Poster #20

IMPAACT P1110: Raltegravir (RAL) Pharmacokinetics (PK) and Safety in HIV-1 Exposed Neonates: Dose-Finding Study in Infants born to Mothers receiving Raltegravir-Containing ART

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Background:

- RAL is a potent and selective HIV-1 integrase inhibitor with potential for use in prophylaxis and early treatment of neonates at risk for perinatal HIV-1 infection.
- RAL is primarily metabolized by UGT1A1, whose activity is known to be extremely low at birth followed by a dramatic increase over the first weeks to months of life. [1,2] At high plasma concentrations (50-100 times greater than typical peak concentrations of 5000 ng/mL), RAL can displace bilirubin from albumin, placing a newborn infant at risk for kernicterus.[3]
- IMPAACT P1097 demonstrated that RAL crossed the placental well and elimination of trans-placentally acquired RAL in infants whose mothers received RAL during pregnancy was highly variable and prolonged.[4] Direct administration of RAL to a neonate with in utero exposure poses the potential risk of accumulation of RAL to excessive concentrations.
- In November 2017, RAL oral granules for suspension was Food and Drug Administration (FDA) approved for use in full-term neonates weighing ≥2 kg. Current pediatric FDA approval and dosing recommendations are based on evaluations conducted in IMPAACT P1110 in 42 neonates born to mothers with HIV-1 infection who did not receive RAL during pregnancy. These infants were treated for up to 6 weeks starting from birth and followed for safety for a total of 24 weeks.[5,6]
- The FDA approved dosing for RAL is based on P1110 pharmacokinetics (PK) and safety results from infants born to mothers who did not receive RAL during pregnancy. Based on PK modeling and simulations, the FDA recommends that initial neonatal RAL doses should be delayed until 24-48 hours after birth if a pregnant woman receives RAL 2-24 hours before delivery.
- We now report the pharmacokinetic and safety analyses of daily RAL dosing in neonates enrolled in P1110 whose mothers received RAL prior to delivery.

Materials and Methods:

- IMPAACT P1110 is a Phase 1, multicenter trial enrolling full-term neonates exposed to HIV and at risk of acquiring HIV-1infection, with *in utero* raltegravir exposure (RAL exposed) or without *in utero* raltegravir exposure (RAL naive). Study design included two cohorts: Cohort 1 infants received two single raltegravir doses 1 week apart and Cohort 2 infants received daily raltegravir dosing for the first 6 weeks of life.
- PK samples were analyzed for RAL concentrations using a validated HPLC-MS-MS method LLOQ=22.5 nM.
- PK data from Cohort 1 and from older infants and children were combined in a population PK model. [7,8] 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 to be evaluated in Cohort 2. [9-11]
- RAL daily dosing regimen evaluated:
  - *1.5 mg/kg daily through Day 7*
  - *3 mg/kg twice daily on Days 8 to 28 of life*
  - *6 mg/kg twice daily after 4 weeks of age*
- Protocol exposure targets were:
  - AUC_{24} 12-40 mg*h/L
  - AUC_{12} 6-20 mg*h/L
  - C_{12} or C_{24} > 33 ng/mL
  - Cmax ≤ 8723.6 ng/mL
- AUC was estimated using the trapezoidal method.
- RAL-naive neonates (born to mothers who did not receive RAL) initiated therapy with RAL within 48 hours of birth. For RAL-exposed neonates (born to mothers who received RAL within 2-24 hours of delivery) a delay in initiation of therapy with RAL of 12-60 hours of birth was evaluated.
- Infants were followed with clinical and laboratory safety evaluations through 24 weeks of age.

Results

Demographics:

- 10 mother-infant pairs (4 Thailand, 4 Brazil, 1 USA, 1 South Africa) enrolled.
- Infants [n(%) or median (range)]:
  - Sex: 4(40%)/6(60%) female/male
  - Gestational age: 39 weeks (38-40)
  - Birth weight: 3.09 Kg (2.77-3.36)
  - Mode of delivery: 3(30%) vaginal; 7(70%) caesarian section
  - Timing of 1st RAL dose: 30.3 hours (16.6-51.4)

Figure 1: RAL plasma concentrations RAL-exposed infants (infants born to mothers who received RAL 2-24 hours prior to delivery) are presented below:

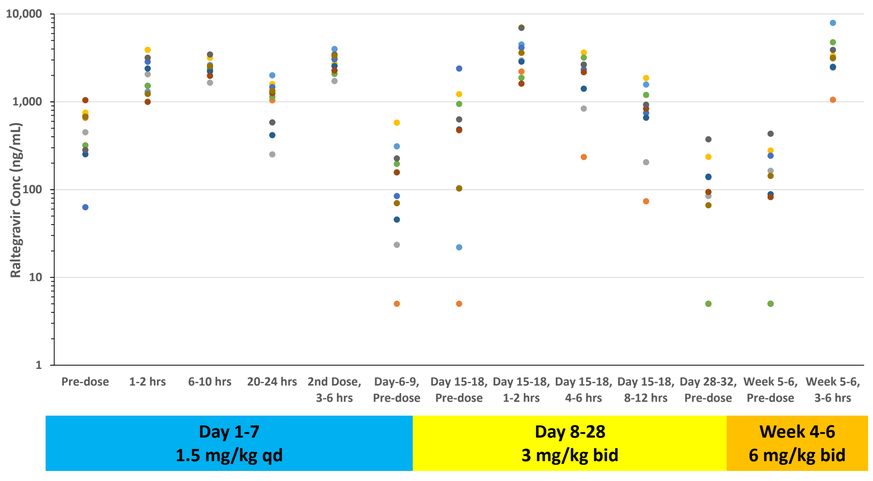

Figure 2: RAL plasma concentrations RAL-naive infants (infants born to mothers not on RAL) are presented below (presented previously) [5]:

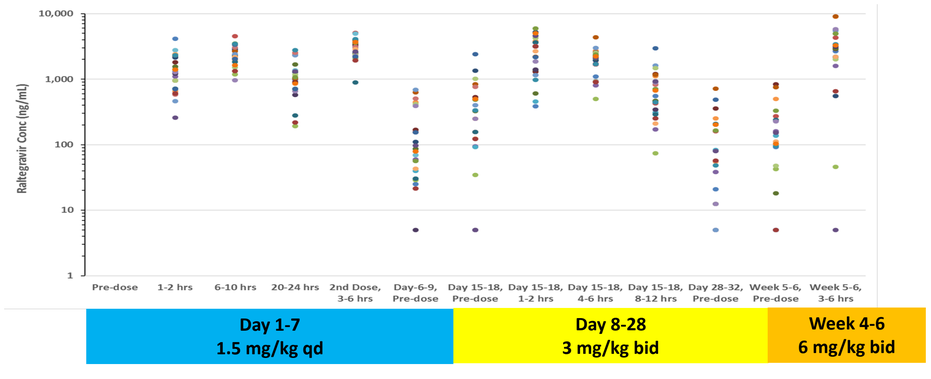

Table 1: RAL PK parameters [geometric mean (range) for RAL naive and RAL exposed neonates:

PK Parameter	After Initial Dose: 1.5 mg/kg Once Daily RAL-naive (N = 25)		After Initial Dose: 1.5 mg/kg Once Daily RAL-exposed (N = 10)		Days 15–18: 3.0 mg/kg Twice Daily RAL-naive (N = 24)		Days 15–18: 3.0 mg/kg Twice Daily RAL-exposed (N = 9)	
	Geometric Mean (CV)	PK Target	Geometric Mean (CV)	PK Target	Geometric Mean (CV)	PK Target	Geometric Mean (CV)	PK Target
AUC (mg*h/L)	38.2 (38.4%)	Above: 11 Met: 13 Below: 0	42.9 (24.6%)	Above: 6 Met: 4 Below: 0	14.3 (43.3%)	Above: 8 Met: 14 Below: 1	18.3 (48.8%)	Above: 5 Met: 3 Below: 1
Trough (ng/mL)	948 (64.2%)	Above: 25 Below: 0	946.3 (49.7%)	Above: 10 Below: 0	176 (93.8%)	Above: 22 Below: 1	273.6 (75.5%)	Above: 9 Below: 1
C_{max} (ng/mL)	2350 (35.0%)	Above: 0 Below: 25	2565.3 (24.3%)	Above: 0 Below: 10	2850 (41.9%)	Above: 0 Below: 24	3667.4 (46.7%)	Above: 0 Below: 9
T_{max} (hrs)	5.4 (57.5%)	N/A	3.8 (58.3%)	N/A	2.3 (67.1%)	N/A	1.9 (59.4%)	N/A
$T_{1/2}$ (hrs)	15.8 (174.8%)	N/A	14.4 (58.3%)	N/A	2.5 (33.5%)	N/A	2.9 (20.1%)	N/A

PK Targets:
AUC_{24} 12–40 mg*h/L
AUC_{12} 6–20 mg*h/L
Trough Concentrations: >33 ng/mL
C_{max}: < 8724 ng/mL

Key to Acronyms: AUC = area under the curve; C_{max} = maximum concentration; CV = coefficient of variation; PK = pharmacokinetic; $T_{1/2}$ = half-life; T_{max} = time to reach maximum concentration

Safety:

- No drug-related clinical adverse events were observed.
- Laboratory events: Four infants had grade 3 or 4 toxicities: anemia (1), neutropenia (1), hyperbilirubinemia (2).
- No specific therapy was required. All of these toxicities occurred within 6 weeks of life and resolved to at least Grade 2 during subsequent study follow-up.
- No infants were diagnosed with HIV-1 infection during the conduct of this study.

Conclusions*:*

- There are few ARVs with an appropriate formulation and adequate PK data for use in neonates.
- Daily RAL beginning at 12-60 hours of age through 6 weeks was safe and well tolerated in infants born to mothers receiving RAL.
- While GM for RAL PK parameters met protocol exposure targets, some individual infants had AUC_{24} following the initial dose slightly exceeding the target range. This transient overexposure was considered acceptable given the rapid increase in RAL metabolism over the first week of life.
- Our findings confirm that the current FDA dosing recommendations based on PK modeling and simulations are appropriate for use in neonates with in utero RAL exposure.
- P1110 will begin enrolling low birth weight (LBW) neonates in a new version of the protocol. PK washout data from P1097 LBW infants will be used to develop a population PK model for RAL in LBW infants and simulations will be used to select an initial dose for evaluation.

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