IMPAACT P1110: RALTEGRAVIR PHARMACOKINETICS AND SAFETY IN HIV-1 EXPOSED NEONATES: DOSE-FINDING STUDY

CROI 2017
Poster # 757

Diana F. Clarke[1], Edward P. Acosta[2], Anne Chain[3], Mae Cababasay[4], JiaJia Wang[4], Hedy Teppler[3], Betsy Smith[5], Rohan Hazra[6], [7]Stephanie Popson, [7]Bobbie Graham, [8]Kat Calabrese, [9]Yvonne Bryson, [10]Stephen A. Spector, [11]Jos Lommerse, [12]Mark Mirochnick, and the IMPAACT P1110 Protocol Team

[1]Boston Medical Center, Boston, MA, United States; U of Alabama at Birmingham, Birmingham, AL; [3]Merck Research Laboratories; [4]Statistical and Data Analysis Center, Harvard School of Public Health, Boston, MA; [5]NIH, NIAID, Division of AIDS, Bethesda, MD; [6]Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NIH, Bethesda, MD; FSTRF, Buffalo, NY; [8] FHI 360, Durham, NC; [9]UCLA, Los Angeles, CA; [10] UCSD, La Jolla, CA; [11]Certara, Oss, The Netherlands; [12]Boston University School of Medicine, Boston, MA

Objectives

- To evaluate the PK, safety and tolerability of RAL oral granules for suspension when administered to HIV-1 exposed infants

Background

- While antiretroviral drugs (ARVs) are used in neonates for prophylaxis of perinatal transmission or early intensive treatment of neonates with HIV infection, safety and dosing information in neonates are limited
- Raltegravir (RAL) first INSTI to be available in formulation suitable for use in young infants
  - RAL has good safety and tolerability
  - RAL is primarily metabolized by UGT1A1 enzyme
  - UGT1A1 activity low at birth and increases exponentially over the first weeks to months of life[1,2]
  - In vitro study suggests that RAL plasma concentrations may displace unconjugated bilirubin from albumin, increasing neonatal risk of kernicterus, at plasma concentrations 50-100 X greater than typical peak concentrations (~ 5000 ng/mL)[3]
- Raltegravir elimination in neonates following maternal dosing was highly variable and is reflective of low neonatal UGT1A1 enzyme activity at birth [4]
- PK and safety data from an initial cohort of 15 infants receiving 2 single doses of RAL during the first week of life has been previously reported[5]
- A population PK model using NONMEM was developed incorporating PK data from the first 6 infants from initial cohort and from 24 infants and children ages 4 weeks to < 2 years enrolled in IMPAACT P1066, a Phase I/II, multi-center, open-label, non-comparative intensive PK study of RAL in infants and children.[6,7] Model included maturation of:
  - Absorption rate from 16% of max at birth to 90% at 2 weeks
  - Clearance from almost nil to a max at ~ 6 months of age
- Model used to perform simulations of possible daily dosing regimens for new cohort of infants[8]

Regimen	1-7 (wk-1)	8-14 (wk-2)	15-21 (wk-3)	22-28 (wk-4)	29-35 (wk-5)	36-42 (wk-6)	Trough	Cmax	AUC24 (QD)	AUC12 (BID)
1	2 QD	3 BID			4 BID		Day42		Day2+3	
2	3 QD	3 BID			4 BID		Day42		Day2+3	
3	2 QD	2 BID			6 BID		Day28		Day2+3	
4	2 QD	2 BID	6 BID						Day2+3	Day14-16
5	3 QD		3 BID		6 BID		Day 14		Day2+3	
6	2 QD	4 QD	6 BID						Day2+3	Day14-16
7	2 QD	3 BID			6 BID				Day2+3	
8	2 QD	6 QD			6 BID		Day 28		Day2+3	
9	3 QD	3 BID			6 BID				Day2+3	
10	1.5 QD	3 BID			6 BID					

Acknowledgements

The authors wish to thank the infants that participated in these protocols and their families and the staff of the participating research sites. Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH).

Materials and Methods

- Infants born to HIV infected mothers and at high risk of mother to child HIV transmission were enrolled
- Inclusion Criteria:
  - Full-term infant aged ≤ 48 hours of age
  - Gestational age at birth at least 37 weeks & weight ≥ 2 kg
- Exclusion criteria:
  - Mother did not receive RAL during pregnancy
  - Elevated bilirubin requiring phototherapy
  - Receipt of disallowed medications - phenytoin, phenobarbital, rifampin
- Raltegravir Dosing Table:

	Oral granules for suspension	Frequency
Day 1 to 7 of life	1.5 mg/kg	Once daily
Day 8 to 28 of life	3.0 mg/kg	Twice daily
After 4 weeks of age	6.0 mg/kg	Twice daily

- Sampling Schedule:
  - First dose: Pre-dose, 1-2 hours post-dose, 6-10 hour post-dose, and 20-24 hours post-dose;
  - Second dose: 3-6 hours post-dose
  - Day 6-9 of life: pre-dose
  - Day 15-18 of life: Pre-dose, 1-2 hours post-dose, 4-6 hours post-dose, 8-12 hours post-dose
  - Day 28-32 of life: pre-dose
  - Week 5-6 of life: pre-dose, 3-6 hours
  - PK samples were analyzed for RAL concentrations using a validated HPLC-MS-MS method LLOQ=10 ng/mL
- Protocol exposure targets for each subject are AUC_{24} 12-40mg*h/L, AUC_{12} 6-20 mg*h/L, C_{12} or C_{24} > 33ng/mL, and C_{max} < 8724 ng/mL
- Safety was assessed based on clinical and laboratory evaluations
  - Hematology including CBC and platelet count
  - Chemistries including AST, ALT, creatinine, total and direct bilirubin
  - HIV nucleic acid test (HIV NAT)

Results

- Twenty-six RAL-naïve infants were enrolled in Cohort 2. Evaluable PK results and 6 week safety data are available for 25 infants.

Demographics

- 26 infants: 17 Brazil, 3 South Africa, 6 USA
- Sex: 12 (46%) female /14 (54%) male
- Gestational Age: 38.5 weeks (37.0-40.9)
- Birth Weight (kg): 2.93 (2.39-3.75)
- Mode of Delivery: 5 (19%)vaginal/ 21 (81%) cesarean
- Race: Black or African American 18 (69%); White 3 (12%); Other 5 (19%)
- Ethnicity: Hispanic/Latino 19 (73%); Not Hispanic/Latino 7 (27%)

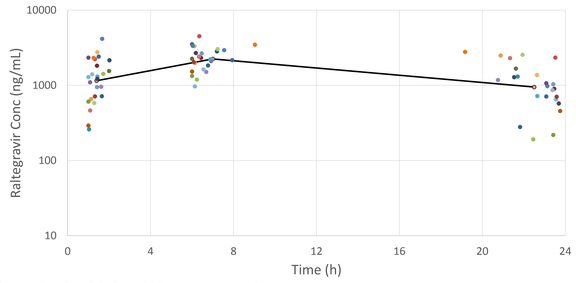
Safety Evaluations

- No drug-related adverse events were observed
- No infants required interventions for elevated bilirubin levels
- All HIV NAT test results were negative

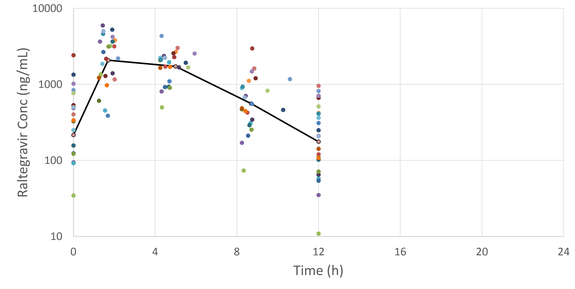
Results

PK Parameters	After initial dose: 1.5 mg/kg Once Daily (n=25)		Day 15-18: 3.0 mg/kg Twice Daily (n=24)	
	Geometric Mean (CV)	Target	Geometric Mean (CV)	Target
AUC (mg*h/L)	38.2 (38.4%)	Above - 11 Met - 13 Below - 0	14.3 (43.3%)	Above - 8 Met - 14 Below - 1
Trough (ng/mL)	948 (64.2%)	Above - 25 Below - 0	176 (93.8%)	Above - 22 Below - 1
Cmax (ng/mL)	2350 (35.0%)	Above - 0 Below - 25	2850 (41.9%)	Above - 0 Below - 24
Tmax (ng/mL)	5.4 (57.5%)	-------	2.3 (67.1%)	-------
T1/2 (hrs)	15.8 (174.8%)	-------	2.5 (33.5%)	-------
PK targets: AUC24: 12-40 mg*h/L, AUC12: 6-20 mg*h/L, Trough concentrations > 33 ng/mL				

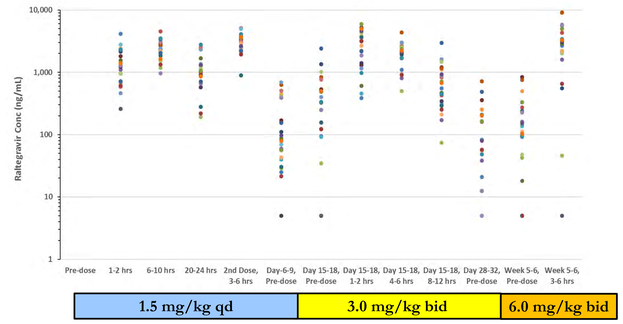
<48 hours of life – initial dose 1.5 mg/kg qd



Day 15-18 of life - 3.0 mg/kg bid



Raltegravir concentrations from all sampling time points



Conclusions

- Daily RAL was safe and well tolerated during the first 6 weeks of life.
- All GM protocol exposure targets were met.
- In some infants AUC_{24} following the initial dose was slightly above target range but this was considered acceptable given the rapid increase in RAL metabolism over the first week of life.
- The PK targets and the safety guidelines have been met for RAL-unexposed infants in cohort 2 using the specified dosing regimen.
- Subsequent groups to be studied in P1110:
  - Infants born to mothers who received RAL during pregnancy up through delivery
  - Low birth weight infants

References

[1] Krekels EH, Danhof M, Tibboel D, et.al. Ontogeny of hepatic glucuronidation; methods and results. Curr Drug Metab. 2012;13:728-43.

[2] Kawade N, Onishi S., The prenatal and postnatal development of UDP-glucuronyltransferase activity towards bilirubin and the effect of premature birth on this activity in the human liver. Biochem J. 1981;196:257-60.

[3] Clarke DF, Wong RJ, Wenning L, Stevenson DK, Mirochnick M. Raltegravir in vitro effect on Bilirubin Binding. Pediatr Infect Dis J. 2013;32:978-80.

[4] Clarke DF, Acosta EP, Rizk ML, et.al. Raltegravir pharmacokinetics in neonates following maternal dosing. J Acquir Immun Defic Syndr. 2014;67:310-315.

[5] Clarke, D., E. P. Acosta, J. Lommerse, A. Chain, H. Witjes, E. Capparelli, H. Teppler, C. Welebob, Y. Bryson, M. P. Cababasay, D. Wang, B. Graham, A. Calabresi, M. Rizk, L. Wenning, T. Kerbusch, S. Spector, B. Smith, M. Mirochnick and P1110 Team (2015). Raltegravir (RAL) pharmacokinetics (PK) and safety in HIV-1 exposed neonates at high risk of infection (IMPAACT P1110). 8th International AIDS Conference. Vancouver, Canada.

[6] Nachman S, Alvero C, Acosta EP, et.al. Pharmacokinetics and 48-Week Safety and Efficacy of Raltegravir for Oral Suspension in Human Immunodeficiency Virus Type-1-infected Children 4 Weeks to 2 Years of Age. J Ped Infect Dis 2015; doi: 10.1093.jpids/piu146.

[7] Rizk ML, Du L, Bennetto-Hood C, et.al. Population pharmacokinetic analysis of raltegravir pediatric formulations in HIV-infected children 4 weeks to 18 years of age. J Clin Pharmacol 2015; 55:748-756.

[8] Lommerse, J., D. Clarke, A. Chain, H. Witjes, H. Teppler, E. Capparelli, E. P. Acosta, M. Rizk, L. Wenning, T. Kerbusch, S. Spector, B. Smith and M. Mirochnick (2015). Raltegravir dosing in neonates (IMPAACT P1110) – Use of allometry and maturation in PK modeling to develop a daily dosing regimen for investigation during the first weeks of life. Population Approach Group Europe (PAGE) Conference. Hersonissos, Crete, Greece.