Objectives

To describe the PK of raltegravir (RAL, Isentress®) in 0-6 week old infants and to determine a prospective daily dosing regimen for the prevention or treatment of HIV infection in IMPACT P1110 using a two cohort adaptive design where PK data from 2 single doses in Cohort 1 are included in PK modeling to guide daily dosing in Cohort 2.

Background

• 3.2 million children are infected with HIV worldwide; of whom almost 800 die every day because of lack of access to treatment and care
• The World Health Organization (WHO) guidelines include raltegravir as an important product needed for certain pediatric populations
• RAL is metabolized via UGT-1A1, where activity is known to be extremely low immediately after birth followed by a dramatic increase over the first few days of life

Data

• IMPACT P1110 is an open label, non-comparative dose-finding study of raltegravir in HIV exposed neonates at high risk of acquiring HIV-1 infection [1,2,5]
• An initial cohort (Cohort-1) of 6 full-term infants received two 3 mg/kg doses of raltegravir:
  • first dose within 48 hours after birth
  • second dose at 7-10 days of life
• Plasma samples for PK profiles were collected around the first dose (intensive) and the second dose
• PK concentrations were measured by a validated LC/MS assay. LLOQ=2.25 nM. Concentrations below LLOQ were imputed as 11.25 nM
• The PK data of Cohort-1 were combined with the pediatric PK data of 24 HIV infected infants and children from the IMPACT P0606 study (Phase II, multi-center, open-label, non-comparative intensive PK study)

Table 1: Overview of PK data used for modeling

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Study</th>
<th>Data points</th>
<th>Number of infants</th>
<th>Weight range (kg)</th>
<th>Age (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>P1110</td>
<td>48</td>
<td>6</td>
<td>2.0-3.0</td>
<td>birth-6 months</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>P1110</td>
<td>128</td>
<td>19</td>
<td>2.5-15</td>
<td>&lt;2 years-6 months</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>P0606</td>
<td>128</td>
<td>11</td>
<td>0.5-13</td>
<td>&lt;2 years-6 months</td>
</tr>
</tbody>
</table>

Figure 1: RAL core – time plots of the raw PK data

1. Time-dependency of clearance

An existing 2-compartment model describing RAL PK in pediatrics and adults was carefully adjusted using knowledge generated from a initial 1-compartment model for the cohort-1 neonates. The 2-compartment model accounted for body weight changes by standard allometric scaling (Table 2). The individual predictions (EBEs) of the clearance for each individual was plotted against time and was corrected for the allometric scaling as applied in the PK model. An exponential function was fitted (using gnlx) to the body-weight corrected data and translated into a time-dependent clearance function in the PK model (Figure 2, Table 2).

2. Time-dependency of absorption rate

A similar approach was applied to describe the time-dependent absorption observed for the absorption rate (Figure 3, Table 2).

Table 2: Allometric scaling in the RAL PK model for neonates and pediatrics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Allometric Scaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>L/day</td>
<td>CLbase x (body weight/70.0)^0.75</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>CLbase x (body weight/70.0)^0.75</td>
</tr>
</tbody>
</table>

Neonate PK model development

Special attention was paid to a number of specific characteristics of raltegravir pharmacokinetics in neonates:

• Raltegravir is metabolized via UGT-1A1, a glucuronosyltransferase known to have very low activity at birth which matures in about 6 months to its full capacity [3,4]
• Important differences in the neonatal gastrointestinal tract that may impact absorption of medications
• Feeding was restricted in the neonates enrolled in P1110. The potential effect of food on absorption was not evaluated
• Body weight changes (expressed as %) are significant, even in a relatively short period of time
• The Cohort-1 data alone suggest that the neonates should be modeled using a 1-compartment model, but when combined with the Cohort-4 and 5 data a 2-compartment model is more suitable

Figure 3: Time-dependent absorption rates

Prospective dosing regimen design

• The model was used to simulate Cohort 2 subjects in order to design regimens that best meet PK exposure targets (Cmax < 19.63 μM; Cmin > 75 nM; RALC12 (BID) < 45 μM.hr; RALC24 (QD) < 90 μM.hr) as shown to be defined for safety and efficacy from the studies in older infants, children and adults [5]
• A simulated full PK profile is shown in Figure 6, from which the changing trough levels and AUCs can be derived (Figure 7)
• The simulations demonstrated that trough levels decrease rapidly due to the increase of the clearance especially in the first 7 days after birth. Therefore, a change to a higher daily dosing (BID) regimen is needed after about 7 days in order to maintain Cthroug > 75 nM while keeping the AUC within a safe range (Figure 7)
• The regimen selected for further evaluation was proposed at 1.5 mg/kg once a day from birth to day 7 of life, followed by 3 mg/kg twice a day until 4 weeks of age, then 6 mg/kg twice a day (as depicted in Figures 6 and 7 ). This aligns with the approved pediatric dosing regimen of 6 mg/kg raltegravir twice a day for children of 4 weeks and older

Figure 6: Simulated full PK profile of a typical subject from Cohort 2

Summary

RAL is metabolized via UGT-1A1, where activity is known to be extremely low immediately after birth followed by a dramatic increase over the first 7 days of life until the enzyme is fully matured after about 6 months [3,4]. Using time-dependent clearance and absorption rate relationships, the population PK model shown here described the observed data in neonates well. From our model simulations, we were able to inform a daily dosing regimen for evaluation in Cohort 2 of P1110. Further modeling and simulations will be performed as neonates are enrolled in cohort 2 to verify the proposed dosing regimen.