Raltegravir (RAL) Pharmacokinetics (PK) and Safety in HIV-1 Exposed Neonates at High Risk of Infection: IMPAACT P1110


Disclosures: Travel support from Merck & Co., Inc., Kenilworth, NJ USA to attend HIV Pediatric Workshop.
ARVs in Neonates

- Safety and dosing information for antiretroviral drugs (ARVs) in neonates are limited
  - Prophylaxis and early treatment
- RAL first INSTI to be studied in young infants
- Study design for this unique patient population
  - Population PK and simulations to facilitate drug development in neonates
  - Design is being adapted for additional ARVs to be studied in neonates
- Collaboration between IMPAACT and industry for pediatric drug development
Population PK Approach to Neonatal-Dose Finding

• Pharmacokinetic analysis that uses sophisticated statistical techniques
• Sparse sampling data sets
• Estimates the population average and variance of PK parameters
Background and Rationale

- RAL has good safety and tolerability
- RAL is primarily metabolized by UGT1A1 enzyme
  - UGT activity low at birth and increases exponentially over the first weeks to months of life
  - High RAL plasma concentrations in vitro displace unconjugated bilirubin from albumin, potentially increasing neonatal risk of kernicterus (Clarke, et.al. PIDJ 2013)
  - RAL concentrations 50-100 X greater than typical peak concentrations (~ 5000 ng/mL)
Study Objectives

• To evaluate the PK, safety and tolerability of RAL oral granules for suspension when administered to HIV-1 exposed infants
Infant Inclusion/Exclusion Criteria

• Full-term infant aged ≤ 48 hours of age
• Infant gestational age at birth at least 37 weeks and weight ≥ 2 kg
• Exclusion criteria:
  – Elevated bilirubin requiring phototherapy
  – Receipt of disallowed medications - phenytoin, phenobarbital, rifampin
Neonates enrolled into 2 sequential cohorts:

– Cohort 1 (n=16): Infants received 2 single RAL doses one week apart (Clarke, et al. IAS 2015)

– Cohort 2 (n=30): Two groups of infants receive daily RAL dosing for first 6 weeks of life
  • Initial group: Infants born to mothers not receiving RAL
  • Subsequent group: Infants born to mothers who received RAL during pregnancy up through delivery
Determination of Cohort 2 Daily RAL Dose

• Population PK modeling and simulations using NONMEM
  – Data set included RAL concentration data from Cohort 1 and from infants and children enrolled in IMPAACT P1066
  – Developmental changes in absorption and clearance explored, with best fit if:
    • Absorption rate changed from 16% of max at birth to 90% at 2 weeks
    • Clearance changed from almost nil to a max at ~ 6 months of age
PK Targets and RAL Dose Selection

• Simulations used to evaluate potential Cohort 2 dosing regimens (Lommerse, et al. PAGE 2015)

• PK Targets:
  – Cmin > 33 ng/mL; Cmax < 8724 ng/mL
  – AUC12 (BID dosing) 6-20 mg*h/L
  – AUC24 (QD dosing) 12-40 mg*h/L

• Selected Cohort 2 dosing regimen:
  – Birth to day 7 of life: 1.5 mg/kg QD
  – 1 week to 4 weeks of age: Dose 3 mg/kg BID
  – 4 weeks to 6 weeks of age: 6 mg/kg BID
## Evaluation of Possible Dosing Regimens

Red – well outside of PK exposure target  
Orange – close to PK exposure target  
Green – within PK exposure target

<table>
<thead>
<tr>
<th>Regimen</th>
<th>1-7 (wk-1)</th>
<th>8-14 (wk-2)</th>
<th>15-21 (wk-3)</th>
<th>22-28 (wk-4)</th>
<th>29-35 (wk-5)</th>
<th>36-42 (wk-6)</th>
<th>Trough</th>
<th>Cmax</th>
<th>AUC24 (QD)</th>
<th>AUC12 (BID)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>2 QD</td>
<td></td>
<td></td>
<td></td>
<td>3 BID</td>
<td></td>
<td>Day42</td>
<td></td>
<td>Day2+3</td>
<td>Day2+3</td>
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<tr>
<td>2</td>
<td>3 QD</td>
<td>3 BID</td>
<td></td>
<td></td>
<td>4 BID</td>
<td></td>
<td>Day42</td>
<td></td>
<td>Day2+3</td>
<td>Day2+3</td>
</tr>
<tr>
<td>3</td>
<td>2 QD</td>
<td>2 BID</td>
<td></td>
<td></td>
<td>6 BID</td>
<td></td>
<td>Day28</td>
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<td>Day2+3</td>
<td>Day2+3</td>
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<tr>
<td>4</td>
<td>2 QD</td>
<td>2 BID</td>
<td></td>
<td></td>
<td>6 BID</td>
<td></td>
<td>Day2+3</td>
<td></td>
<td>Day14-16</td>
<td>Day14-16</td>
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<tr>
<td>5</td>
<td>3 QD</td>
<td>3 BID</td>
<td></td>
<td></td>
<td>6 BID</td>
<td></td>
<td>Day 14</td>
<td></td>
<td>Day2+3</td>
<td>Day2+3</td>
</tr>
<tr>
<td>6</td>
<td>2 QD</td>
<td>4 QD</td>
<td></td>
<td></td>
<td>6 BID</td>
<td></td>
<td>Day2+3</td>
<td></td>
<td>Day14-16</td>
<td>Day14-16</td>
</tr>
<tr>
<td>7</td>
<td>2 QD</td>
<td>3 BID</td>
<td></td>
<td></td>
<td>6 BID</td>
<td></td>
<td>Day2+3</td>
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<td>Day2+3</td>
<td>Day2+3</td>
</tr>
<tr>
<td>8</td>
<td>2 QD</td>
<td>6 QD</td>
<td></td>
<td></td>
<td>6 BID</td>
<td></td>
<td>Day 28</td>
<td></td>
<td>Day2+3</td>
<td>Day2+3</td>
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<tr>
<td>9</td>
<td>3 QD</td>
<td>3 BID</td>
<td></td>
<td></td>
<td>6 BID</td>
<td></td>
<td>Day2+3</td>
<td></td>
<td>Day2+3</td>
<td>Day2+3</td>
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<tr>
<td>10</td>
<td>1.5 QD</td>
<td>3 BID</td>
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<td>6 BID</td>
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Predicted RAL exposure for a typical cohort 2 subject receiving selected regimen during first 6 weeks of life
Cohort 2 PK Sampling

• Intensive PK sampling
  1. Initial dose of 1.5 mg/kg: pre-dose and 1-2, 6-10 and 20-24 hours post-dose
  2. Between 15-18 days of life after dose increased to 3 mg/kg BID: pre-dose and 1-2, 4-6, and 8-12 hours post-dose

• Sparse sampling
  1. After 2nd dose; each dose change; and at week 5-6 of life after dose increased to 6 mg/kg BID: pre-dose and 2 hour post-dose
Cohort 2 Demographics

- 12 infants: 7 from Brazil, 3 from South Africa, 2 from USA
- Infant demographics [n or median (range)]
  - Gender: 4 female/8 male
  - Gestational Age: 38 weeks (37-40)
  - Birth Weight (kg): 2.8 (2.4-3.7)
  - Mode of Delivery: 4 vaginal/8 caesarian section
# Cohort 2 Intensive PK results

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>Trough</th>
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<tr>
<td></td>
<td>Mean (range)</td>
<td>Met target</td>
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<tr>
<td><strong>AUC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial dose – 1.5 mg/kg QD (n=12)</td>
<td>37.0 (18.6-78.3) mg*h/L</td>
<td>8/12</td>
</tr>
<tr>
<td>Increased dose - 3.0 mg/kg BID (n=12)</td>
<td>11.8 (4.7-24.5) mg*h/L</td>
<td>9/12</td>
</tr>
</tbody>
</table>

PK targets: AUC24: 12-40 mg*h/L, AUC12: 6-20 mg*h/L, Trough concentration >33 ng/mL
Safety Evaluations

• No safety concerns observed with daily RAL administration through 6 weeks of life
  – Physical Exam
  – Hematology including CBC with differential and platelet count
  – Chemistries including AST, ALT, creatinine, total and direct bilirubin
  – HIV nucleic acid test (HIV NAT)
Initial Dose 1.5 mg/kg QD
Conclusions

• Population analysis and simulations can be used to facilitate drug development in neonates
• With initial 1.5 mg/kg dose, Cmin within target but AUC24 slightly above target range
  – Given the rapid increase in RAL metabolism over the first week of life, this exposure was considered acceptable
• With 3 mg/kg BID: day 15-18, AUC12 and Cmin within target range
• Daily RAL was well tolerated in infants receiving this regimen during the first 6 weeks of life
• P1110 Cohort 2 RAL-naïve (closed): 26 infants enrolled as of July 7
• Further modeling efforts are ongoing to allow enrollment of infants exposed to RAL in utero.
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