Safety was assessed based on clinical and laboratory evaluations in infants born to HIV-infected mothers and at high risk of mother to child HIV transmission were enrolled. Inclusion Criteria: o Full-term infant aged ≥ 48 hours of age o Gestational age at birth ≥ 37 weeks & weight ≥ 2 kg Exclusion criteria: o Mother did not receive RAL during pregnancy o Elevated bilirubin requiring phototherapy o Receipt of disallowed medications - phenytoin, phenobarbital, ritonavir

Raltegravir Dosing Table:

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Oral dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;48 hours of life</td>
<td>1.5 mg/kg</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Day 1 to 7 of life</td>
<td>5.0 mg/kg</td>
<td>Once daily</td>
</tr>
<tr>
<td>Day 8 to 28 of life</td>
<td>5.0 mg/kg</td>
<td>Twice daily</td>
</tr>
<tr>
<td>After 4 weeks of age</td>
<td>5.0 mg/kg</td>
<td>Twice daily</td>
</tr>
</tbody>
</table>

Sampling Schedule:
- First dose: Pre-dose, 1-2 hours post-dose, 6-10 hours 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.
- Week 5-6 of life: pre-dose, 3-6 hours.

PK parameters include:
- AUC (mg*h/L)
- Trough (mg/mL)
- Cmax (ng/mL)
- T1/2 (hr)
- Mean (CV)

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

**PK Parameters**

<table>
<thead>
<tr>
<th>After initial dose</th>
<th>1.5 mg/kg Once daily (n=7)</th>
<th>Day 15-18: 3.0 mg/kg Twice daily (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric Mean (CV)</td>
<td>Target</td>
<td>Geometric Mean (CV)</td>
</tr>
<tr>
<td>AUC (mg*h/L)</td>
<td>38.2 (38.4%)</td>
<td>40.5 (22.7%)</td>
</tr>
<tr>
<td>Trough (mg/mL)</td>
<td>9.48 (6.24%)</td>
<td>9.90 (7.25%)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>2350 (35.5%)</td>
<td>2680 (31.9%)</td>
</tr>
<tr>
<td>T1/2 (hrs)</td>
<td>15.8 (17.4%)</td>
<td>2.3 (67.1%)</td>
</tr>
</tbody>
</table>

**Results**

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

**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 ≥ 37 weeks & weight ≥ 2 kg
- Exclusion criteria:
  - Mother did not receive RAL during pregnancy
  - Elevated bilirubin requiring phototherapy
  - Receipt of disallowed medications - phenytoin, phenobarbital, ritonavir

**Safety Evaluations**

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

**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 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 have been studied in P1110:
  - Infants born to mothers who received RAL during pregnancy up through delivery
  - Low birth weight infants

**References**