Pharmacokinetic study of islatravir and etonogestrel implants in macaques

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BACKGROUND
Prevention of HIV and unintended pregnancies are public health priorities. Methods that provide sustained release of drugs can improve patient adherence and increase efficacy of medications that require consistent dosing. Long-acting (LA) implants have been successfully used for contraception including the FDA-approved Nexplanon implant which releases the hormone etonogestrel (ENG) to prevent unintended pregnancy for up to 3 years. LA products for HIV pre-exposure prophylaxis (PrEP) are building upon these models. Islatravir (ISL) is a novel nucleoside reverse transcriptase translocation inhibitor that is phosphorylated within cells to the active metabolite ISL-triphosphate (ISL-TP). The long half-life and potency of ISL make it an attractive candidate for delivery by an implant for LA PREP.

Here, we evaluated safety and pharmacokinetics of ISL and ENG implants in female pig-tailed macaques.

METHODS
Figure 1. Study Design

Figure 1. Implants were placed subcutaneously in the upper inner arms of macaques. Three in vitro release rates of ISL were investigated: low (42 µg/day), mid (75 µg /day), and high (42 + 75 = 117 µg /day). ENG implants (40 µg /day) were evaluated concurrently in the mid ISL study group.

- Specimen collection: blood once a week, mucosal biopsies every two weeks.
- Drug level testing: ISL, ENG, and progesterone (p4) in plasma.
- Intracellular ISL-TP in peripheral blood mononuclear cells (PBMCs), and mucosal biopsies.
- Implant site reactions: erythema and edema evaluated weekly by two veterinarians using a modified Draize scale.

RESULTS

Figure 2. Concentrations of ISL-TP in PBMCs

Table 1. Concentrations of ISL in plasma and ISL-TP in PBMCs and rectal/vaginal tissues

Table 1. Concentrations of ISL in plasma and ISL-TP in PBMCs and rectal/vaginal tissues

<table>
<thead>
<tr>
<th>ISL</th>
<th>Cumulative IVRR</th>
<th>Duration (days)</th>
<th>Plasma ISL (ng/ml)</th>
<th>PBMC ISL-TP (fmol/10^6 PBMCs)</th>
<th>Vaginal ISL-TP (fmol/g)</th>
<th>Rectal ISL-TP (fmol/g)</th>
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<tbody>
<tr>
<td>Low</td>
<td>42 µg/day</td>
<td>35</td>
<td>0.39 [0.36 - 0.54]</td>
<td>26.7 [21.8 - 32.6]</td>
<td>8.7 [8.5 - 11.6]</td>
<td>19.7 [8.5 - 27.3]</td>
</tr>
<tr>
<td>Mid</td>
<td>75 µg/day</td>
<td>90</td>
<td>0.59 [0.49 - 0.75]</td>
<td>42.5 [20.1 - 96.5]</td>
<td>10.6 [8.4 - 21.6]</td>
<td>29.3 [26.2 - 30.0]</td>
</tr>
<tr>
<td>High</td>
<td>117 µg/day</td>
<td>90</td>
<td>0.88 [0.66 - 3.4]</td>
<td>79.5 [46.5 - 229.0]</td>
<td>16.5 [10.7 - 64.1]</td>
<td>39.3 [26.0 - 45.4]</td>
</tr>
</tbody>
</table>

Plasma ISL and PBMC ISL-TP values were calculated once steady state was achieved; Low ISL (day 7-35), Mid ISL (d7-90), High ISL (d7-90). Vaginal and rectal ISL-TP levels were determined at day 21 post implantation.

Figure 3. Concentrations of p4 and ENG in plasma

Figure 3. Plasma p4 (A) and ENG (B) in macaques that received an ISL implant (75 µg /day), followed by an ENG implant and lastly ISL implant removal. Data for each macaque, PT-1, PT-2, and PT-3, is shown.

CONCLUSIONS
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