The Pharmacokinetics of Tenofovir and Tenofovir Diphosphate Following Administration of Tenofovir Alafenamide vs Tenofovir Disoproxil Fumarate

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Abst#_6
Disclosures

♦ All coauthors are employees of Gilead Sciences
♦ These studies were funded by Gilead Sciences
Introduction

- TDF is a preferred NRTI in US/EU guidelines
  - A component in the approved single-tablet regimen (STR) containing elvitegravir 150 mg (EVG, E), cobicistat 150 mg (COBI, C), emtricitabine 200 mg (FTC, F) and TDF 300 mg (E/C/F/TDF; Stribild®, STB)

- TAF is an investigational prodrug of TFV with distinct metabolism designed to maximize antiviral potency and clinical safety
  - A component in the fixed-dose combination F/TAF and E/C/F/TAF STR
Introduction

TDF has limitations and can be improved

♦ Nephrotoxicity
  – Dose adjustment in renal insufficiency
  – Declining GFR, proteinuria, urinary phosphate wasting, glycosuria

♦ Osteopenia/osteoporosis
  – Associated with loss of bone mineral density

♦ Likely relationship between TFV exposure and renal + bone toxicity
  – High-dose subcutaneous TFV administered to nonhuman primates causes PRT dysfunction and bone demineralization
  – Positive correlation between TFV clearance and/or AUC and renal + bone effects

**TAF: Targeted Prodrug of Tenofovir (TFV)**

- TAF is more stable in plasma compared to TDF\(^1\)
- Intact TAF transits directly into target cells where it is activated to tenofovir disphosphate (TFV-DP)\(^1-3\)
  - ↑ intracellular levels of active moiety TFV-DP
  - ↓ circulating TFV relative to TDF may ↓ nephrotoxicity

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TAF Is More Stable in Plasma vs TDF; Lower Dose Provides Higher Potency, Lower TFV Systemic Exposures

<table>
<thead>
<tr>
<th></th>
<th>T1/2 [min]</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Human plasma</td>
<td>T-cell extract</td>
</tr>
<tr>
<td>TVF</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>TDF</td>
<td>0.4</td>
<td>71</td>
</tr>
<tr>
<td>TAF</td>
<td>90</td>
<td>28</td>
</tr>
</tbody>
</table>

**TDF:** Hydrolysis in blood is fast, hydrolysis in T-cells is relatively slow

**TAF:** More stable in blood, hydrolysis in T-cells faster than TDF

TAF Nonclinical PK in Dogs

Oral PK in Dogs (5 mg/kg)

Clinical POC PK: TFV Lower in Plasma and TFV-DP Higher in PBMCs With TAF vs TDF

Up to 7x More TFV-DP in PBMCs

Proof-of-concept study in treatment-naïve HIV-infected subjects

Based on Clinical POC PK and Antiviral Activity, TAF 25 mg Selected for Phase 2/3

TAF 8 mg: similar anti-HIV activity to TDF 300 mg
TAF 25 mg: more potent anti-HIV activity than TDF 300 mg
- Higher intracellular TFV-DP: potential for improved efficacy
- Lower plasma TFV: potential for improved safety
- Selected for further clinical development

TAF Availability Increased by COBI via Inhibition of Intestinal Pgp

<table>
<thead>
<tr>
<th>Mean (%CV)</th>
<th>TAF 8 mg + COBI</th>
<th>TAF 8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{last} (ng•h/mL)</td>
<td>188 (27)</td>
<td>81 (44)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>142 (33)</td>
<td>71 (73)</td>
</tr>
</tbody>
</table>
TAF 10 mg in E/C/F/TAF STR

Mean TAF Plasma Concentration (ng/mL ± SD)

FTC 200 mg + TAF 25 mg
E/C/F/TAF (TAF 10 mg)
F/TAF 25 mg FDC was shown to be bioequivalent to E/C/F/TAF STR.

<table>
<thead>
<tr>
<th>TAK PK Parameter Mean (%CV)</th>
<th>F/TAF 25mg</th>
<th>E/C/F/TAF 10 mg</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{last} (ng·h/mL)</td>
<td>374 (43)</td>
<td>369 (41)</td>
<td>100 (96.5, 104)</td>
</tr>
<tr>
<td>AUC_{inf} (ng·h/mL)</td>
<td>396 (43)</td>
<td>390 (39)</td>
<td>98.5 (94.6, 103)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>281 (63)</td>
<td>268 (60)</td>
<td>104 (95.5, 112)</td>
</tr>
</tbody>
</table>

*F/TAF (200/25 mg) (test) vs E/C/F/TAF (reference)
Objective of Phase 2/3 PK Substudy

♦ Evaluate the PK of plasma TFV and intracellular TFV-DP in peripheral blood mononuclear cell (PBMC) in HIV-infected subjects receiving either E/C/F/TAF or the approved STB
Phase 2/3 PK Substudy Design and Methods

♦ One Phase 2 and two Phase 3 randomized, double-blind, multi-site studies were conducted to evaluate the safety and efficacy of E/C/F/TAF vs STB in antiretroviral treatment-naïve adult subjects.

♦ Studies designed with a PK Substudy at or between Weeks 4 or 8 to evaluate steady-state TFV and TFV-DP in subjects receiving E/C/F/TAF vs STB.

♦ Data pooled across all 3 studies.

♦ Plasma TFV
  – E/C/F/TAF: n=55
  – STB: n=36

♦ Intracellular TFV-DP
  – E/C/F/TAF: n=31
  – STB: n=19
Phase 2/3 PK Substudy Data Analysis

♦ Bioanalyses conducted by QPS
  – Plasma TFV concentrations were determined via LC/MS/MS
  – Intracellular PBMC TFV-DP concentrations were determined via LC/MS/MS in combination with PBMC cell counting via DNA quantitation procedure

♦ PK parameters estimated using noncompartmental methods and WinNonlin® software v6.3

♦ A parametric (normal theory) ANOVA was used for generation of 90% CI for geometric mean ratio (GMR) for TFV and TFV-DP
  – Test treatment: E/C/F/TAF
  – Reference treatment: STB
Intracellular TFV-DP 4.4-Fold Higher Following E/C/F/TAF vs STB

Higher Intracellular TFV-DP

TFV Geomean

E/C/F/TAF n=31

STB n=19

GMR (90% CI)

AUC$_{tau}$ (ng·h/mL)

12.2

2.79

437 (286, 669)
Plasma TFV 91% Lower Following E/C/F/TAF vs STB

<table>
<thead>
<tr>
<th>TFV Mean (%CV)</th>
<th>E/C/F/TAF</th>
<th>STB</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_{\tau}) (ng·h/mL)</td>
<td>307 (19)</td>
<td>3480 (24)</td>
<td>8.90 (8.20, 9.65)</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>17.4 (19)</td>
<td>420 (28)</td>
<td>15.0 (13.5, 16.7)</td>
</tr>
<tr>
<td>C(_{\tau}) (ng/mL)</td>
<td>10.5 (22)</td>
<td>71.7 (31)</td>
<td>4.21 (3.84, 4.62)</td>
</tr>
</tbody>
</table>
TFV Exposure Following TDF-Containing Regimens vs E/C/F/TAF

Conclusions

- Administration of E/C/F/TAF resulted in markedly higher intracellular TFV-DP concentrations with substantially lower plasma TFV relative to STB.

- Higher intracellular concentrations from E/C/F/TAF versus STB demonstrate stable and effective loading of the active moiety TFV-DP into the target cells by TAF.

- Lower plasma TFV exposures from E/C/F/TAF versus STB or other TDF-containing regimens may potentially reduce off-target effects associated with TFV, in particular renal and bone toxicity.
Acknowledgments

We extend our thanks to study participants and their families as well as the study teams.