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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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Objectives: Evaluate a 6-week dosing regimen during an adaptive trial design.

Methods: The rapid maturation of UGT-1A1, a hepatic enzyme clearing raltegravir (RAL), was characterized in a population PK-model [2] using data from 6 neonates (P1110, cohort-1). The model was applied to design a safe and efficacious 6-week dosing regimen (P1110, cohort-2) and evaluated using an optimized sampling scheme (13 samples/subject).

Results: RAL UGT-1A1 clearance was near-nil at birth and becomes fully maturated around 4 months (t½=2.8 weeks). The oral absorption rate was 0.08 (1/hr) at birth and increased 9-fold within one week. The updated PK model validated the 6-week regimen (1.5 mg/kg QD week 1; 3 mg/kg BID weeks 2-4; 6 mg/kg BID weeks 5-6) attaining the therapeutic window (trough>75 nM and AUC24<90 uM.hr, Figure). PK parameters remained within 20% from the original model estimates, but the peripheral volume (V3) was reduced by 50% (3.2 L for 4 kg neonate), which is analogous to prior pediatric PK-model where V3=body weight.

Conclusions: Significant accumulation of RAL in the first few days of life was well predicted and no adjustment of the 6-week dosing regimen was required.

References:

1. IMPAACT-P1110, A PHASE I TRIAL TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF RALTEGRAVIR IN HIV-1-EXPOSED NEONATES AT HIGH RISK OF ACQUIRING HIV-1 INFECTION. http://impaactnetwork.org/DocFiles/P1110/P1110V110DEC12_CM1LoA1CM2CM3_15Jan15.pdf