NAT)

## Results

- Twenty-six RAL-naïve infants were enrolled in Cohort 2. Evaluable PK results and 6 week safety data are available for 25 infants.

**Demographics**

- 26 infants: 17 Brazil, 3 South Africa, 6 USA
- Sex: 12 (46%) female /14 (54%) male
- Gestational Age: 38.5 weeks (37.0-40.9)
- Birth Weight (kg): 2.93 (2.39-3.75)
- Mode of Delivery: 5 (19%)vaginal/ 21 (81%) cesarean
- Race: Black or African American 18 (69%); White 3 (12%); Other 5 (19%)
- Ethnicity: Hispanic/Latino 19 (73%); Not Hispanic/Latino 7 (27%)

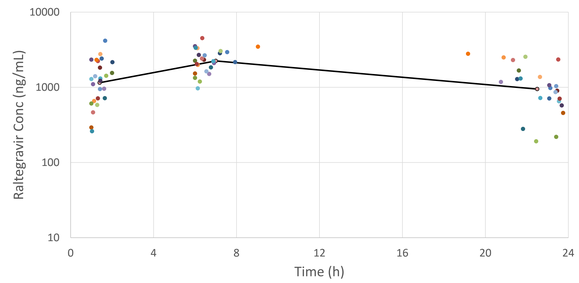
**Safety Evaluations**

- No drug-related adverse events were observed
- No infants required interventions for elevated bilirubin levels
- All HIV NAT test results were negative

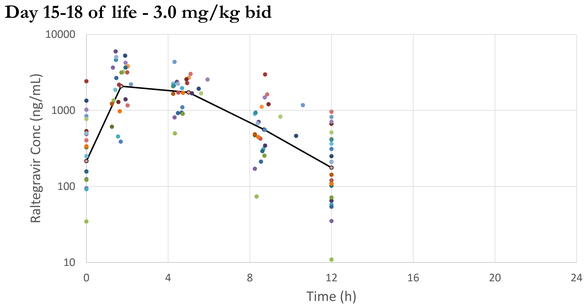
## Results

| PK Parameters | After initial dose: 1.5 mg/kg Once Daily (n=25) | | Day 15-18: 3.0 mg/kg Twice Daily (n=24) | |
|---|---|---|---|---|
| | Geometric Mean (CV) | Target | Geometric Mean (CV) | Target |
| AUC (mg*h/L) | 38.2 (38.4%) | Above - 11 Met - 13 Below - 0 | 14.3 (43.3%) | Above - 8 Met - 14 Below - 1 |
| Trough (ng/mL) | 948 (64.2%) | Above - 25 Below - 0 | 176 (93.8%) | Above - 22 Below - 1 |
| Cmax (ng/mL) | 2350 (35.0%) | Above - 0 Below - 25 | 2850 (41.9%) | Above - 0 Below - 24 |
| Tmax (ng/mL) | 5.4 (57.5%) | ------- | 2.3 (67.1%) | ------- |
| T1/2 (hrs) | 15.8 (174.8%) | ------- | 2.5 (33.5%) | ------- |
| PK targets: AUC24: 12-40 mg*h/L, AUC12: 6-20 mg*h/L, Trough concentrations > 33 ng/mL | | | | |

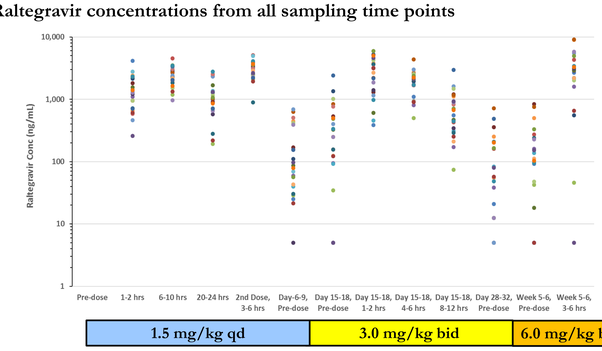
**<48 hours of life – initial dose 1.5 mg/kg qd**




**Day 15-18 of life - 3.0 mg/kg bid**

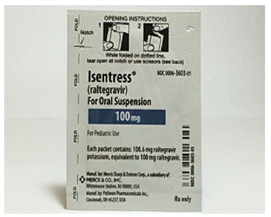



**Raltegravir concentrations from all sampling time points**




## Conclusions

- Daily RAL was safe and well tolerated during the first 6 weeks of life.
- All GM protocol exposure targets were met.
- In some infants $AUC_{24}$ following the initial dose was slightly above target range but this was considered acceptable given the rapid increase in RAL metabolism over the first week of life.
- The PK targets and the safety guidelines have been met for RAL-unexposed infants in cohort 2 using the specified dosing regimen.
- Subsequent groups to be studied in P1110:
  - Infants born to mothers who received RAL during pregnancy up through delivery
  - Low birth weight infants

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