**Background:**

- **RAL:** A potent and selective HIV-1 integrase inhibitor with potential for use in prophylaxis and early treatment of neonates at risk for perinatal HIV-1 infection.
- **RAL** is primarily metabolized by UGT1A1, whose activity is known to be extremely low at birth followed by a dramatic increase over the first weeks to months of life. At high plasma concentrations (50-100 times greater than typical peak concentrations of 5000 ng/mL), RAL can displace bilirubin from albumin, placing a newborn infant at risk for kernicterus.

- **IMPAACT P1110** demonstrated that RAL crossed the placental wall and elimination of trans-placentally acquired RAL in infants whose mothers received RAL during pregnancy was highly variable and prolonged. Direct administration of RAL to a neonate with a utero-exposure poses the potential risk of accumulation of RAL to excessive concentrations.

- In November 2017, RAL oral granules for suspension was Food and Drug Administration (FDA) approved for use in full-term neonates weighing 2.5 kg. Current pediatric FDA approval and dosing recommendations are based on evaluations conducted in IMPAACT P1110 in 42 neonates born to mothers with HIV-1 infection who did not receive RAL during pregnancy. These infants were treated for up to 6 weeks starting from birth and followed for safety for a total of 1.5 years.

- The FDA approved dosing for RAL is based on P1110 pharmacokinetics (PK) and safety results from infants born to mothers who did not receive RAL during pregnancy. Based on PK modeling and simulations, the FDA recommends that initial neonatal RAL doses should be delayed until 34-48 hours after birth if a pregnant woman receives RAL 2-24 hours before delivery.

- We now report the pharmacokinetic and safety analyses of daily RAL dosing in neonates enrolled in P1110 whose mothers received RAL prior to delivery.

**Materials and Methods:**

- **IMPAACT P1110** is a Phase 1, multicenter trial enrolling full-term neonates exposed to HIV and at risk of acquiring HIV-infection with in utero RAL exposure (RAL exposed) or without in utero RAL exposure (RAL naive). Study design included two cohorts: Cohort 1 infants received two single raltegravir doses 1 week apart and Cohort 2 infants received daily raltegravir dosing for the first 6 weeks of life.

- **PK** samples were analyzed for RAL concentrations using a validated HPLC-MS/MS method L100-22.25 M.

- **PK data** from Cohort 1 and from older infants and children were combined in a population PK model. Population modeling using NONMEM 7.3, NORMEMM7.3 and R3.1.0 was employed to estimate PK parameters, which were then used in simulations of potential dosing regimens to be evaluated in Cohort 2.

- **RAL** daily dosing regimen evaluated:
  - 1.5 mg/kg daily through Day 7
  - 3 mg/kg twice daily on Days 8 to 28 of life
  - 6 mg/kg twice daily after 4 weeks of age

- **Protocol exposure targets were:**
  - AUC0-24 ≥ 120-40 mg*h/L
  - AUC0-24 ≥ 60-20 mg*h/L
  - Cmax ≥ 31 nmol/L
  - Cmin ≥ 8723.6 nmol/L

- **AUC** was estimated using the trapezoidal method.

- **Concentration-time profile** of RAL-exposed neonates (born to mothers who receive RAL) initiated therapy with RAL within 48 hours of birth. For RAL-exposed neonates (born to mothers who received RAL within 2-24 hours of delivery) a delay in initiation of therapy with RAL of 12-40 hours of birth was evaluated.

- Infants were followed with clinical and laboratory safety evaluations through 24 weeks of age.

**Results**

**Demographics:**

- 10 mother-infant pairs (4 Thailand, 4 Brazil, 1 USA, 1 South Africa) enrolled.

- Infants (N=10) median (range):
  - Sex: 4 (male)/6 (female)
  - Gestational age: 39 weeks (38-40)
  - Birth weight: 3.09 kg (2.77-3.36 kg)
  - Mode of delivery: 3 (30%) N/A
  - Gestational age: 39 weeks (38-40)

**Safety:**

- **No drug-related clinical adverse events were observed.**

- **Laboratory events:**
  - Four infants had grade 3 or 4 toxicities: anemia (1), neutropenia (1), hyperbilirubinemia (2).

**Acknowledgements:**

- **We wish to thank the women and infants who participated in the protocol and the staff of the participating International Maternal Pediatric Adolescent AIDS Clinical Trials sites.**

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- **Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with funding from the Clinical Trials Network (CTN).**

- **Acknowledgments:**

**Table 1: RAL PK parameters [geometric mean (range) for RAL naive and RAL exposed neonates:**

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>After Initial Dose: 1.5 mg/kg Once Daily (N = 20)</th>
<th>After Initial Dose: 1.5 mg/kg Once Daily (N = 20)</th>
<th>After Initial Dose: 1.5 mg/kg Once Daily (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric Mean (CV)</td>
<td>PK Target</td>
<td>Geometric Mean (CV)</td>
<td>PK Target</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>38.4 (38.4%)</td>
<td>AUC0-24 (mg*h/L)</td>
<td>42.9 (24.6%)</td>
</tr>
<tr>
<td>Cmin (nmol/L)</td>
<td>94.8 (25.4%)</td>
<td>AUC0-24 (mg*h/L)</td>
<td>946.3 (49.7%)</td>
</tr>
<tr>
<td>T1/2 (hrs)</td>
<td>1.5 mg/kg qd</td>
<td>Cmax (nmol/L)</td>
<td>1.5 mg/kg qd</td>
</tr>
<tr>
<td>1.5 mg/kg qd</td>
<td>6-20 mg*h/L</td>
<td>3 mg/kg bid</td>
<td>2563.2 (24.3%)</td>
</tr>
<tr>
<td>3 mg/kg bid</td>
<td>Below: 0</td>
<td>Below: 0</td>
<td>Below: 0</td>
</tr>
<tr>
<td>6 mg/kg bid</td>
<td>Below: 0</td>
<td>Below: 0</td>
<td>Below: 0</td>
</tr>
</tbody>
</table>

**Key to Acronyms:**

- **AUC** = area under the curve;
  - **Cmax** = maximum concentration;
  - **CV** = coefficient of variation;
  - **PK** = pharmacokinetic;
  - **T1/2** = half-life;
  - **Tmax** = time to reach maximum concentration;

**Safety:**

- **No drug-related clinical adverse events were observed.**

- **Laboratory events:**
  - Four infants had grade 3 or 4 toxicities: anemia (1), neutropenia (1), hyperbilirubinemia (2).

**Conclusions:**

- There are few ARVs with an appropriate formulation and adequate PK data for use in neonates.

- Daily RAL beginning at 60-120 hours of age was safe and well tolerated in infants born to mothers receiving RAL.

- Use of RAL for maternal PK parameters met protocol exposure targets, some individual infants had AUC0-24 following the initial dose slightly exceeding the target range. This transient overexposure was considered acceptable given the rapid increase in RAL metabolism over the first week of life.

- Our findings confirm that the current FDA dosing recommendations based on PK modeling and simulations are appropriate for use in neonates with in utero RAL exposure.

- P1110 will begin enrolling low birth weight (≤500 g) neonates in a new version of the protocol. Our washout data from P1097 LBW infants will be used to develop a population PK model for RAL in LBW infants and simulations will be used to test an initial dose for evaluation.

**Reference:**


