IMPAACT P1101

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

Protocol Version 3.0

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IMPAACT

International Maternal Pediatric Adolescent AIDS Clinical Trials Network

STUDY RATIONALE

- Need for ART agents that are well-tolerated, potent, and have minimal interactions with Rifampicin-containing TB therapy.
- Raltegravir (RAL)
  - Chewable tablets approved for the treatment of HIV-1 infection in pediatric patients 2 to <12 years of age and weighing at least 10 kg
  - Granules approved for oral suspension in December 2013 for children four weeks of age and older, weighing ≥ 3 kg to < 20 kg
- Rifampicin induces phase II enzymes such as UDP-glucuronosyl transferase and RAL undergoes glucuronidation in the liver
- *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)*

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 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.

IMPAACT P1101 STUDY DESIGN

- Children diagnosed with TB, taking rifampicin-containing TB treatment, but no ARV are eligible for enrolment

  Cohort 1: ≥ 2 to < 6 years old
  Cohort 2: ≥ 6 to < 12 years old
  } Enrolling under Version 2.0

  Cohort 3: ≥ 4 weeks to < 2 years old (awaiting approval of Version3.0)

- Cohorts enroll simultaneously
  - Mini cohort 6 participants in each
  - Additional 6 if mini cohort passes safety and PK
- Regimen:
  - Chewable formulation of Raltegravir 12mg/kg (double approved dose) and 2 NRTI's
    - For cohort 3 Chewable formulation will be studied as a dispersible tablet
  - 12-hour intensive PK at 5-8 days after raltegravir started
  - Add 4th drug (standard of care e.g. EFV/LPV/r)
  - Discontinue raltegravir after TB treatment stopped – continue with SOC regimen
  - Participants followed for 3 months after raltegravir stopped

RATIONALE FOR STUDYING RAL CHEWABLE AS A DISPERSIBLE TABLET

- Administration of RAL granules for oral suspension formulation is complex
- Merck has generated biocomparison and modeling data indicating that the RAL chewable tablet used in 25 mg dose increments → appropriate PK in children < 10 kg
  - Data indicate that the 25 mg chewable tablet can be used as a dispersible tablet, meeting WHO dispersibility criteria after simple crushing or pre-wetting .
- A uniform pediatric formulation of raltegravir which is chewable and dispersible assists the harmonization process for ARV formulations recommended by the WHO

STATISTICAL DESIGN
SAFETY AND PK GUIDELINES

Safety Guidelines for the Evaluation of Starting Doses For the First (n=6) of Each Age Mini-Cohort and final evaluation for full cohort (n=12) – data through 1st 4 weeks on RAL

- No Death or a life threatening Grade 4 adverse event (AE) deemed at least possibly related to the RAL, any Grade 4 event probably or definitely attributable to RAL
- No more than 1/3 participants have permanently discontinued RAL due to a Grade 3 or Grade 4 adverse event deemed at least possibly related RAL

12 Hour- intensive PK sampling: 5-8 days after starting RAL, performed in real time and reported to the protocol team, no individualized PK-driven dose adjustments

PK Guidelines

The full cohort can be enrolled after the mini-cohort (n = 6) at a RAL dose achieves:

- A geometric mean (GM) RAL $AUC_{0\text{-}12hr}$ of approximately 14 to 45 μM-hr; AND
- An approximate GM $C_{12h} \geq 75$nM, and meets safety criteria,

The data from all n=12 participants will be used in the evaluation of dose using the same criteria.

Note: If any individual has an $AUC_{0\text{-}12hr} \geq 63$ μM-hr, the participant will stop taking RAL.

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STUDY STATUS

- The study is conducted at four sites in South Africa

Cohort	Dose	Total On Tx	Total Off Tx/ On Study	Total Off Study	Enrollment Status
Cohort I ≥ 2 to < 6 yo	12mg/kg BID RAL chewable	6	2	4	(n=12) Fully Accrued **Final Dose Recommended**
Cohort II ≥ 6 to < 12 yo	12mg/kg BID RAL chewable	3	0	6	(n=9) 4 more participants needed to complete the full cohort
Cohort III ≥ 4 wks to < 2 yo	12mg/kg BID RAL chewable as a dispersible	-	-	-	Expected to begin enrollment in late 2017, pending site approvals of V3

P1101 Pharmacokinetic Results for RAL
Cohort I: 2 to <6 yo

	Age (yrs)	Weight (kg)	Dose (mg/kg)	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	C_{12h} (ng/mL)	AUC_{12} (mgxh/L)	C_{12h} (nM)	AUC_{12} (µMxh)
avg	3.5	14.6	12.4	5.5	1.2	7124.5	139.5	14.7	313.8	33.0
sd	1.2	3.8	1.3	4.1	0.9	5426.4	106.3	7.4	239.3	16.6
min	2.0	10.1	10.5	1.4	0.5	1328.5	18.8	4.0	42.3	9.0
max	5.0	22.9	14.9	14.3	3.2	17413.0	334.9	25.8	753.5	58.1
gm	3.3	14.2	12.3	4.3	0.9	5207.6	101.8	12.8	229.1	28.8

Protocol Defined PK Targets

GM C12h: ≥ 75nM (> 33 ng/mL)

GM AUC_{12}: 14 to 45 µMxhr (6.2 to 20 mgxh/L)

N = 12

P1101 Pharmacokinetic Results for RAL
Cohort II: 6 to <12 yo

	Age (yrs)	Weight (kg)	Dose (mg/kg)	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	C_{12h} (ng/mL)	AUC_{12} (mgxh/L)	C_{12h} (nM)	AUC_{12} (µMxh)
avg	8.5	22.3	12.3	3.8	1.2	5808.7	130.8	16.8	294.3	37.9
sd	1.7	2.7	1.3	2.0	0.6	2130.9	108.7	5.5	244.6	12.3
min	6.0	17.3	9.9	1.8	0.5	3029.2	48.3	10.1	108.7	22.7
max	11.0	26.0	13.8	7.7	2.0	9647.6	354.6	28.1	797.9	63.3
gm	8.3	22.2	12.2	3.4	1.0	5461.1	102.2	16.1	229.9	36.3

Protocol Defined PK Targets

GM C12h: ≥ 75nM (> 33 ng/mL)

GM AUC_{12}: 14 to 45 µMxhr (6.2 to 20 mgxh/L)

N = 8

SAFETY

To date, there have been no death, life-threatening Grade 4 AEs deemed at least possibly related to RAL or Grade 4 AE at least probably/definitely related to RAL; only (1) permanently discontinued treatment early due to Grade 4 LFTs possibly related to RAL

The following were assessed by the site and P1101 Protocol Team as at least possibly related to RAL:

Cohort I

- (1) Participant 3 yo male
- At week 4 had Grade 3 AST and Grade 3 ALT
- Assessed by the site and Protocol Team as possibly related to RAL.
- RAL and other ARVs were temporarily held for 3 weeks, then resumed RAL+ARVs.
- Currently on study at Week 13

Cohort II

- (1) Participant, 9 yo female
- Beginning at week 2 on study, participant had a Grade 4 AST, Grade 4 ALT, Grade 3 Total Bilirubin, Grade 2 Rash, Grade 4 Drug induced hepatitis
- All events were assessed as possibly related to RAL.
- Per the Study Monitoring Committee (SMC), the event was assessed as possibily related to RAL, and treatment was permanently discontinued with close follow-up.

VIROLOGIC RESPONSE

- RNA data shows that all participants ***(except one)*** achieved at least 1-$\log_{10}$ drop in HIV-1 RNA from entry or undetectable by week 4 onwards, while on-treatment.
  - The only exception is a participant enrolled in Cohort II under protocol Version 1.0, who permanently discontinued RAL ***at week 2*** due to Grade 4 LFTs (deemed to be at least possibly related to RAL).
- One participant in Cohort I with temporary RAL hold due to Grade 3 AST and Grade 3 ALT at Week 4 on study.
  - Had 3 $\log_{10}$ decrease in HIV-1 RNA from baseline to week 4
  - Viral rebound shortly after temporarily holding RAL.
  - Team is waiting confirmation of HIV-1 RNA results since resumption of therapy.

LESSONS

- Co-treating HIV/TB patients is challenging, need to anticipate more events because the children are sick, and are receiving polypharmacy
- Attribution of events to study drug (RAL) has caused some confusion
- Despite difficulties, important to persist with studies in these children if we want to improve treatment regimens for these populations

FUTURE PLANS

- **Cohort I**: Abstract for CROI 2018
- **Cohort II**: The final dosing recommendations will be made upon completion of accrual of the full cohort, expected to be completed by October 2017.
- **Cohort III**: Enrollment into this cohort is expected to be begin in late 2017, pending site IRB/MCC approvals of protocol Version 3.0.

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