Pharmacokinetics of Co-encapsulated Truvada® with Ingestible Sensor to Assess Adherence

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Quote from Jerry Garcia

“Let my inspiration flow in token lines suggesting rhythm that will not forsake me till my tale is told and done”

The Grateful Dead – 1977
• High medication adherence is critical to successful HIV pre-exposure prophylaxis (PrEP)

• An FDA-cleared device, using an edible ingestion sensor (IS), external wearable patch and paired mobile device, can detect and record ingestion events
Co-encapsulation of IS

The system consists of a 1 mm³ ingestion sensor (1 x 1 x 0.45 mm microchip)

Proteus Digital Health, Redwood City, CA
Biopharmaceutics Classification System

• The BCS classifies drugs based on their aqueous solubility and intestinal permeability

  Class 1: High Solubility – High Permeability ← FTC
  Class 2: Low Solubility – High Permeability
  Class 3: High Solubility – Low Permeability ← TFV
  Class 4: Low Solubility – Low Permeability

• Class 1 & 3 drugs are eligible for a waiver of vivo bioavailability and bioequivalence studies.
Study Design

- 60 participants (HIV Negative)
- Phase I System Initiation 2 Weeks
- Phase II System Persistence 12 Weeks
- Follow up Week 24, 48, 72, 96

PK Sub-study
12 participants
Days 14 & 15
PK Sub-Study Design

• Cross-over, multiple dose, steady state, fasting
• **Day 14**
  • Participants taking IS-Truvada® sampled at pre-dose, 2, 4, 6, 8, and 24 hours post-dose.
• **Day 15**
  • participants were given native Truvada® with PK sampling at pre-dose, 2, and 4 hours post-dose.
Analysis

• Plasma FTC and TFV was measured using a GCLP validated assay.

• C2, a surrogate for Cmax, and C4 were compared between formulations using the population method ratio test.

• PK parameters \( (\text{AUC}_{0-\text{tau}}, \ CL/F, T_{1/2}) \) calculated by non-compartmental methods.

• Co-encapsulated IS–Truvada® is currently undergoing dissolution studies at Gilead Sciences.
## Results: IS vs Native Truvada® (FTC)

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>N</th>
<th>GM Ratio</th>
<th>90% CI</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>12</td>
<td>0.96</td>
<td>0.87, 1.12</td>
<td>equivalent</td>
</tr>
<tr>
<td>C4</td>
<td>12</td>
<td>0.94</td>
<td>0.90, 1.04</td>
<td>equivalent</td>
</tr>
</tbody>
</table>

### Mean FTC Concentrations

- **IS**
- **Native**

![Graph of Mean FTC Concentrations](image)
## PK Results

### FTC Steady-State Pharmacokinetics

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>IS-Truvada Mean (%CV)</th>
<th>Truvada – Literature (^1) Mean (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{\text{max}}) (ng/mL)</td>
<td>1679 (27)</td>
<td>1650 (18)</td>
</tr>
<tr>
<td>(T_{\text{max}}) (hr)</td>
<td>2 (0)</td>
<td>2.98 (20)</td>
</tr>
<tr>
<td>(C_{\text{min}}) (ng/mL)</td>
<td>97 (48)</td>
<td>75 (22)</td>
</tr>
<tr>
<td>(AUC_{0-24}) (ng · hr/mL)</td>
<td>10916 (29)</td>
<td>10700 (11)</td>
</tr>
<tr>
<td>(CL/F) (L/hr)</td>
<td>195 (24)</td>
<td>190 (12)</td>
</tr>
<tr>
<td>(T_{1/2}) (hr)</td>
<td>6.7 (11)</td>
<td>10.7 (16)</td>
</tr>
</tbody>
</table>

### Results: IS vs Native Truvada® (TFV)

<table>
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<tr>
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<th>N</th>
<th>GM Ratio</th>
<th>90% CI</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>12</td>
<td>1.04</td>
<td>0.89, 1.16</td>
<td>equivalent</td>
</tr>
<tr>
<td>C4</td>
<td>12</td>
<td>0.99</td>
<td>0.87, 1.12</td>
<td>equivalent</td>
</tr>
</tbody>
</table>

**Mean TFV Concentrations**

- **IS**
- **Native**

[Graph showing mean TFV concentrations over time after dose (h).]
PK Results

TFV Steady-State Pharmacokinetics

<table>
<thead>
<tr>
<th>PK Parameter</th>
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<th>Truvada – Literature Mean (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>263 (39)</td>
<td>288 (22)</td>
</tr>
<tr>
<td>$T_{max}$ (hr)</td>
<td>2 (0)</td>
<td>2.4 (38)</td>
</tr>
<tr>
<td>$C_{min}$ (ng/mL)</td>
<td>59 (49)</td>
<td>54 (20)</td>
</tr>
<tr>
<td>$AUC_{0-24}$ (ng ∙ hr/mL)</td>
<td>2706 (42)</td>
<td>2800 (18)</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>59 (41)</td>
<td>50 (18)</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>17 (53)</td>
<td>15 (24)</td>
</tr>
</tbody>
</table>

Limitations

• Somewhat sparse sampling limited accuracy of Cmax in IS and native formulations and T_{1/2} in the IS formulation.

• Abbreviated sampling of Native formulation did not allow for comparison of AUCs.
Conclusion

• This is one of first reports of how to combine a novel sensor-based technology with oral medications

• Co-encapsulation of IS with Truvada® produces FTC and TFV pharmacokinetics that are in good agreement with literature values.

• This IS technology will allow for definitive determination of medication ingestion times to accurately assess adherence.
Acknowledgments

Thanks to the research staff at the UCSD Antiviral Research Center and to the participants who took part.

Gilead Sciences supplied Truvada® (FTC/TDF)

Proteus Digital Health, Inc

Special thanks to Dr. Sara Browne for giving me the opportunity to work on this project.