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Raltegravir (RAL) Pharmacokinetics (PK) and Safety in HIV-1 Exposed Neonates at High Risk of Infection (IMPAACT P1110)

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Background:

- RAL is a potent and selective HIV-1 integrase inhibitor with potential for use in prophylaxis and treatment of neonates at high risk for perinatal HIV-1 infection.
- RAL is primarily metabolized by UGT1A1, whose activity is low at birth and increases exponentially over the first weeks of life. [1, 2]
- In vitro data have shown that at high RAL plasma concentrations (~50 times typical peak concentrations in HIV infected adults), RAL has the potential to displace bilirubin from albumin, increasing neonatal risk for kernicterus.[3]
- IMPAACT P1097 demonstrated that RAL readily crosses the placenta and that elimination of transplacentally acquired RAL in infants whose mothers received RAL during pregnancy is highly variable and prolonged.[4]
- The objectives of IMPAACT P1110 are to evaluate the pharmacokinetics and safety of RAL and to determine an appropriate neonatal dose during the first 6 weeks of life using a two cohort adaptive design, where PK data from Cohort 1 are included in PK modeling to guide daily dosing in Cohort 2.

Materials and Methods:

- IMPAACT P1110 is a Phase I multicenter PK study of RAL in full-term HIV-1 exposed neonates at high risk of acquiring HIV-1-infection.
- Cohort 1 infants received RAL administered as a single oral dose within 48 hours of birth in addition to standard of care ARVs for PMTCT prophylaxis, and a second dose administered at 7-10 days of life.
- Initial dose studied was 3 mg/kg and doses were adjusted on a rolling basis.
- RAL-exposed infants born to mothers receiving RAL prior to and during delivery were excluded initially but later were allowed to enroll and receive a lower initial dose.
- PK sampling was done around the initial dose (pre-dose and 1-2 hours, 4-8 hours, 12 hours, 24 hours post-dose, random sample on day 3-4 of life) and second dose (pre-dose and 1-2 hours, 24 hours post-dose).
- PK samples were analyzed for RAL concentrations using a validated HPLC-MS-MS method LLOQ=22.5 nM.
- Protocol exposure limits from noncompartmental analysis for each subject were Cmax ≤ 19.6 µM and AUC12 ≤ 63 µMxhr.
- A population PK model was developed incorporating Cohort 1 PK data with RAL concentration data from 24 infants and children ages 4 weeks to < 2 years enrolled in IMPAACT P1066, a Phase I/II, multi-center, open-label, noncomparative intensive PK study of RAL in infants and children.[5]
- Population modeling using PsN/3.7.6, NONMEM/7.3.0 and R/3.1.0 was performed to estimate RAL PK parameters, which were then used in simulations of potential dosing regimens.
- The regimen that best met PK exposure targets (Ctrough, Cmax, AUC) defined for safety and efficacy from studies in older infants, children, and adults was selected for evaluation in a second cohort of neonates.

Results:

- 13 mother-infant pairs (10 from USA, 2 from Brazil, 1 from South Africa) enrolled in Cohort 1 - 10 infants born to mothers who did not receive RAL prior to delivery and 3 infants born to mothers who received RAL prior to and during delivery.
- Infant Demographics [n(%) or median (range)] for Cohort 1 infants:
  - Gender: 6(46%)/7(54%) female/male
  - Gestational age: 39.0 weeks (36.0-39.6)
  - Birth weight: 3.02 kg (2.39-4.20)
  - Mode of delivery: 3(23%)/10(77%) vaginal/caesarian section
- Evaluable RAL concentration data following initial dose and week 1 dose are available for 12 of the 13 neonates (Figure 1).
- Interim analysis of the PK data from the first 6 RAL naïve infants who received 3 mg/kg initial doses revealed that the Cmax upper limit was not exceeded by any subject, but two patients exceeded the AUC12 upper limit.
- For subsequent enrollments, the initial dose was reduced to 2 mg/kg for RAL-naïve and 1.5 mg/kg for RAL-exposed infants.
- RAL PK parameters for Cohort 1 following initial doses are included in Table 1.
- All infants received 3 mg/kg for the second dose administered at 7-10 days of life.
- Applying protocol exposure limits for the 12 infants with evaluable PK, all 12 infants had a Cmax ≤ 19.6 µM.
- However, AUC12 ≤ 63 µMxhr was exceeded after initial dose in 3/6 infants who received 3 mg/kg; 2/3 infants who received 2 mg/kg; and 1/3 RAL-exposed infants who received 1.5 mg/kg initial dose.
- RAL was well tolerated: 1 infant had a low absolute neutrophil count (ANC) thought to be possibly related to RAL administration; none of the infants had an elevation in bilirubin requiring phototherapy.

Figure 1. RAL Concentration-Time Plots

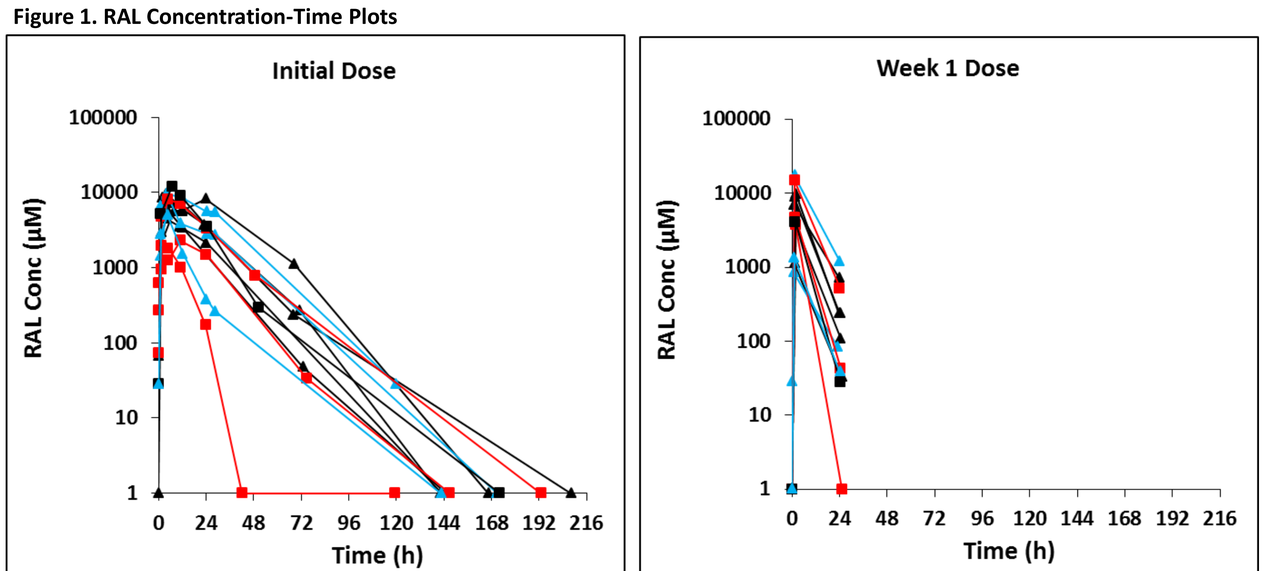


Table 1: RAL PK parameters from non-compartmental analysis [geometric mean (range)] for Cohort 1 initial doses

	Age at Initial dose (hrs)	Cmax (µM)	AUC12 (µM*hr)	T ½ (hrs)	Tmax (hrs)	C24h (µM)	Vz/F (L/kg)	Cl/F (L/kg/hr)
3 mg/kg (no maternal RAL) n=6	17.2 (9.9-25.4)	7.56 (4.51-11.96)	66.3 (42.5-104.1)	11.8 (7.9-15.7)	6.5 (4.1-24.0)	3.25 (1.49-8.22)	0.56 (0.35-0.80)	0.033 (0.021-0.053)
2 mg/kg (no maternal RAL) n=3	27.1 (24.2-33.1)	7.66 (5.01-9.73)	63.3 (39.2-99.0)	17.2 (6.3-32.8)	4.4 (4.3-4.7)	1.81 (0.38-5.60)	0.68 (0.43-0.86)	0.074 (0.039-0.109)
1.5 mg/kg (maternal RAL) n=3	34.1 (22.8-44.9)	3.31 (1.98-8.02)	29.0 (17.5-78.0)	8.7 (6.0-11.7)	4.6 (1.8-11.0)	0.95 (0.17-3.33)	0.62 (0.32-1.31)	0.049 (0.019-0.151)

Population Modeling and Simulations

- RAL concentration data from an initial cohort of 6 infants receiving 3 mg/kg doses were combined with data from 24 infants age 4 weeks to 2 years enrolled in IMPAACT P1066.[5] (Table 2)
- Population modeling of the combined data set were performed using NONMEM.
- Clearances and volume of distribution were allometrically scaled.
- A preliminary 2-compartment NONMEM model, based on an existing model describing RAL PK in pediatrics and adults,[6] was used to generate time-dependent functions for absorption and clearance:
  - Absorption rate changed from 16% of max at birth to 90% within 2 weeks.
  - Clearance changed from almost nil to a max at~ 6 months of life.
- The time-dependency of PK parameters for absorption and clearance (CLmax, CLbase, CLtau, KAmax, KAbase and KAtau), as parametrized in Table 3, were estimated in the final 2-compartment NONMEM model (Figure 2).
- PK parameter estimates with confidence intervals are given in Table 4.
- Using this population model, simulations were run of various dosing regimens in the first 6 weeks of life.
- The dosing regimen through 6 weeks of age that best met the following revised PK exposure targets defined for safety and efficacy from recent studies in older infants, children and adults was selected for use in Cohort 2 (Table 5):
  - Cmax < 19.63 µM (19,630 nM)
  - Cmin > 75 nM
  - AUC12 (BID) < 45 µM*hr, AUC24 (QD) < 90 µM*hr

Table 2: Data used for PK modeling

	Cohort-1	Cohort 4	Cohort 5
Study	P1110	P1066	P1066
Total number of subjects	6	13	11
Number of data points	48	121	128
Age range	1-10 days	6 mos – 2 yrs	4 wks - 6 mos
Weight range (kg)	2.9-3.8	5.5-14	3.7-10.4
Gender (M/F)	3/3	8/5	7/4

Figure 2: Final PK model

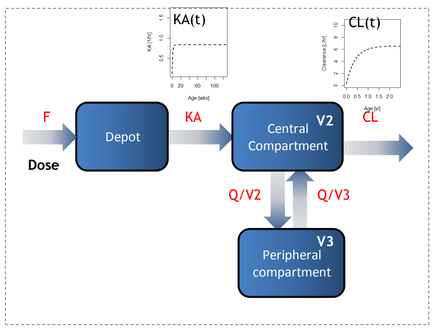


Table 3: Allometric scaling and time-dependent parameterization for V, CL, and KA

Parameter	Abbr.	Unit	Allometric Scaling
Volume of distribution (central compartment)	V2	L	$V2 = \theta_{V2}*(BW/25)^1$
Clearance	CL	L/hr	$CL = CL(t)*(BW/25)^{0.75}$ $CL(t) = \theta_{CLbase} + \theta_{CLmax}*(1-\exp(-\theta_{\tau,CL}*AGE))$
Oral absorption rate	KA	1/hr	$KA = KA(t)$ $KA(t) = \theta_{KAbase}+\theta_{KAmax}*(1-\exp(-\theta_{\tau,KA}*AGE))$
Volume of distribution (peripheral comp.)	V3	L	$V3 = \theta_{V3}*(BW/25)^1$
Inter-compartment clearance	Q	L/hr	$CL = \theta_{Q}*(BW/25)^{0.75}$

Table 4: Final PK parameter estimates

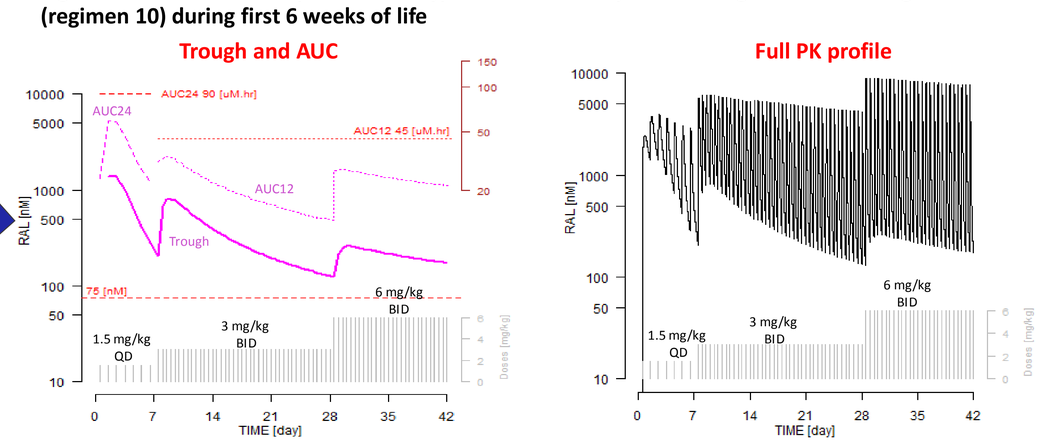
Parameter	Unit	Value	CI-95%		Parameter	Value	CI-95%	
		THETA				OMEGA		
V2	L	**11.51**	5.34	24.78	IIV-CLmax	**0.18**	0.08	0.27
V3	L	**26.47**	15.75	44.47	IIV-Q	**0.61**	0.13	1.10
CLMAX	L/hr	**12.73**	10.60	14.86	IIV-KAmax	**0.46**	0.19	0.73
Q	L/hr	**1.22**	0.76	1.97		SIGMA		
KAMAX	1/hr	**0.76**	0.32	1.20	RUV-prop	**0.56**	0.49	0.62
F	-	**1**			RUV-add	**4.44**	0	82.21
CLbase	L/hr	**0**						
CLtau	1/years	**10.57**	3.69	17.45				
KAbase	1/hr	**0.08**	2.66	0.00				
KAtau	1/years	**49.44**	0	218.73				

Table 5: Evaluation of Typical RAL Exposure Parameters with Potential Dosing Regimens (in mg/kg)

Red **– well outside of PK exposure target** ***Orange*** **– close to PK exposure target** ***Green*** **– within PK exposure target**

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					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					

Figure 3: Predicted RAL exposure for a typical Cohort 2 subject receiving the selected regimen (regimen 10) during first 6 weeks of life



Conclusions:

- There are few ARVs with an appropriate formulation and adequate PK data for use in neonates.
- After combining RAL concentration data from a small group of neonates receiving only 2 RAL doses with that from older infants and children receiving daily dosing, a population PK model and simulations were used to facilitate development of a daily dosing neonatal RAL regimen for evaluation in a second cohort of infants.
- P1110 will begin enrolling RAL-unexposed infants into Cohort 2 with the dose selected from the PK modeling and simulations: 1.5 mg/kg once a day from birth to day 7, followed by 3 mg/kg twice a day until 4 weeks of age, then 6 mg/kg twice a day to age 6 weeks.
- RAL-exposed infants will be excluded from Cohort 2 until additional PK data are obtained for this group.
- PK results for Cohort 2 will be evaluated on a rolling basis and dosing will be adjusted based on these results.

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