

Diana F. Clarke¹, Edward P. Acosta², Anne Chain³, Mae Cababasay⁴, JiaJia Wang⁴, Hedy Teppler³, Betsy Smith⁵, Rohan Hazra⁶, ⁷Stephanie Popson, ⁷Bobbie Graham, ⁸Kat Calabrese, ⁹Yvonne Bryson, ¹⁰Stephen A. Spector, ¹¹Jos Lommerse, ¹²Mark Mirochnick, and the IMPAACT P1110 Protocol Team

¹Boston Medical Center, Boston, MA, United States; ²U of Alabama at Birmingham, Birmingham, AL; ³Merck Research Laboratories; ⁴Statistical and Data Analysis Center, Harvard School of Public Health, Boston, MA; ⁵NIH, NIAID, Division of AIDS, Bethesda, MD; ⁶Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NIH, Bethesda, MD; ⁷FSTRF, Buffalo, NY; ⁸FHI 360, Durham, NC; ⁹UCLA, Los Angeles, CA; ¹⁰UCSD, La Jolla, CA; ¹¹Certara, Oss, The Netherlands; ¹²Boston 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 birth⁴
- 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 reported⁵
- 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 infants⁸

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				Day 42	Day 2+3		
2	3 QD		3 BID		4 BID		Day 42	Day 2+3		
3	2 QD		2 BID		6 BID		Day 28	Day 2+3		
4	2 QD	2 BID		6 BID			Day 2+3	Day 14-16		
5	3 QD		3 BID		6 BID		Day 14	Day 2+3		
6	2 QD	4 QD		6 BID			Day 2+3	Day 14-16		
7	2 QD		3 BID		6 BID			Day 2+3		
8	2 QD		6 QD		6 BID		Day 28	Day 2+3		
9	3 QD		3 BID		6 BID		Day 2+3			
10	1.5 QD		3 BID		6 BID					

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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 AUC₂₄ 12-40mg*h/L, AUC₁₂ 6-20 mg*h/L, C₁₂ or C₂₄ > 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

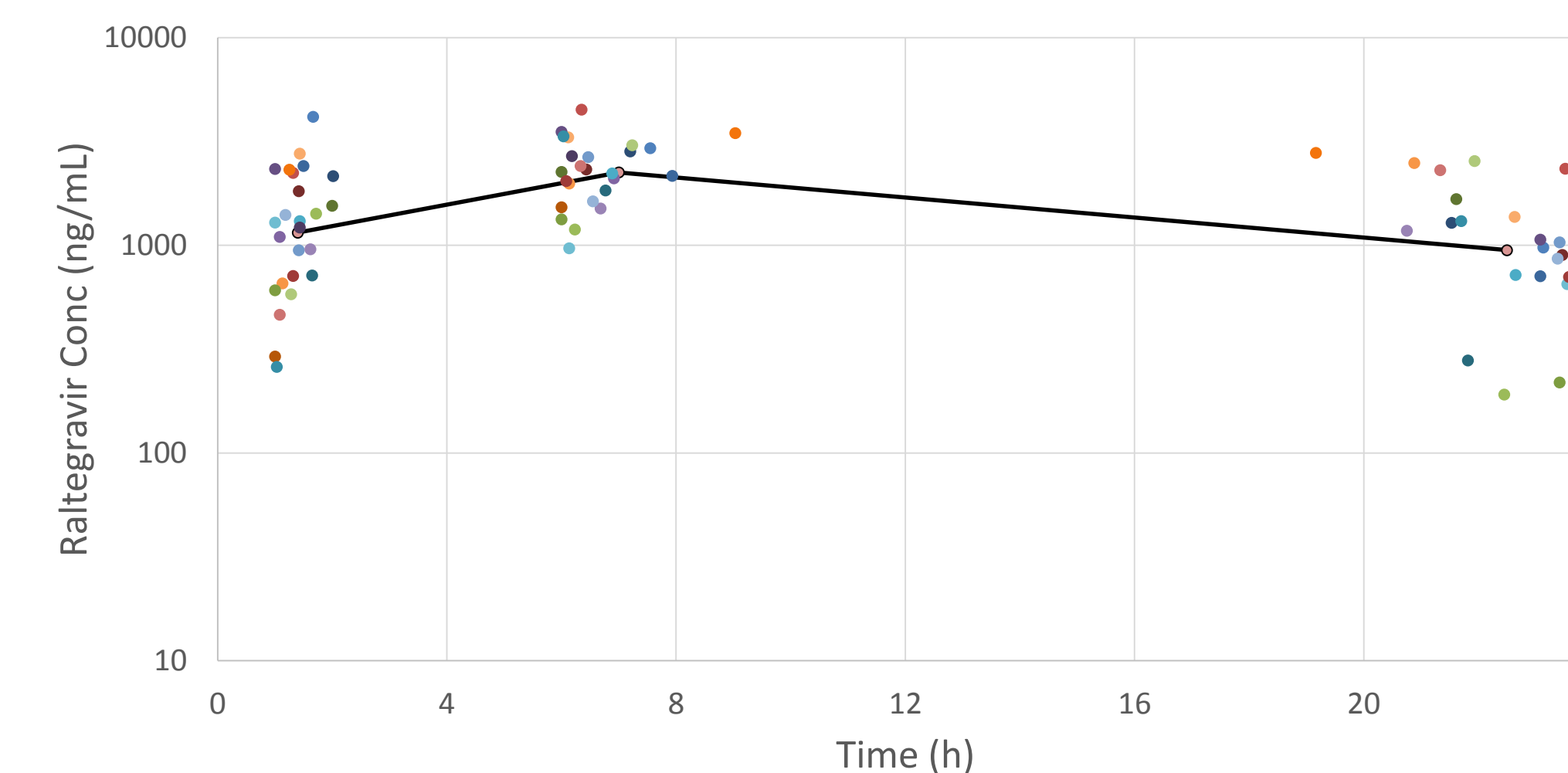
- No drug-related adverse events were observed
- No infants required interventions for elevated bilirubin levels
- All HIV NAT test results were negative

Results

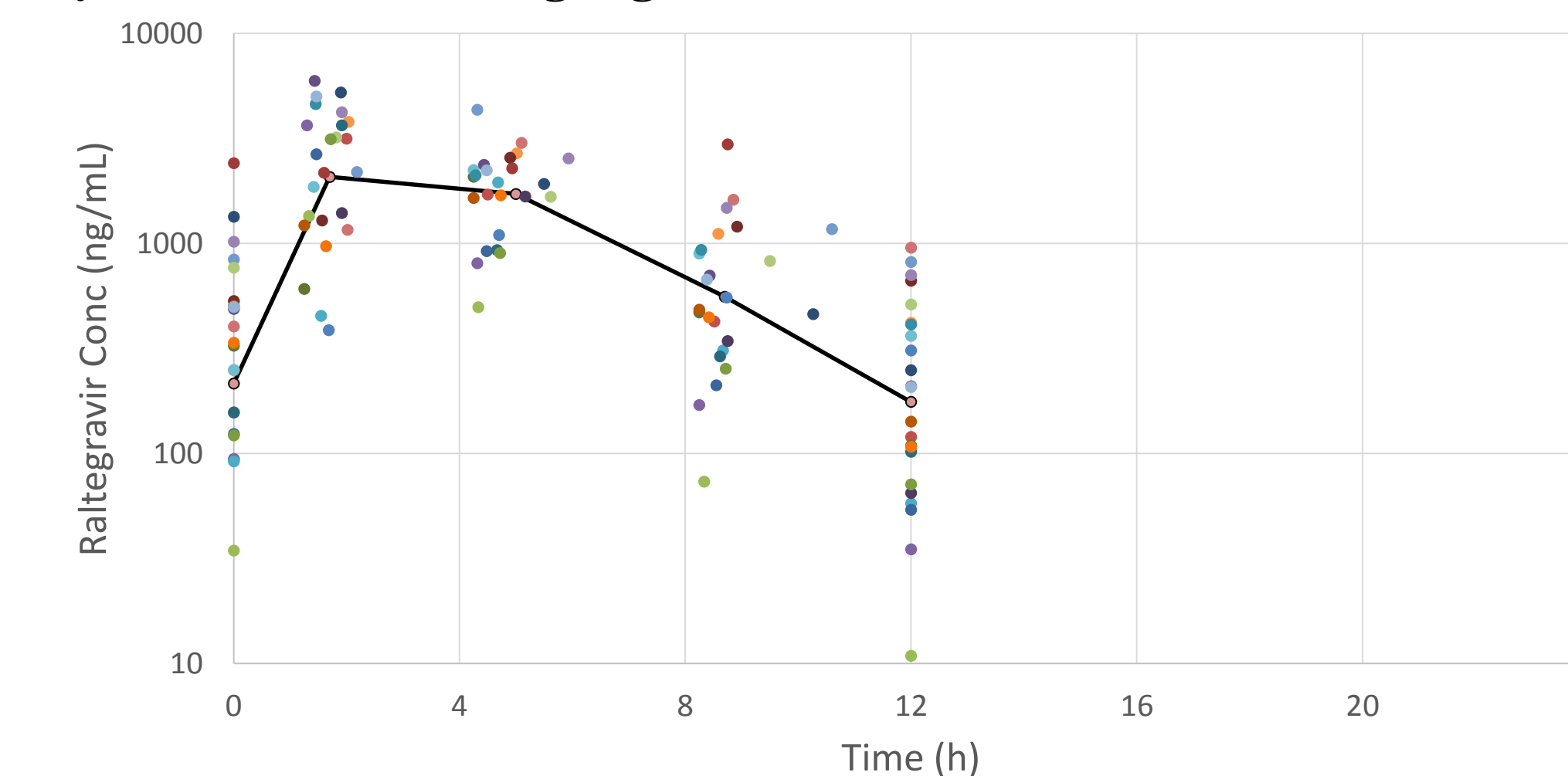
	After initial dose: 1.5 mg/kg Once Daily (n=25)		Day 15-18: 3.0 mg/kg Twice Daily (n=24)	
	Geometric Mean (CV)	Target	Geometric Mean (CV)	Target
AUC (mg*h/L)	38.2 (38.4%)	Above - 11 Met - 13 Below - 0	14.3 (43.3%)	Above - 8 Met - 14 Below - 1
Trough (ng/mL)	948 (64.2%)	Above - 25 Below - 0	176 (93.8%)	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

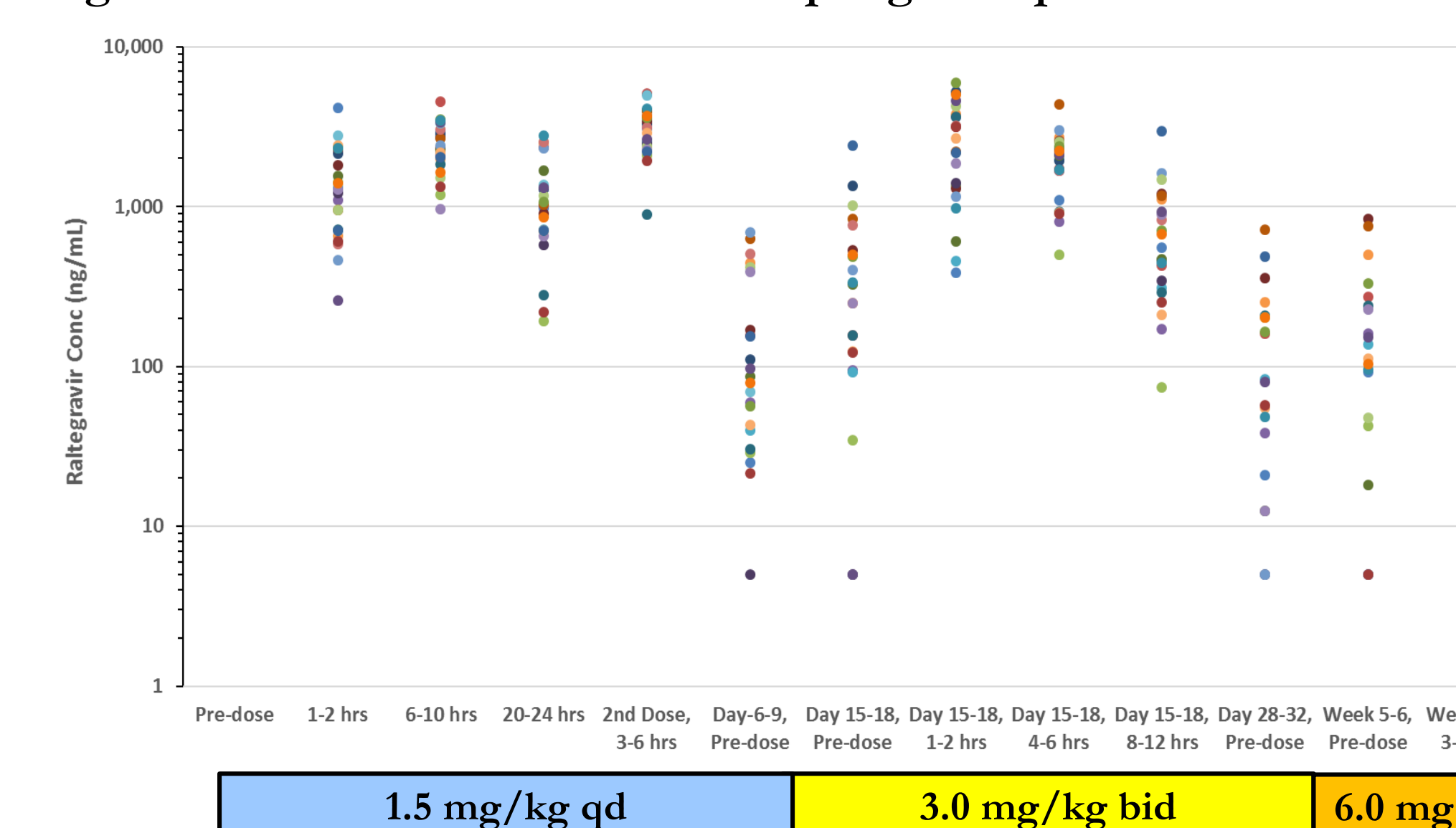
<48 hours of life – initial dose 1.5 mg/kg qd



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 AUC₂₄ 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



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