# 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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# 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 ➔ adequate RAL plasma $C_{max}$ 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.

# SECONDARY 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 ≥ 75 nM | (≥ 33 ng/mL) |
| GM RAL $AUC_{0\text{-}12h}$ | of approximately 14 to 45* μM-hr | (6.2 to 20 mg-h/L) |

*Note: Protocol mandates that individuals with an $AUC_{0\text{-}12h}$ ≥ 63 μM-hr* must stop taking RAL*

*(Their PK and safety data will be used in the assessment of the dose for that cohort)*

*Mean $AUC_{0\text{-}12h}$ 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

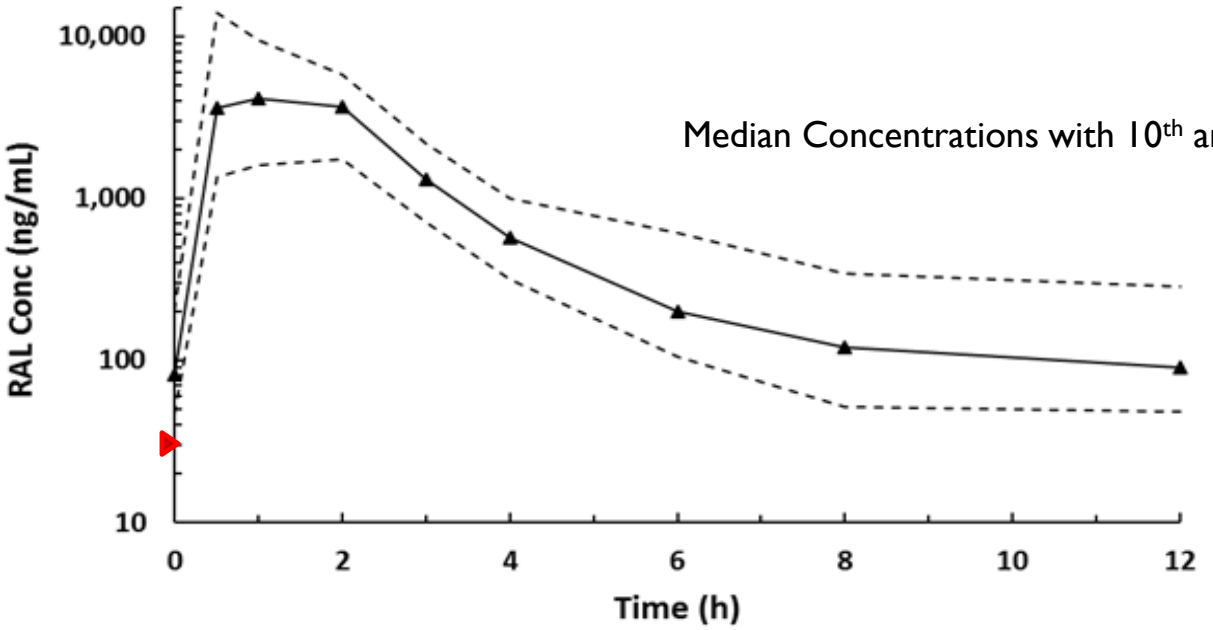
- Death or a life threatening Grade 4 AE deemed at least possibly related to the RAL,
- Any Grade 4 event that is probably or definitely attributable to RAL,
- No more than 33% of the participants have permanently discontinued RAL due to a Grade 3 or Grade 4 AE deemed at least possibly related RAL, then the starting dose for the full-cohort passed the final safety guidelines.

# STUDY STATUS (13 JUNE 2018)

| Cohort | Dose | Total Accrual N | Total On Tx | Total Off Tx / On Study | Total Off Study | Status |
|---|---|---|---|---|---|---|
| Cohort I ≥ 2 to < 6 yo | 12mg/kg BID RAL chewable | 12 | 0 | 0 | **12** | Final Dose Recommended |
| Cohort II ≥ 6 to < 12 yo | 12mg/kg BID RAL chewable | 14 | 2 | 1 | 11 | Final Dose Recommended Follow-up for 3 continues |
| Cohort III ≥ 4wks to < 2 yo | 12mg/kg BID RAL chewable as a dispersible | 4 | 3 | 1 | 0 | Open at all 4 sites since Dec 2017 |

*Cohort I: All (12) all completed treatment.*
*Cohort II: Early Discontinuations: (1) due to liver toxicity; (1) due to non-compliance; (2) due to $AUC_{0\text{-}12h} \geq 63$ μM-hr ( both asymptomatic)*
*Cohort III: Early Discontinuation: (1) due to $AUC_{0\text{-}12h} \geq 63$ μM-hr (asymptomatic)*

# Results From Intensive PK Studies : Cohort I (≥2 to 6 yo)



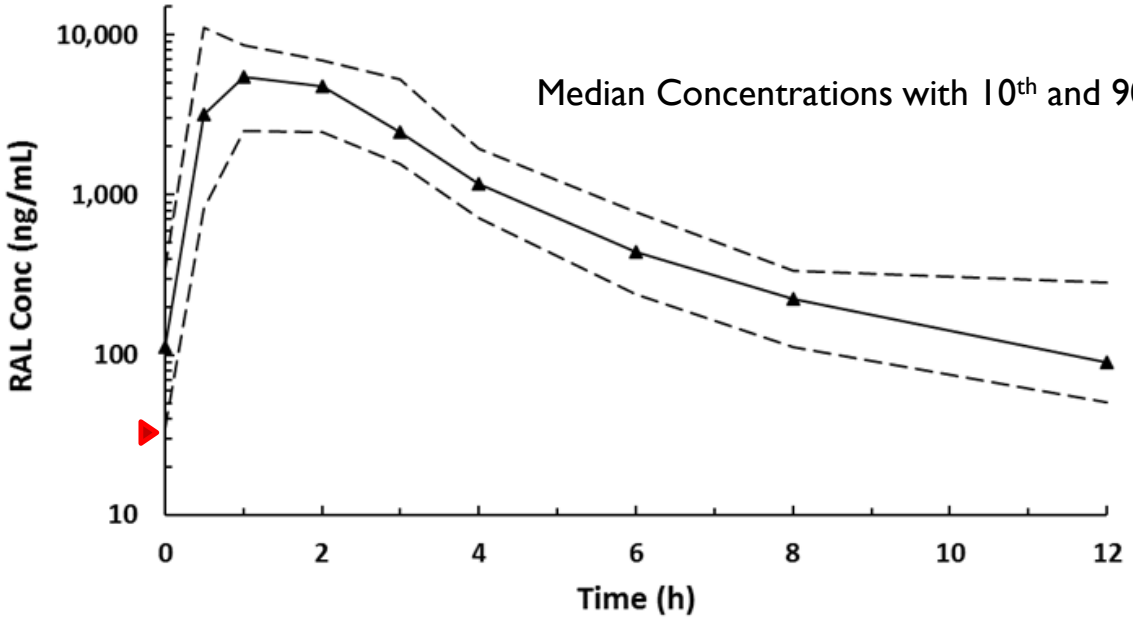

Median Concentrations with 10th and 90th Percentiles (n =12)

PK Results

| | | | |
|---|---|---|---|
| GM $AUC_{12h}$ | 28.8 µM-h | (CV=50%) | Target: 14-45 µM-h |
| GM $C_{12h}$ | 229 nM | (CV=76%) | Target: ≥ 75 nM (33ng/ml) |

# 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.

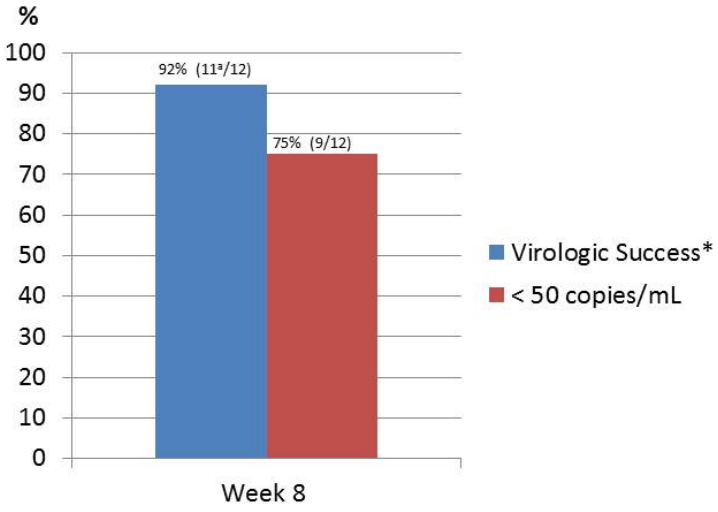
**Cohort 2**

- 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 RESPONSE *CONFIDENTIAL AND PRELIMINARY*

## Cohort I

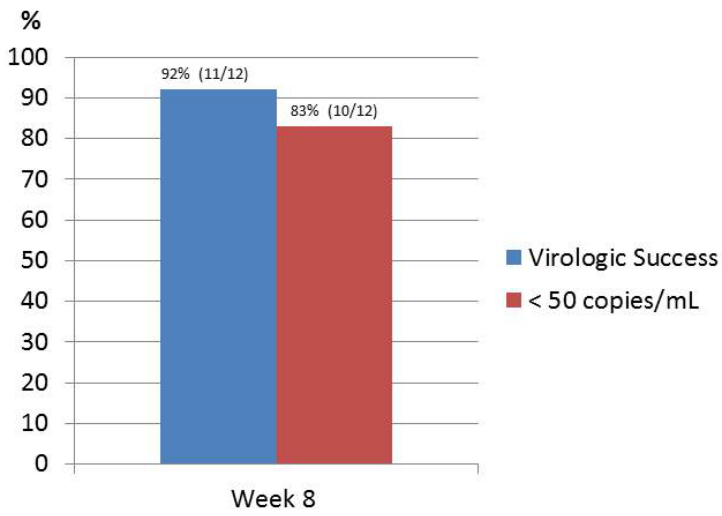
Virologic Response
(As Treated Analysis)




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

## Cohort II

Virologic Response
(As Treated Analysis)




Note: Week 8 $Log_{10}$HIV-RNA Change from Baseline: Median: -2.78, IQR (-3.41,-2.09).

Virologic Success: Achieving at least 1- $log_{10}$ copies/mL drop from baseline <u>Or</u>
HIV RNA ≤ 400 copies/mL at Week 8

# 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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