Raltegravir PK in neonates – An adaptive trial design to define an appropriate regimen for neonates from birth to 6 weeks of age.

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Introduction

- 3.2 million children are infected with HIV worldwide; of whom almost 800 die every day
- Mother-to-child HIV transmission is the most common route of HIV infection in newborn babies
- The World Health Organization (WHO) guidelines include raltegravir as an important product needed for certain pediatric populations
- Raltegravir has been approved for treatment of infants 4 weeks and older. Preferably treatment should start immediately after birth to continuously suppress viral replication without interruptions
- A daily dosing regimen was designed to treat neonates from birth up to 6 weeks of age [1], which includes two dose increases to keep raltegravir concentration sufficiently high, namely:
  - Week 1 (Day-1 to 7) 1.5 mg/kg QD; Weeks 2-4 (Day-8 to 28) 3 mg/kg BID; Weeks 5-6 (Day-29 to 42) 6 mg/kg BID

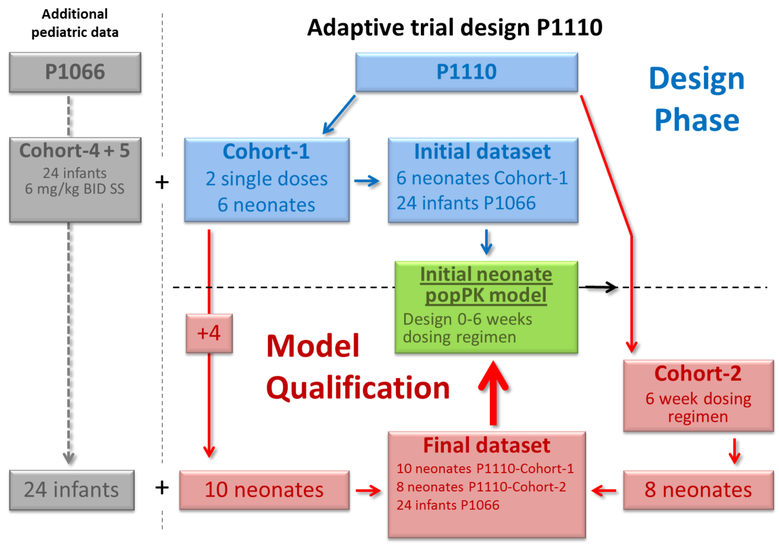

Figure 1. Adaptive trial design for the treatment of neonates with raltegravir in P1110

Objective

- To demonstrate the appropriateness of the dosing regimen of raltegravir (RAL, Isentress®) in neonates aged 0-6 week for the prevention or treatment of HIV infection in IMPAACT P1110 trial based on popPK modeling in a two cohort adaptive design

Design Phase: developed neonate popPK model

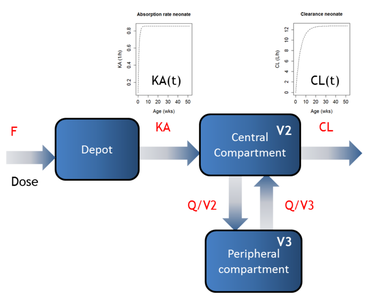

Figure 2. Raltegravir naïve neonate PK model.

Raltegravir neonate popPK model was developed [1] using:

- Data from 6 neonates (P1110, Cohort-1, two doses in 2 weeks) increased by data from 24 infants (P1066, Cohorts 4+5)
- 2-compartment model with allometric scaling on V2, V3, CL and Q
- Special developed clearance maturation and age-dependent oral absorption rate constant functions:

$$CL(t) = CL_{base} + CL_{max}(1 - e^{-\tau_{CL}*Age})$$
$$KA(t) = KA_{base} + KA_{max}(1 - e^{-\tau_{KA}*Age})$$

- This interim popPK model was applied to the design dose regimen for the next cohort of neonates, dosed daily from birth up to 6 weeks of age (Cohort-2)
- This poster describes the appropriateness of this dose regimen using actual PK data from Cohort-2

Model Qualification: Data

Table 1. Aggregated data set to fit parameters of the neonate popPK model

Study No	Neonates P1110		Infants P1066		Overall
Cohort No	1	2	4	5	
Total number of subjects	10	8	13	11	42
Number of data points	89	104	121	123	424
Age range at enrollment	0-2 days	0-2 days	6 months to < 2 years	4 weeks to < 6 months	
Age range for PK sampling	0-2 weeks	0-6 weeks	6 months to < 2 years	5 weeks to < 6 months	1 day – < 2 years
Weight range (kg)	2.3-4.2	2.6-5.0	5.5-14	3.7-10.4	2.3 - 14
Sex (M/F)	4/6	6/2	8/5	7/4	25/17

- P1110, Cohort-1
  - 10 full-term neonates who received two 3 mg/kg doses of raltegravir, first dose within 48 hours after birth and second dose at 7-10 days of life
  - 4 or 5 PK samples were collected at the first dose and 3 samples at the second dose
- P1110, Cohort-2
  - 8 full-term neonates who have been dosed from birth up to 6 weeks using the following regimen:
    - Week 1 (Day-1 to 7) 1.5 mg/kg QD; Weeks 2-4 (Day-8 to 28) 3 mg/kg BID; Weeks 5-6 (Day-29 to 42) 6 mg/kg BID
  - 13 PK samples per subject were collected (Figure 3)
- P1066, Cohort 4 + 5
  - 24 infants who are on steady state using a 6 mg/kg BID dosing regimen

Model Qualification: Methods & Update parameter estimates

1. Update of existing popPK model using PK data of neonates dosed according to the 6-week regimen
2. Assessment of PK criteria for a predicted typical individual from the updated popPK model:
   - AUC_{0-24} to remain lower than 90 uM.hr at QD (week-1)
   - AUC_{0-12} to remain lower than 45 uM.hr at BID (weeks 2-6)
   - Trough concentrations to remain above 75 nM throughout full 6-week period
   - C_{max} to remain below 19.63 uM during the full 6-week period

- The neonate popPK model consists of 2 time-dependent functions to describe maturation of clearance and development of oral absorption: both functions to be updated by estimation of its parameters: let the data speak
- RAL concentrations were measured by a validated LCMS assay. LLOQ=22.5 nM. Concentrations below LLOQ were imputed by 11.25 nM. No data were excluded from analysis
- The neonate PK model (Figure 2) was fitted to all data using NONMEM v7.3.0. Post-processing and generation of graphs was carried out using R version 3.1.3

Table 2. Parameter estimates of final neonate popPK raltegravir model

Parameter	Abbr.	Allometric Scaling	Model parameter	Estimate	Unit	95% confidence interval
Volume of distribution (central compartment)	V2	$V2 = \theta_{V2}*(BW/25)^1$	θ_{V2}	9.58	L	6.3-14.6
Clearance	CL	$CL = CL(t)*(BW/25)^{0.75}$ $CL(t) = \theta_{CLbase} + \theta_{CLmax}*(1-exp(-\theta_{CLtau}*AGE))$	θ_{CLbase} θ_{CLmax} θ_{CLtau}	0 (Fixed) 10.8 12.9	L/hr L/hr 1/year	- 8.52 – 13.1 9.36 – 16.4
Oral absorption rate	KA	$KA = KA(t)$ $KA(t) = \theta_{KAbase} + \theta_{KAmax}*(1-exp(-\theta_{KAtau}*AGE))$	θ_{KAbase} θ_{KAmax} θ_{CKAtau}	0.08 0.67 139	1/hr 1/hr 1/year	0 – 26.6 0.14 – 1.20 0 - 452
Volume of distribution (peripheral comp.)	V3	$V3 = \theta_{V3}*(BW/25)^1$	θ_{V3}	12.7	L	9.01 – 17.9
Inter-compartment clearance	Q	$CL = \theta_Q*(BW/25)^{0.75}$	θ_Q	1.43	L/hr	0.98 – 2.09

Interindividual variability	Estimate	95% confidence interval
IIV – V3	0.642	0.021 – 1.26
IIV - CLmax	0.403	0.315 – 0.491
IIV - KAmax	0.479	0.294 – 0.663

Residual error	Estimate	95% confidence interval
RUV - proportional	0.532	0.476 – 0.588
RUV - additive	12.2	0 – 42.8

Final Results Neonate PK model

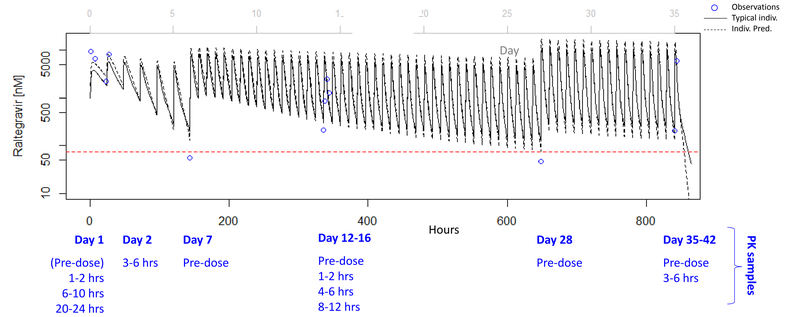

Figure 3. Example of a neonate from Cohort-2, all 13 PK samples collected according to the PK sampling scheme

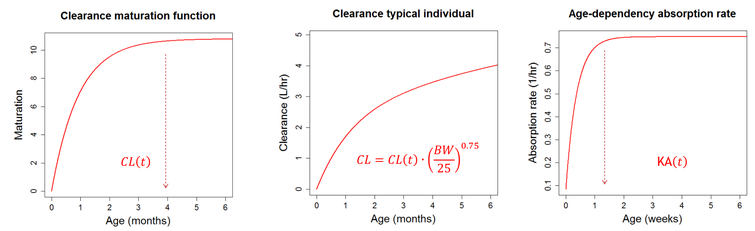

Figure 4. Age-dependent development of clearance and oral absorption in neonates

- UGT-1A1 enzyme complex fully matured at 4 months of age, but raltegravir clearance is still increasing due to growth
- Absorption rate constant reaches a maximum approximately one and a half week after birth

Validated 6-week dosing regimen

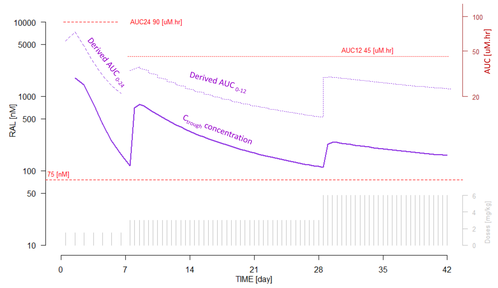

Figure 5. Time-course changes of summary PK parameters, namely raltegravir trough concentrations, AUC_{0-24} for QD regimen and AUC_{0-12} for BID regimen)

- Shown are the predicted PK characteristics for a typical neonate dosed according to applied regimen
- Typical individual remains within all PK criteria (also C_{max} < 19.63 uM, not shown)

Conclusions

- It has been shown by the updated neonate popPK model that the applied dosing regimen for the treatment of neonates from birth up to 6 weeks of age is adequate:
  - Week 1 (Day-1 to 7) 1.5 mg/kg QD; Weeks 2-4 (Day-8 to 28) 3 mg/kg BID; Weeks 5-6 (Day-29 to 42) 6 mg/kg BID
- It is remarkable that the interim popPK model, based on very limited neonate PK data from 6 neonates only, has been sufficiently accurate to design an adequate 6-week dosing regimen for these neonates: augmentation of the neonate data by pediatric data to anchor the PK for neonates at an older age has been a successful approach

References

1. Lommerse J, Clarke DF, Chain A *et al*. 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. PAGE 24 (2015) Abstr 3627 [www.page-meeting.org/?abstract=3627]
2. Du L, Rizk M, and Wenning L. Population PK modeling analysis report to support the pediatric filing of raltegravir (MK-0518) granules for suspension formulation in HIV infected pediatric patients 4 weeks to less than 2 years of age. Merck Modeling and Simulation Report, May 14, 2013.

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