Establishing darunavir dosing recommendations in treatment-naïve and treatment-experienced pediatric patients

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Darunavir pediatric clinical development program
DELPHI: Study design

PART I (n=44)
- 20 to <30kg: DRV/rtv 300/50mg bid
- 30 to <40kg: DRV/rtv 375/60mg bid
- 40 to <50kg: DRV/rtv 450/100mg bid

GROUP A (n=22)
- 20 to <30kg: DRV/rtv 375/50mg bid
- 30 to <40kg: DRV/rtv 450/60mg bid
- 40 to <50kg: DRV/rtv 600/100mg bid

GROUP B (n=22)

PART II (n=80)
- DRV/rtv administered at recommended pediatric dose according to weight

Week 2: dose selection

6–17 years
On HAART ≥12 years

DELPHI=Darunavir Evalulation in Pediatric, HIV-Infected, treatment-experienced patients

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DELPHI=Darunavir Evaulation in Pediatric, HIV-Infected, treatment-experienced patients

## DELPHI: Week 48 PK

<table>
<thead>
<tr>
<th>DRV pharmacokinetics*</th>
<th>DELPHI pediatric patients N=80</th>
<th>POWER 1 and 2 adult patients N=119</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median AUC$_{24h}$, ng·h/mL (range)</td>
<td>122,956 (67,054–201,280)</td>
<td>123,336 (67,714–212,980)</td>
</tr>
<tr>
<td>Median C$_{0h}$, ng/mL (range)</td>
<td>3722 (1836–7194)</td>
<td>3539 (1255–7368)</td>
</tr>
</tbody>
</table>

*Estimated using population pharmacokinetic analysis

- **Target adult DRV exposures achieved in all weight bands and age groups**
- **Trough concentrations (C$_{0h}$) in all children were well above the EC$_{50}$ value for resistant HIV of 550 ng/mL**

Ariel: Phase II, open-label, single-arm study designs

- Treatment-experienced children 3 to <6 years
- Weight 10 to <20kg
- HIV-1 RNA >1000 copies/mL
- <3 DRV RAMs at screening
- On HAART for ≥12 weeks

### ARIEL: Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>ARIEL (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>11 (52)</td>
</tr>
<tr>
<td><strong>Median age at screening, years (range)</strong></td>
<td>4.4 (3.0–6.0)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Multiple</td>
<td>2 (10)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>10 (48)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>11 (52)</td>
</tr>
</tbody>
</table>

| Disease characteristics             |              |
| **Mean baseline log_{10} HIV-1 RNA, copies/mL (SE)** | 4.34 (0.183) |
| **Median CD4 cell count, cells/mm³ (range)**        | 927 (209–2429) |
| **Median CD4% (range)**                       | 27.7 (15.6–51.1) |

SE=standard error
**ARIEL: Week 48 PK**

- Week 2 PK suggested potential underdosing
- Dose adjustment from DRV/rtv 20/3 mg/kg bid to 25/3 mg/kg bid (10 to <15 kg) and 375/50 mg bid (15 to <20 kg)

<table>
<thead>
<tr>
<th></th>
<th>Pre-Week 2 dose change</th>
<th>Post-Week 2 dose change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=19)*</td>
<td>Adult exposure, %†</td>
</tr>
<tr>
<td><strong>DRV AUC_{0–12h} geometric mean, μg•h/mL (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>63.8 (26.7)</td>
<td>106</td>
</tr>
<tr>
<td>10 to &lt;15kg</td>
<td>65.5 (25.7)</td>
<td>109</td>
</tr>
<tr>
<td>15 to &lt;20kg</td>
<td>62.1 (29.4)</td>
<td>103</td>
</tr>
</tbody>
</table>

*n=10 for the lower-weight and n=9 for the higher weight category; †60.3μg•h/mL from POWER 1 and 2 trials with DRV/r 600/100mg bid; §n=5 and n=14, respectively
Darunavir pediatric clinical development program

- Waiver granted
- ARIEL substudy
- Modeling and simulation
- DIONE

Age (years):
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

qd bid
**DIONE: Study design**

**Inclusion criteria**
- Treatment-naive adolescents aged 12 to <18 years
- Weight ≥40 kg
- HIV-1 RNA ≥1000 copies/mL

**Treatment phase 48 weeks**
- Primary analysis at Week 24
- Follow-up

**DRV/rtv 800/100mg qd + AZT/3TC or ABC/3TC (N=12)**

**Week 2**
- Intensive PK

**DIONE= DarunavIr Once-daily in treatment-Naïve adoEscents**
### DIONE: Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>DIONE (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Median age at screening, years (range)</td>
<td>14.4 (12.6–17.3)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
</tr>
<tr>
<td>Multiple</td>
<td>0</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>11 (92)</td>
</tr>
</tbody>
</table>

### Disease characteristics

<table>
<thead>
<tr>
<th>Disease characteristics</th>
<th>DIONE (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline $\log_{10}$ HIV-1 RNA, copies/mL (SE)</td>
<td>4.72 (0.172)</td>
</tr>
<tr>
<td>Median CD4 cell count, cells/mm³ (range)</td>
<td>282 (204–515)</td>
</tr>
<tr>
<td>Median CD4% (range)</td>
<td>18.3 (12.1–40.8)</td>
</tr>
</tbody>
</table>

SE=standard error
**DIONE: DRV pharmacokinetics**

### Intensive pharmacokinetics

- **DIONE Week 2 (n=12)**
- **ARTEMIS Week 4 (n=9)**
- **ARTEMIS Week 24 (n=13)**

### Population pharmacokinetics

- **DRV AUC\(_{0-24h}\) geometric mean, μg•h/mL (SD)**
  - **DIONE (N=12)**: 80.7 (23.6)
  - **Adults (ARTEMIS) (N=335)**: 89.7 (27.0)
- **DRV C\(_0\)h geometric mean, ng/mL (SD)**
  - **DIONE (N=12)**: 1930 (865)
  - **Adults (ARTEMIS) (N=335)**: 2027 (1168)

### Graphs

- **DRV plasma concentration (ng/mL) vs. Time (hours)**
- **DRV AUC\(_{0-24h}\) (μg•h/mL)**

- **10,000**
- **8000**
- **6000**
- **4000**
- **2000**
- **0**

- **0 4 8 12 16 20 24**

- **DIONE Week 2 (n=12)**
- **ARTEMIS Week 4 (n=9)**
- **ARTEMIS Week 24 (n=13)**

- **130%**
- **89.7 μg•h/mL**
- **80%**

- **DRV AUC\(_{0-24h}\) geometric mean**, **μg•h/mL**
  - **80.7 (23.6)**
  - **89.7 (27.0)**

- **DRV C\(_0\)h geometric mean**, **ng/mL**
  - **1930 (865)**
  - **2027 (1168)**
Darunavir pediatric clinical development program

- Waiver granted
- ARIEL
- Modeling and simulation
- DIONE

**Age (years):**

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
ARIEL: PK substudy

• Optional for patients with confirmed HIV-1 RNA <50 copies/mL at Week 32
• DRV/rtv 40/7 mg/kg qd dose determined with population PK model using data from the Week 2 analysis
• Ten patients participated: 5 female; 7 weighed ≥15kg, 3 weighed 14 to <15kg

<table>
<thead>
<tr>
<th></th>
<th>ARIEL qd sub-study (n=10)</th>
<th>Adult (ARTEMIS)(^1) (N=335)</th>
<th>Adults, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV AUC(_{0-24h}) geometric mean, μg•h/mL (SD)</td>
<td>115 (40.6)</td>
<td>89.7 (27.0)</td>
<td>128</td>
</tr>
<tr>
<td>DRV C(_{0h}) geometric mean, ng/mL (SD)</td>
<td>3029 (1715)</td>
<td>2027 (1168)</td>
<td>149</td>
</tr>
</tbody>
</table>

• No treatment-related or grade ≥2 AEs were reported
• All patients retained HIV-1 RNA <50 copies/mL during the two-week substudy

AUC\(_{0-24h}\)=AUC between 0 to 24 hours

1. Janssen data on file
ARIEL: PK substudy

- Virologically suppressed (<50 copies/mL) patients at ≥ Week 24 switched to DRV/r 40/7mg/kg qd

![Graph showing DRV plasma concentration over time for different study weeks and patient groups.](image-url)

1. Janssen data on file *Adults
Darunavir pediatric clinical development program

- Waiver granted
- ARIEL substudy
- Modeling and simulation
- DIONE

Age (years):

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

qd bid
DRV population PK model

\[
\frac{CL}{F_i} = \frac{CL_{int}/F \left( \frac{1}{1 + K^\text{AFF} \cdot AAG_i} \right) \left( \frac{WT_i}{70} \right)^\theta \cdot e^{n_i}}{F_{rel}}
\]

\[
\frac{V2}{F_i} = \frac{V2/F \left( \frac{WT_i}{70} \right)^\theta \cdot e^{n_i}}{F_{rel}}
\]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CL_{int}/F) (L/h)</td>
<td>51.0</td>
</tr>
<tr>
<td>Influence of weight on (CL/F)</td>
<td>0.504</td>
</tr>
<tr>
<td>(K^\text{AFF}) of AAG (dL/mg)</td>
<td>0.0304</td>
</tr>
<tr>
<td>(V2/F) (L)</td>
<td>137</td>
</tr>
<tr>
<td>Influence of weight on (V2/F)</td>
<td>0.774</td>
</tr>
<tr>
<td>(Q/F) (L/h)</td>
<td>19.1</td>
</tr>
<tr>
<td>(V3/F) (L)</td>
<td>254</td>
</tr>
<tr>
<td>(K_A) (L)</td>
<td>0.528</td>
</tr>
<tr>
<td>(F_{rel})</td>
<td>1.18</td>
</tr>
<tr>
<td>Multiplicative residual error</td>
<td>0.0717</td>
</tr>
</tbody>
</table>
Modeling and simulation of pediatric DRV qd

Body weight (kg)

AUC (µg•h/mL)

- 10–15kg 35mg/kg
- 15–30kg 600mg
- 30–40kg 675mg
- 30–65kg 800mg

89.7 µg•h/mL

130%

80%
Conclusions: Recommended DRV/rtv pediatric dosing

**ARV-experienced**

- **3 to <6 years**
  - 10 to <15kg: 20/3mg/kg bid
  - 15 to <20kg: 375/50mg bid

- **6 to <12 years**
  - ≥20 to <30kg: 375/50mg bid
  - ≥30 to <40kg: 450/60mg bid
  - ≥40kg: 600/100mg bid

- **12 to <18 years**
  - ≥20 to <30kg: 375/50mg bid
  - ≥30 to <40kg: 450/60mg bid
  - ≥40kg: 600/100mg bid

**ARV-naïve**

- **10 to <15kg**
  - 35/7mg/kg qd
  - 600/100mg qd
  - 675/100mg qd

- **30 to <40kg**
  - 675/100mg qd

- **≥40kg**
  - 800/100mg qd

**US and EU**

- US and EU

**US only**

- US only
Acknowledgments and disclosures

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  – the patients and their families for their participation and support during the studies
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