IMPAACT P1101

PHASE I/II DOSE-FINDING, SAFETY, TOLERANCE AND PHARMACOKINETIC STUDY OF A RALTEGRAVIR-CONTAINING ANTIRETROVIRAL THERAPY REGIMEN IN HIV-INFECTED AND TB CO-INFECTED INFANTS AND CHILDREN

Protocol Version 3.0

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PROTOCOL CO-CHAIR

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STUDY RATIONALE

- HIV/TB co-infection commonly encountered
- Rifampicin (RIF) induces CYP3A4 and phase II enzymes such as UDP-glucuronosyltransferases, altering the metabolism of many drugs (including ARVs)
- ARTs are needed that are well tolerated, potent, and have minimal interactions with Rifampicin-containing TB therapy

  Current options: Efavirenz, “superboosted” lopinavir/ritonavir

- RIF enhances glucuronidation and clearance of Raltegravir (RAL)

  In adults, doubling the dose of RAL when given in conjunction with RIF partially overcame this PK interaction \( \Rightarrow \) adequate RAL plasma \( C_{\text{max}} \) and AUC (no safety concerns)*

*Wenning et al AAC 2009
Primary Objectives

- To determine the pharmacokinetics and appropriate dose of RAL when administered with a RIF-containing anti-TB therapy in HIV/TB co-infected infants and children that generates PK parameters generally comparable to those seen in HIV-infected infants and children in the absence of RIF.

- To determine safety and tolerance of RAL-containing ART when administered with a RIF-containing anti-TB therapy in HIV/TB co-infected infants and children.
SECONDDARY OBJECTIVES

- To describe the short-term treatment outcomes of infants and children using a RAL-containing ART regimen co-treated with a RIF-containing TB treatment.

- To explore whether infants and children receiving a RAL-containing ART regimen, co-treated with a RIF-containing TB treatment, develop ARV drug associated resistance mutations.
AGE COHORTS

- Cohort I: ≥ 2 to < 6 years
- Cohort II: ≥ 6 to < 12 years
- Cohort III: ≥ 4 weeks to < 2 years of age
PHARMACOKINETIC TARGETS FOR RALTEGRAVIR

GM $C_{12h}$ of approximately $\geq 75$ nM ($\geq 33$ ng/mL)

GM RAL $AUC_{0-12h}$ of approximately 14 to 45* $\mu$M-hr (6.2 to 20 mg-h/L)

Note: Protocol mandates that individuals with an $AUC_{0-12h} \geq 63$ $\mu$M-hr* must stop taking RAL
(Their PK and safety data will be used in the assessment of the dose for that cohort)

*Mean $AUC_{0-12h}$ in the RAL QTc study (P024)
STATISTICAL DESIGN
SAFETY GUIDELINES

MINI-COHORT: Initial Safety Guidelines for the Evaluation of Starting Doses For the First (n=6) of Each Age Mini-Cohort

The dose will pass if none of the 6 participants from the mini-cohort has experienced:

- Death or a life threatening Grade 4 adverse event (AE) deemed at least possibly related to the RAL,
- Any Grade 4 event that is probably or definitely attributable to RAL,
- No more than 2/6 participants have permanently discontinued RAL due to a Grade 3 or Grade 4 adverse event deemed at least possibly related RAL, then the starting dose for the mini-cohort passed the initial safety guidelines.

FULL-COHORT: Final Evaluation of Starting Doses For the Full-Cohort of Each Age Group (all n=12)

The dose will pass if none of the 12 participants from the full-cohort has experienced

- Death or a life threatening Grade 4 AE deemed at least possibly related to the RAL,
- Any Grade 4 event that is probably or definitely attributable to RAL,
- No more than 33% of the participants have permanently discontinued RAL due to a Grade 3 or Grade 4 AE deemed at least possibly related RAL, then the starting dose for the full-cohort passed the final safety guidelines.
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose</th>
<th>Total Accrual N</th>
<th>Total On Tx</th>
<th>Total Off Tx / On Study</th>
<th>Total Off Study</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort I ≥ 2 to &lt; 6 yo</td>
<td>12mg/kg BID RAL chewable</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>Final Dose Recommended</td>
</tr>
<tr>
<td>Cohort II ≥ 6 to &lt; 12 yo</td>
<td>12mg/kg BID RAL chewable</td>
<td>14</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>Final Dose Recommended</td>
</tr>
<tr>
<td>Cohort III ≥ 4wks to &lt; 2 yo</td>
<td>12mg/kg BID RAL chewable as a dispersible</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>Open at all 4 sites since Dec 2017</td>
</tr>
</tbody>
</table>

*Cohort I: All (12) all completed treatment. 
Cohort II: Early Discontinuations: (1) due to liver toxicity; (1) due to non-compliance; (2) due to AUC<sub>0-12h</sub> ≥ 63 μM-hr (both asymptomatic)
Cohort III: Early Discontinuation: (1) due to AUC<sub>0-12h</sub> ≥ 63 μM-hr (asymptomatic)*
Results From Intensive PK Studies: Cohort I (≥2 to 6 yo)

PK Results

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
<th>CV</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM AUC_{12h}</td>
<td>28.8 µM-h</td>
<td>50%</td>
<td>14-45 µM-h</td>
</tr>
<tr>
<td>GM C_{12h}</td>
<td>229 nM</td>
<td>76%</td>
<td>≥ 75 nM (33ng/ml)</td>
</tr>
</tbody>
</table>

Median Concentrations with 10^{th} and 90^{th} Percentiles (n = 12)
Results From Intensive PK Studies: Cohort II (≥6-12 yo)

Confidential and Preliminary

PK Results

GM AUC$_{12h}$ 38.8 µM-h (CV=38%)  Target: 14-45 µM-h

GM C$_{12h}$ 228 nM (CV=78%)  Target: ≥ 75 nM (33ng/ml)
SAFETY RESULTS CONFIDENTIAL AND PRELIMINARY

Cohort 1
- 3 yo male
- Week 4
  - Grade 3 AST/ALT
- Possibly related to RAL.
- RAL and other ARVs were temporarily held for 3 weeks, then resumed RAL+ARVs until the end of the study.

Cohort 2
- 9 yo female
- Week 2
  - Grade 4 AST/ALT
  - Grade 3 Total Bilirubin
  - Grade 2 Rash
  - Grade 4 Drug induced hepatitis
- All events were assessed as possibly related to RAL (Core Team/SMC)
- Treatment was permanently discontinued with close follow-up.
- IRIS and medication other than RAL could have explained this event.
Virologic Success: Achieving at least 1-\(\log_{10}\) copies/mL drop from baseline OR HIV RNA \(\leq 400\) copies/mL at Week 8

Note: Week 8 \(\log_{10}\) HIV-RNA Change from Baseline: Median: \(-3.16\), IQR: \((-3.79, -2.55)\).

Note: Week 8 \(\log_{10}\) HIV-RNA Change from Baseline: Median: \(-2.78\), IQR: \((-3.41, -2.09)\).
FUTURE PLANS

- **Cohort I:** Data presented at CROI 2018

- **Cohort II:** Current dose has passed PK and safety targets
  - Data to be presented at 10th International Workshop on HIV-Pediatrics
  - Follow-up continues for 3 participants
  - Co-publication of data from of Cohorts I and II planned

- **Cohort III:** Enrollment continuing
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