Safety and Pharmacokinetic Assessment of 28 Day Anti-HIV Dapivirine Intravaginal Microbicide Rings

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Abstract

Background: Dapivirine (TAF233) is a non-nucleoside reverse transcriptase inhibitor currently in development as a potential means of preventing sexually-acquired infections. Dapivirine has demonstrated potent antiretroviral activity in vitro and in vivo, offering a potential means of preventing sexually-acquired infections.

Methods: Dapivirine (25 mg) was inserted into two types of ring drug delivery system: matrix or reservoir. Dapivirine concentrations were analyzed on an in-house high performance liquid chromatography method at pre-specified time points over a 24-hour period on Day 1 (post-insertion) and Day 28 (post-removal) and at sequential time points over a 33-day (28-day treatment; 5-day follow-up) period. Safety measurements were monitored to assess local and systemic safety.

Results: Dapivirine concentrations were considerably higher for matrix than for reservoir rings during the entire study period. Dapivirine concentrations were 75 times greater on Day 1 with a 2 to 4 fold increase over the 28 day period. Differences in dapivirine concentrations between the two ring types increased over the 28 day period. Differences in higher concentration levels were considered to be clinically relevant. Dapivirine concentrations in vaginal fluids were greater post ring insertion. The 95% CI of the ratio was considered to be useful in predicting clinical relevance due to potential differences in drug-related adverse effects. Mean digestion rates of dapivirine were similar and only slightly higher in matrix rings than reservoir rings. Mean digestion rates of placebo rings were similar and only slightly higher in matrix rings than reservoir rings.

Conclusions: Dapivirine IVR types were safe and well tolerated in the study population. Pharmacokinetic assessment supports development of dapivirine matrix ring as a potential non-oral antiretroviral microbicide.

Study Objective

To evaluate the feasibility of using matrix and reservoir IVRs containing 25 mg dapivirine to deliver drug for 28 consecutive days

• Safety and tolerability vs. placebo
• Pharmacokinetic concentrations
• Concentrations in vaginal fluids

Study Design

Double-blind, placebo-controlled trial conducted in 2 Phase I and II settings.

• 24 healthy, HIV-negative women 18 to 35 years of age.
• 1:1:1:1 randomization to 25 mg matrix, 25 mg reservoir, 25 mg placebo, or placebo IVR polyethylene glycol.
• Periodic/gynecologic examinations, adverse events assessed, and subject-reported gender symptoms documented at each study visit.
• Hematology, liver and renal function, and urinalysis prior to screening and final visit.
• Random samples of vaginal fluid samples (near IVR, cervix, introitus) collected at the indicated time points.

Intravaginal Ring (IVR) Structures

• Two-compartment drug reservoir configuration
• Matrix IVR: 25 mg dapivirine dispersed evenly throughout ring
• Reservoir IVR: inner core containing 25 mg dapivirine, and an outer drug reservoir.
• Placebo rings were matrix type without drug
• Weight approximately 7 grams

Timeline of Study Events (IPM018)

Safety Results

• 25 mg matrix and 25 mg reservoir IVRs were safe and well tolerated for 28 days
• No clinically relevant changes from baseline were noted in any parameter
• No AEs were considered definite or possibly related to the IVR
• All AEs were considered not related to the IVR
• Plasma concentrations of dapivirine were above the EC50 (>1000-fold less than plasma levels)

Results

• Dapivirine is in development as a microbicide gel and intra-vaginal ring (IVR) for prevention of HIV transmission.
• EC50 of 0.9 ng/mL and IC50 of 9 ng/mL against HIV-1.
• Future studies will assess safety and efficacy including vaginal and systemic resistance endpoints.

Table 1. Number and Percentage of Subjects with Treatment Emergent Adverse Events Assessed as Possibly Related to the IVR

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo IVR</th>
<th>25 mg Matrix IVR</th>
<th>25 mg Reservoir IVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Number of Subjects</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>% of Subjects</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Figure 1. Plasma Concentrations of Dapivirine Assessed Post IVR Insertion

Figure 2. Mean Vaginal Fluid Concentrations of Dapivirine Assessed Post IVR Insertion

Figure 3. Residual Dapivirine Concentrations in Vaginal Fluids after 28 Days of Use

Summary and Conclusions

• Both matrix and reservoir IVRs containing 25 mg dapivirine were safe and well tolerated for 28 days.
• Dapivirine was effectively distributed throughout the cervical/vaginal area at concentrations 1,000- to 10,000-fold (reservoir IVR) to 3- to 10-fold (matrix IVR) greater than the EC50 against HIV-1.
• Dapivirine concentrations in rabbits were very low (<0.001 ng/mL) post IVR insertion.
• Pharmacokinetic and safety data support the future development of dapivirine IVRs as a monthly dosed microbicide.