GS-7340 Demonstrates Greater Declines in HIV-1 RNA than Tenofovir Disoproxil Fumarate During 14 Days of Monotherapy in HIV-1 Infected Subjects

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Introduction

- GS-7340 is a novel amidate prodrug that was designed to deliver high concentrations of tenofovir diphosphate to lymphoid cells.
- The targeted delivery to lymphatic tissue should allow for a low dose and minimal systemic levels of tenofovir.
- Chronic safety studies in dogs and rats demonstrate a greater therapeutic index relative to TDF.
GS-7340: Targeting Lymphoid Cells

- GS-7340 is 400-fold more potent than tenofovir in PBMCs\(^1\)
- GS-7340 is 200-fold more stable in plasma than TDF resulting in circulating levels of prodrug\(^1\)
- GS-7340 is rapidly metabolized inside the lysosomes of lymphoid cells by the enzyme cathepsin A\(^2\)

\(^1\) Lee et al. Antimicrob Agents Chemother 2005

M Markowitz, et al., CROI 2011; Paper # 152LB.
Increased Distribution to PBMCs *In Vivo*

Plasma to PBMC ratio following administration of TFV, TDF or GS-7340 to dogs (10 mg-eqv/kg)\(^1\)

![Graph showing AUC vs. Subcutaneous and Oral administration of Tenoflovir (TFV), TDF, and GS-7340. The ratio of Plasma to PBMC is 1:140 for GS-7340, 1:1.4 for TFV, and 1:5 for TDF.](image)

\(^1\)Lee et al. Antimicrob Agents Chemother 2005

M Markowitz, et al., CROI 2011; Paper # 152LB.
Objectives

• **Primary Objectives**
  – To evaluate the antiviral potency of 2 different doses of GS-7340 as compared to TDF
    • Primary endpoint: DAVG at Week 2
  – To determine the safety of GS-7340 over 14 days

• **Secondary Objectives**
  – To determine the plasma and intracellular PK of GS-7340
  – To determine the viral dynamics of HIV-1 RNA in plasma
Study Design

• HIV-1-infected adults
  – ART Treatment-naïve
  – HIV-1 RNA ≥ 15,000 c/mL
  – CD4 count ≥ 200 cells/mm³

• Randomized, double-blind 3 arm study
  – TDF 300 mg (active control arm)
  – GS 7340 - 50mg
  – GS 7340 - 150 mg

• Monotherapy for 14-day once-daily dosing
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TDF 300mg (N=10)</th>
<th>GS-7340 50 mg (N=10)</th>
<th>GS-7340 150 mg (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean)</strong></td>
<td>34.8 ± 7.6</td>
<td>36.6 ± 9.7</td>
<td>35.4 ± 6.5</td>
</tr>
<tr>
<td><strong>Sex (males)</strong></td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>6</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Black</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Latino</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Mean HIV-1 RNA</strong></td>
<td>5.03 ± 0.77</td>
<td>4.73 ± 0.58</td>
<td>4.72 ± 0.30</td>
</tr>
<tr>
<td><strong>Mean CD4 cell count</strong></td>
<td>384 ± 153</td>
<td>454 ± 201</td>
<td>432 ± 108</td>
</tr>
</tbody>
</table>
## Primary Efficacy Endpoint

<table>
<thead>
<tr>
<th>Treatment (10 pts/arm)</th>
<th>Mean DAVG$<em>2$ [log$</em>{10}$ c/mL]</th>
<th>p-value vs. TDF 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF 300 mg</td>
<td>- 0.54 $\pm$ 0.32</td>
<td>-</td>
</tr>
<tr>
<td>GS-7340 50 mg</td>
<td>- 0.95 $\pm$ 0.32</td>
<td>0.0211</td>
</tr>
<tr>
<td>GS-7340 150 mg</td>
<td>- 1.07 $\pm$ 0.14</td>
<td>0.0002</td>
</tr>
<tr>
<td>Treatment (10 pts/arm)</td>
<td>Mean ΔVL Day 14 [(\log_{10} \text{c/mL})]</td>
<td>p-value of mean ΔVL vs. TDF 300 mg</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>TDF 300 mg</td>
<td>-0.94 ± 0.49</td>
<td>-</td>
</tr>
<tr>
<td>GS-7340 50 mg</td>
<td>-1.57 ± 0.53</td>
<td>0.0257</td>
</tr>
<tr>
<td>GS-7340 150 mg</td>
<td>-1.71 ± 0.24</td>
<td>0.0010</td>
</tr>
</tbody>
</table>
M. Markowitz, et al., CROI 2011; Paper #152LB.
Tenofovir Levels in Plasma:
PK Profile on Day 1

TDF 300 mg
GS-7340 150 mg
GS-7340 50 mg

* p-value <0.001

M Markowitz, et al., CROI 2011; Paper # 152LB.
Tenofovir Diphosphate in PBMCs

* p-value <0.05

M Markowitz, et al., CROI 2011; Paper # 152LB.
Safety and Resistance

- No dose interruptions or discontinuations
- No serious adverse events
- No clinically significant laboratory abnormalities
- Most frequent adverse events were mild to moderate headache and nausea
- No resistance mutations to GS-7340 or TDF were detected at day 14 in any subject
Summary

- Monotherapy with GS-7340 at 50 or 150 mg led to significantly greater decreases in HIV-1 RNA and at lower systemic tenofovir exposures than with TDF 300 mg.
- GS-7340 is a next generation oral prodrug of tenofovir that has the potential to improve upon the efficacy and safety of TDF for the treatment of HIV.
- The lower dose of GS-7340 will permit the development of new single tablet regimens that are not possible today.
- GS-7340 has the potential of making tenofovir more widely available in resource limited settings given the relative manufacturing expense compared to TDF.