Background: 
RAL is a potent and selective HIV-1 integrase inhibitor with potential for use in prophylaxis and treatment of neonates at high risk for perinatal HIV infection. RAL is primarily metabolized byUGT1A1, whose activity is low at birth and increases exponentially over the first weeks of life.

In vitro data have shown that at high RAL plasma concentrations (~50 times typical peak concentrations in HIV-infected adults), RAL has the potential to displace filitrexab from albumin, increasing neonatal risk for keratopathy.

IMPAACT P1097 demonstrated that RAL readily crosses the placenta and that elimination of RAL in infants who received RAL during pregnancy is highly variable and prolonged.

The objectives of IMPAACT P1110 are to evaluate the pharmacokinetics and safety of RAL and to determine an appropriate neonatal dose for use within the first few weeks of life.

Materials and Methods: 
IMPAACT P1110 is a Phase I multicenter PK study of RAL in full-term HIV-exposed neonates at high risk of acquiring HIV-1 infection.

Cohort 1 infants received RAL administered as a single oral dose within 48 hours of birth in addition to standard of care. A preliminary 2 mg/kg dose was selected for evaluation in a second cohort of infants with evaluable PK. All 12 infants had a PK parameter estimate with confidence intervals given in Table 4.

However, AUC12 was exceeded after initial dose in 3/6 infants who received 3 mg/kg; 2/3 infants who received 2 mg/kg; and 1/3 RAL infants.

Inter-compartment analysis for each subject was performed to estimate RAL PK parameters, which were used to generate time-dependent functions for absorption and clearance:

- Absorption rate
- Clearance
- Volume of distribution

The objective of IMPAACT P1110 is to evaluate the pharmacokinetics and safety of RAL and to determine an appropriate neonatal dose for use within the first few weeks of life.

The dosing regimen for 6 weeks of age that best met the following revised PK exposure targets defined for safety and efficacy from recent studies in older infants, children, and adults was selected for evaluation in a second cohort of neonates.

The regimen that met PK exposure targets (Cmax, AUC) defined for safety and efficacy from studies in older infants, children, and adults was selected for evaluation in a second cohort of neonates.

Results: 
- 13 mother-infant pairs (10 from USA, 2 from Brazil, 1 from South Africa) enrolled in Cohort 1 - 10 infants born to mothers who did not receive RAL prior to delivery and 3 infants born to mothers who received RAL prior to and during delivery.
- Infant Demographics: 10 [median (IQR)] infants received 1 mg/kg; 2 [2.5 (1.6, 4.3)] infants received 2 mg/kg; and 1 [2.4 (1.0, 2.4)] infant received 3 mg/kg.

Evaluable RAL concentration data following initial dose and week 1 dose are available for 12 of the 13 neonates (Figure 1).

Intermediate analysis of the PK data from the first 6 RAL naive infants who received 3 mg/kg initial doses revealed that the Cmax upper limit was not exceeded by any subject, but two patients exceeded the AUC12 upper limit.

For subsequent enrollments, the initial dose was reduced to 2 mg/kg for RAL-naive and 1.5 mg/kg for RAL-exposed infants.

RAL PK parameters for Cohort 1 following initial doses are included in Table 1.

All infants received 3 mg/kg for the second administration at 7-10 days of life.

Applying exposure protocol limits for the 12 infants with evaluable PK, all 12 infants had a Cmax ≤ 19.6 µM. However, AUC12 ≤ 6.1 µM was exceeded after initial dose in 3/6 infants who received 3 mg/kg; 2/3 infants who received 2 mg/kg, and 1/3 RAL-exposed infants who received 1.5 mg/kg initial dose.

RAL was well tolerated: 1 infant had a low absolute neutrophil count (ANC) thought to be possibly related to RAL.

Table 1: RAL PK parameters from non-compartmental analysis (geometric mean [range]) for Cohort 1 initial doses

<table>
<thead>
<tr>
<th>RAL PK Parameter</th>
<th>Adult at Initial Dose</th>
<th>Infant at Initial Dose</th>
<th>Infant at Week 1 Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µM)</td>
<td>3.31 ± 0.32 (2.60-4.46)</td>
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</tr>
<tr>
<td>AUC12 (µM·h)</td>
<td>25.3 ± 2.5 (21.7-29.0)</td>
<td>25.3 ± 2.5 (21.7-29.0)</td>
<td>25.3 ± 2.5 (21.7-29.0)</td>
</tr>
<tr>
<td>T max (h)</td>
<td>2.5 ± 0.2 (2.0-3.0)</td>
<td>2.5 ± 0.2 (2.0-3.0)</td>
<td>2.5 ± 0.2 (2.0-3.0)</td>
</tr>
<tr>
<td>T max (h)</td>
<td>2.5 ± 0.2 (2.0-3.0)</td>
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</tr>
<tr>
<td>CL (L/h)</td>
<td>0.86 ± 0.08 (0.73-1.0)</td>
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</tr>
<tr>
<td>V/F (L/kg)</td>
<td>4.4 ± 0.4 (3.7-5.1)</td>
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</tr>
<tr>
<td>Inter-compartment</td>
<td>0.86 ± 0.08 (0.73-1.0)</td>
<td>0.86 ± 0.08 (0.73-1.0)</td>
<td>0.86 ± 0.08 (0.73-1.0)</td>
</tr>
</tbody>
</table>

Table 2: Data used for PK modeling

Table 3: Initial doses for each subject were analyzed with a validated HPC-AMS method ILOL=22.5 ± M.

Protocol exposure limits from CLEAR and RAL exposures were exceeding 80% of the maximum expected exposure for PK parameters in 3/6 infants who received 3 mg/kg; 2/3 infants who received 2 mg/kg; and 1/3 RAL-exposed infants who received 1.5 mg/kg initial dose.

Table 4: Final PK parameter estimates

Table 5: Evaluation of Typical RAL Exposure Parameters with Potential Dosing Regimens (in µg/kg)

Figure 3: Predicted RAL exposure for a typical Cohort 2 subject receiving the selected regimen (regimen 6) during the first 6 weeks of life.

Conclusions: 
- There are few ARVs with an appropriate formulation and adequate PK data for use in neonates.
- After combining RAL concentration data from a small group of neonates receiving only 2 RAL doses with that from older infants and children receiving daily dosing, a population PK model and simulations were used to facilitate development of a dosing neonatal RAL regimen for evaluation in a second cohort of infants.
- P1110 will begin enrolling RAL-exposed infants into Cohort 2 with the dose selected from the PK modeling and simulations: 1.5 mg/kg once a day from birth to day 7, followed by 3 mg/kg twice a day until 4 days of age, then 6 mg/kg twice a day for 6 weeks.
- RAL-exposed infants will be excluded from Cohort 2 until additional PK data are obtained for this group.
- PK results for Cohort 2 will be evaluated on a rolling basis and dosing will be adjusted based on these results.

Acknowledgments: 
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