Pharmacokinetic modelling of darunavir/ritonavir dose reduction (800/100 mg to 400/100mg once daily) containing regimen in virologically suppressed HIV-infected patients as maintenance treatment: ANRS-165 DARULIGHT sub-study

Minh P Lò,1,2†, Jean-Michel Molina,1 Vincent Medalen,3 François Rafti,4 Marie-Laure Chaiàx,5 Sebastien Gallien,5 El Mountacer Billah El Abbassi,3 Christine Katalma,6 Pierre Debelle,7 Yazdan Yazdpanarpan,3†, Juliette Saillard,3 Gilles Plevy,2,3†

Background
- HIV-1 infected patients with controlled viraemia (plasma HIV-1 RNA<50 copies/mL for 12x months)
- Maintenance: [1] no DRV/C, efavirenz
- Objectives of a maintenance treatment:
  - Improve long-term tolerance and safety
  - Without jeopardizing future lines of treatment
- Darunavir is well suited for maintenance:
  - Darunavir PK enhancer
  - Approved at the dose: 800/100mg QD as induction treatment3,14 applicable in maintenance7
- High barrier to resistance mutation
- Forgiveness

Materials and Methods
- Non compartmental analysis for DRV, R and NRTI:
  - MxOUC2, Cmmax
  - Statistics: intra-individual comparisons via Wilcoxon/Fisher's exact tests and geometric mean ratio (GMR)
  - Population analysis for DRV & RTV
  - Non-linear mixed-effect modeling
  - SAEM algorithm (Monte Carlo 2000L, LMX1)
  - PK parameter estimation: 1 and 2 compartment models, absorption log-time
  - Residual error models: combined, additive & proportional
  - Inter-individual variabilities estimation
  - Covariate effect estimation: ADORV1 (continuous), dosing regimen (categorical),
  - Model evaluation by BIC, adequate GDI plots, and low RSE in PK parameters

Results
- Non compartmental analysis for DRV, RTV & NRTI:

  - DRV: 800/100 mg QD
  - DRV, RTV by UCPS-MS/MS (Water Acq.720)
  - Peak parameter determination
  - DRV/LOQ (ng/mL) and RTV (LOD<10 ng/mL)
  - Unbound fraction separated by Millipore Centricon

Table 1. Patients’ baseline characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Median [IQR (75%)] or %, n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>42.0 [30.5-46.5]</td>
</tr>
<tr>
<td>Gender</td>
<td>Male (73%)</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA (copies/mL)</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>Plasma DRV (ng/mL)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>Plasma RTV (ng/mL)</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>

Figure 2. Pharmacokinetic profiles of total blood plasma darunavir (a), unbound blood plasma darunavir (b) and total blood plasma ritonavir (c). n=15 patients

Table 2. Final model for blood and seminal plasma darunavir and blood plasma ritonavir

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>95% CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td>DRV Blood</td>
<td>Cmmax</td>
<td>6.0</td>
<td>0.76</td>
<td>4.57</td>
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<tr>
<td>DRV Blood</td>
<td>Lin PK</td>
<td>4.6</td>
<td>0.67</td>
<td>3.33</td>
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<tr>
<td>DRV Seminal</td>
<td>Cmmax</td>
<td>6.3</td>
<td>0.71</td>
<td>4.88</td>
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<tr>
<td>DRV Seminal</td>
<td>Lin PK</td>
<td>4.4</td>
<td>0.65</td>
<td>3.33</td>
</tr>
<tr>
<td>RTV Blood</td>
<td>Cmmax</td>
<td>6.7</td>
<td>0.76</td>
<td>4.57</td>
</tr>
<tr>
<td>RTV Blood</td>
<td>Lin PK</td>
<td>4.6</td>
<td>0.67</td>
<td>3.33</td>
</tr>
</tbody>
</table>

Table 3. PK parameters for blood and seminal plasma darunavir and blood plasma ritonavir

Discussion
- Darunavir: PK parameters (Cmx, Cmmax & AUCO-24H) at DRV800/100mg QD and structural models similar to literature1,9
- MxOUC at reported no difference between DRV800/100mg QD and DRV400/100mg QD, similarly in structualised models4
- Total and bound blood and seminal plasma exposure of DRV not significantly different between both doses, despite dose reduction
- Dosing regimen effect (DRV vs DRV 400) on Cmmax (increase of 65% for Cmmax) & Cmmax (linear fitting parameters in the absorption phase (only 2 parts) 5
- Plasma data needed for parameters pro (ax) + literature PK data (Yoshida et al. in 2014) in order to estimate 1h due to sparse data
- Unbound blood fraction is similar in both dosing regimen-(P76)
- Unbound renal fraction (cmax) is higher than blood probably due to the protein composition of seminal plasma6

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References

Figure 4. Prediction corrected VPC plot of the area under the log time curve (AUC0-t) for total blood plasma darunavir (b) and unbound plasma darunavir (c). n=15 patients

Figure 3. Pharmacokinetic parameters of total blood plasma darunavir (a), unbound blood plasma darunavir (b) and total blood plasma ritonavir (c). n=15 patients

Figure 1. Study design of the PK study

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Figure 4. Prediction corrected VPC plot of the area under the log time curve (AUC0-t) for total blood plasma darunavir (b) and unbound plasma darunavir (c). n=15 patients

Figure 5. Total blood plasma exposure of RTV tended to be higher in 400/100 mg QD. than in 800/100mg QD

Figure 6. Impacts of dose regimen on Cmmax of DRV and RTV

Figure 7. Modified balance in inducer/inhibitor between DRV & RTV with the dose reduction

Figure 8. The main clinical trial of the Darulight trial was presented at a recent meeting