Raltegravir (RAL)
Pharmacokinetics (PK) and Safety in Neonates: Washout PK of Transplacental RAL
(IMPAACT P1097)

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Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
Rationale

- Limited safety and dosing information for ARVs in neonates, both for PMTCT and for early treatment
- Urgent need for additional agents for neonates at high risk of HIV-1 infection
- Raltegravir (RAL) could play an important role in prophylaxis and treatment of neonates
  - RAL use associated with rapid decline in HVL
  - Integrase inhibitor - unique mechanism of action
  - Well tolerated in children and adults
  - Recently FDA approved in children ≥ 2 years of age
  - PK in children 4 weeks to 2 years under study
Background

- RAL elimination likely to be much slower in neonates
  - RAL metabolized primarily by UGT1A1
  - Same metabolic pathway as bilirubin
  - UGT1A1 activity greatly reduced in neonates but increases over the first months of life

- Concerns with elevated concentration due to:
  - Competition with bilirubin for albumin binding sites could result in kernicterus
    - Clinical effect unlikely unless RAL concentrations exceed typical peak concentration (~4500 ng/mL) by 50-100-fold\(^1\)
  - Unknown toxicities in infants?

\(^1\)Clarke DF, Wong RJ, Wenning L, Stevenson DK, Mirochnick M. “Effect of raltegravir on bilirubin binding. Submitted for Publication.”
Primary Study Objectives

- To determine the washout pharmacokinetics of RAL in infants born to HIV-infected pregnant women receiving RAL during pregnancy
- To evaluate the safety of in utero/intrapartum exposure to RAL in infants born to HIV-infected pregnant women receiving RAL during pregnancy
- To develop a neonatal RAL dosing regimen to be evaluated in a future protocol
Study Design

- Ongoing multicenter, washout pharmacokinetic trial of RAL in neonates born to HIV-infected pregnant women receiving RAL
- Sample size: 15 evaluable mother-infant pairs
- Mothers enroll at ≥ 35 weeks gestation
- Infants eligible for pharmacokinetic sampling if:
  - Born to mothers who received at least two weeks of RAL 400 mg twice daily prior to delivery
  - All maternal ARVs were continued during labor
  - Infant birth weight ≥ 2 kg, ≥ 37 weeks gestation
  - No serious or life threatening infant medical condition
Methods

- Maternal and umbilical cord blood samples were obtained within one hour of delivery.
- Whole blood samples collected from neonate at 4 time points: 1-5, 8-14, 18-24, and 30-36 hours after birth.
- RAL concentrations determined using a validated HPLC-MS-MS method.
- Half-life ($t_{1/2}$) in neonates estimated using the terminal 3 concentration-time points.
- Data presented as geometric mean (%CV).
- Genotyping for UGT1A1 polymorphisms pending.
Results

Patient population
- 12 mother-infant pairs enrolled but PK data available for 9 mother-infant pairs
- Race: 8 Black or African American; 3 White; 1 mixed race
- Mean gestational age: 37.5 weeks
- Mean weight: 3.33 kg

Mode of delivery: 3 spontaneous vaginal delivery; 1 forceps/vacuum; 8 C-section
Mean (CV) Cord Blood and Maternal Delivery RAL Concentrations (n=9)

<table>
<thead>
<tr>
<th></th>
<th>Cord Blood Concentrations</th>
<th>Maternal Delivery Concentrations</th>
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<tbody>
<tr>
<td><strong>RAL ng/mL</strong></td>
<td>880 (78%)</td>
<td>772 (113%)</td>
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<tr>
<td>Hours after maternal dosing</td>
<td>3.6 (58%)</td>
<td>3.7 (58%)</td>
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<tr>
<td><strong>CORD BLOOD/MATERNAL DELIVERY RATIO</strong></td>
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<tr>
<td>Cord Blood to Maternal Plasma Concentrations</td>
<td>1.14 (55%)</td>
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Cord Blood and Maternal Delivery Concentrations

**Graphs:**
- **Top Graph:**
  - X-axis: Hours Post Maternal Dosing
  - Y-axis: Raltegravir Concentration (ng/mL)
  - Data points for Cord Blood and Maternal Plasma

- **Bottom Graph:**
  - X-axis: Hours Post Maternal Dosing
  - Y-axis: Cord Blood/Maternal Plasma Ratio
  - Data points for Cord Blood/Maternal Plasma Ratio

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Neonatal RAL Washout PK

- Mean neonatal RAL concentration at 30-36 hrs after birth was 407 ng/mL
  - Range: 42.1-1401.5 ng/mL

- Mean neonatal t½ of RAL: 23.2 hours
  - Range: 9.3-87.8 hours
Neonatal RAL Concentration-Time Plots
Conclusions

- Cord blood to maternal plasma concentration ratio increases to ~1.5 by 3-4 hours after maternal dosing
- No safety issues identified over first 20 weeks of life after in utero RAL exposure
- Neonatal RAL elimination is highly variable
- Next step: investigate potential neonatal dosing regimens
  - Simulations combining these data plus PK data from 4 week-6 month olds in P1066 will be used to determine dose size and frequency for subsequent neonatal dosing protocol