Pharmacokinetics, Metabolism and Excretion of Tenofovir Alafenamide (TAF)

F Jin, M Fordyce, W Garner, A Ray, S Tanamly, J Lindow, BP Kearney, and S Ramanathan

Gilead Sciences, Inc., Foster City, CA 94404

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Abstract O-08
Introduction

- Tenofovir alafenamide (TAF) is a new prodrug of tenofovir (TFV)
  - TAF 25 mg provides enhanced delivery of TFV to lymphatic tissues resulting in ~5-fold higher TFV diphosphate (TFV-DP) concentrations in peripheral blood mononuclear cells (PBMCs) and ~90% lower circulating TFV vs TDF 300 mg
  - TAF 25 mg monotherapy in HIV-1 patients resulted in 1.46 log$_{10}$ c/mL reduction in HIV-1 RNA vs 0.97 log$_{10}$ c/mL reduction for TDF$^1$

- In a Phase 2 study comparing EVG/COBI/FTC/TAF to EVG/COBI/FTC/TDF (Stribild™, STB):
  - E/C/F/TAF STR showed similar and high rates of viral suppression at Week 24$^2$
  - E/C/F/TAF STR showed significantly lower bone mineral density change (BMD) (p<0.005) and lesser increase in serum creatinine$^1$

- In animals, TAF is eliminated in urine primarily as its metabolite TFV

Objectives

• To determine following administration of a single, oral dose of radiolabeled $[^{14}\text{C}]$ TAF:
  – mass balance
  – pharmacokinetics of TAF, and its metabolite TFV
  – metabolite profile
  – safety
Methods

- Phase 1, single center, open label, single dose study in healthy male subjects (N=8)
- Single 25 mg oral dose of TAF
  - $^{[14}C]$ labeled-TAF : 100 $\mu$Ci $^{[14}C]$ TAF (equivalent to 0.85 mg TAF)
  - Non-radiolabeled TAF : 24.15 mg
- Radioactivity in whole blood, plasma, urine, and feces analyzed using liquid scintillation counting (LSC)
  - Post 96-hour whole blood and plasma collected (up to the morning of Day 22) until radioactivity in 2 consecutive samples were $\leq 2$-times background or urine & feces collections was discontinued, whichever occurs first
  - Post 96-hour urine and feces collected (up to the morning of Day 22) until radioactivity in 2 consecutive samples were $\leq 1\%$ of dose and cumulative $^{[14}C]$ recovered in urine/feces is $\geq 90\%$ of the administered dose
- Metabolite profiling of TAF performed using HPLC-radiometry and MS/MS
- Intensive TAF and TFV plasma PK assessment for 96 hours
- Safety assessments performed throughout
Results: Safety

- Demographics
  - 8 healthy male subjects enrolled and treated; 6 completed
    - Two discontinuations due to withdrawal of consent
  - Mean age: 29 yrs (range: 19 – 45)
  - Mean weight: 80.3 kg (range: 69.5 – 93.3)
  - Race: 7 White, 1 Other
  - Ethnicity: 4 Hispanic/Latino, 4 Non-Hispanic/Latino

- Safety
  - Study treatments generally well tolerated; all adverse events (AEs) mild (Grade 1)
  - No discontinuation due to an AE
  - Most frequent AEs: vessel puncture site hemorrhage (2 subjects) due to blood sampling on Day 1 and resolved on Day 14
  - One AE considered related to study drug: arthralgia, occurred on Day 2 and resolved on Day 4
  - No treatment-emergent lab abnormalities
Results: $^{14}$C Recovery

Mean (SD) Cumulative Urinary and Fecal Recovery $^{14}$C Radioactivity

- In urine, 87% , 5.5%, and 7.5% (cumulative) identified as TFV, TAF, and uric acid, respectively
- In feces, 99% (cumulative) identified as TFV; represents unabsorbed and/or biliary-excreted TAF
Results: $[^{14}\text{C}]$ Profiling

Mean (SD) Blood and Plasma Concentration $[^{14}\text{C}]$ Radioactivity-Time Profiles

- Two peaks present in the plasma and blood $[^{14}\text{C}]$ radioactivity-time profiles
  - First peak $\sim$2 hours post-dose: TAF predominant species (72.6%)
  - Second peak $\sim$24-48 hours: Uric acid predominant species (97.6%)
Results: Blood to Plasma Ratio

Mean (± SD) Blood: Plasma $[^{14}\text{C}]$ Radioactivity-Time Profile

- Ratio inversion upon clearance of plasma drug concentrations
  - 0.6 at 0.25 hours postdose vs. 2.4 at 216 hours postdose
  - Consistent with loading and persistence of TFV-DP in PBMCs
Results: Plasma Metabolite Profiling

Plasma Concentrations of Metabolite $^{14}$C Radioactivity-Time Profiles

- Low amounts of uric acid as the major circulating metabolite over time
- No impact on serum uric acid concentration
  - Serum uric acid at predose, Day 3, and Day 7 postdose were 5.8, 5.8, and 5.3 mg/dL, respectively
Results: TAF Biotransformation

The metabolism of TAF involved oxidation, hydrolysis, deamination, and dealkylation (depurination) consistent with purine catabolism pathway.
## Results: Plasma TAF and TFV PK

Mean (SD) Plasma TAF and TFV Concentration-Time Profiles

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>AUC&lt;sub&gt;inf&lt;/sub&gt; (ng*hr/mL)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (hr)</th>
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<tbody>
<tr>
<td>TAF (n=8)</td>
<td>78.1 (35)</td>
<td>162 (22)</td>
<td>0.5 (0.5, 0.6)</td>
</tr>
<tr>
<td>TFV (n=8)</td>
<td>7.2 (16)</td>
<td>225 (25)</td>
<td>32 (31, 36)</td>
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C<sub>max</sub> and AUC<sub>inf</sub> expressed as mean (CV%) and T<sub>1/2</sub> expressed as median (Q1, Q3)
Conclusions

• TAF was extensively metabolized and eliminated in urine and feces primarily as metabolites
  – Predominant species detected in feces and urine was TFV
  – Renal excretion of unchanged TAF was minimal

• The predominant species circulating in plasma was uric acid, consistent with purine catabolism
  – No impact on plasma uric acid concentration

• TAF 25 mg was well tolerated