I have financial relationship(s) within the last 12 months relevant to my presentation with Gilead Sciences, Inc. (employment, stock options) AND

My presentation does include discussion of off-label or investigational use FTC for the treatment of HBV
HBV rtN236T Mutant Subpopulations Respond Like Wild-Type During Tenofovir DF (TDF) Monotherapy or Combination Therapy with Emtricitabine (FTC): an Evaluation of Early Viral Load Decay Kinetics

M Curtis 1, ES Svarovskaia 1, Y Zhu 1, K Peschell 1, MD Miller 2, K Borroto-Esoda 1

1Gilead Sciences, Inc., Durham, NC, USA; 2Gilead Sciences, Inc., Foster City, CA, USA

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Oral #134

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• HBV pol/RT resistance mutations have been identified following administration of most oral anti-HBV agents (lamivudine, adefovir dipivoxil, entecavir, and telbivudine)

• No amino acid substitutions associated with resistance to tenofovir DF detected in the HBV pol/RT following 192 weeks of TDF treatment for HBeAg- and HBeAg+ subjects in Studies 102 and 103

• In vitro, the rtN236T ADV-associated resistance mutation confers low-level cross-resistance (2.5-12-fold) to tenofovir

1Snow-Lampart et. al. AASLD 2010, Poster #1365
2Kitrinos et. al. AASLD 2009, Poster #434
Objective

• Evaluate the clinical response to TDF therapy of the rtN236T mutant virus

• Using allele-specific PCR, detect the rtN236T mutation in patient samples prior to and during TDF or FTC/TDF therapy

• Compare early viral load decay kinetics of mutant vs. wild-type in CHB mono-infected patients harboring rtN236T prior to initiation of TDF or FTC/TDF therapy
Study 106: TDF vs FTC+TDF in ADV Refractory Patients

RANDOMIZATION 1:1

Tenofovir 300 mg

Tenofovir 300 mg/FTC 200mg

Blinded TDF or OL FTC/TDF

Blinded FTC/TDF or OL FTC/TDF

Blinded FTC/TDF or OL FTC/TDF

Total Study Duration = 168 Weeks (Blinded or Open Label)

Double Blind

Week 24

Week 48
Primary Analysis

Week 168
End of Study
Mean HBV DNA Over Time by Baseline ADV Resistance Mutations

Viral Load Limit of Detection (169 copies/mL)
Method Background -
Allele-Specific PCR (MULTI-CODE RTx)

Amplified HBV rt region

Target-specific 5' labeled primers

- rtN236N
- rtN236T

- limit of 0.5% for detection of the mutation
- dynamic range from 0.5% to 95%
- Viral Load cut-off 1000 cp/mL
Assay Validation - Detection of rtN236T in a Patient on Long Term Adefovir Therapy*

*Previous studies have shown increased selection of the rtN236T in patients during ADV therapy (Pallier et.al. 2009, Hepatology 49;50-9)
• Baseline samples (n=105) from patients enrolled in Study 106 were tested for rtN236T using AS-PCR

• Patients with rtN236T at baseline were evaluated for levels of rtN236T and rtN236N at each visit through week 24 (or until HBV DNA <1000 copies/mL)

• Differences in viral load decline through week 4 were evaluated using a Wilcoxon signed rank and rank sum test
The rtN236T Mutation was Detected in 14 (13.3%) Patients Prior to Initiating TDF or FTC/TDF

<table>
<thead>
<tr>
<th>Pt</th>
<th>ORIGINAL COHORT</th>
<th>BL HBV DNA Log₁₀ cp/mL</th>
<th>BL MUTATIONS (population sequencing)</th>
<th>BL % rtN236T (AS-PCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>TDF</td>
<td>6.1</td>
<td>rtA₁₈₁A/T,rtN₂₃₆N/T</td>
<td>17.7%</td>
</tr>
<tr>
<td>B</td>
<td>TDF</td>
<td>6.7</td>
<td>rtN₂₃₆N/T</td>
<td>34.3%</td>
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<tr>
<td>C</td>
<td>TDF</td>
<td>6.1</td>
<td>rtA₁₈₁V/A,rtN₂₃₆T/N</td>
<td>52.5%</td>
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<tr>
<td>D</td>
<td>TDF</td>
<td>8.8</td>
<td>rtA₁₈₁A/T/V,rtN₂₃₆T/N</td>
<td>56.4%</td>
</tr>
<tr>
<td>E</td>
<td>TDF</td>
<td>6.9</td>
<td>rtA₁₈₁T,rtN₂₃₆T</td>
<td>93.2%</td>
</tr>
<tr>
<td>F</td>
<td>FTC/TDF</td>
<td>6.0</td>
<td>None</td>
<td>0.5%</td>
</tr>
<tr>
<td>G</td>
<td>FTC/TDF</td>
<td>5.2</td>
<td>None</td>
<td>0.5%</td>
</tr>
<tr>
<td>H</td>
<td>FTC/TDF</td>
<td>6.1</td>
<td>None</td>
<td>1.0%</td>
</tr>
<tr>
<td>I</td>
<td>FTC/TDF</td>
<td>5.8</td>
<td>Unable to genotype*</td>
<td>1.3%</td>
</tr>
<tr>
<td>J</td>
<td>FTC/TDF</td>
<td>4.9</td>
<td>rtL₁₈₀Mrt/M₂₀₄M/V</td>
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<tr>
<td>K</td>
<td>FTC/TDF</td>
<td>7.3</td>
<td>rtA₁₈₁V</td>
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</tr>
<tr>
<td>L</td>
<td>FTC/TDF</td>
<td>7.4</td>
<td>None</td>
<td>8.2%</td>
</tr>
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<td>M</td>
<td>FTC/TDF</td>
<td>6.6</td>
<td>None</td>
<td>14.3%</td>
</tr>
<tr>
<td>N</td>
<td>FTC/TDF</td>
<td>8.4</td>
<td>rtN₂₃₆N/T</td>
<td>17.0%</td>
</tr>
</tbody>
</table>

*rtA₁₈₁V/A, rtN₂₃₆N/T detected by INNO LiPA
Average Decline in rtN236T and WT Populations in Patients on TDF or FTC/TDF

- 3/5 TDF patients had HBV DNA <1000 cp/mL at W24
- 6/9 FTC/TDF patients had HBV DNA <1000 cp/mL at W24
- no significant difference in rates of viral load decline at W4 for the rtN236T virus comparing TDF and FTC/TDF treatment (p=0.933)
The rtN236T Virus Showed Similar Rates of Decline to WT at W4 with TDF

TDF Subject A
(18% rtN236T by AS-PCR; rtA181A/T±rtN236N/T by pop.seq.)

TDF Subject E
(93% rtN236T by AS-PCR; rtA181T ± N236T by pop.seq.)

- Overall, no significant difference between rtN236T and WT rates of early viral load decline (p=0.109)
The rtN236T Virus Showed Similar Rates of Decline to WT at W4 with TDF/FTC

- Overall, no significant difference between rtN236T and WT rates of early viral load decline (p=0.375)
Relative Proportions of rtN236T to WT did not Increase During Therapy with TDF or FTC/TDF

% rtN236T at Baseline and Last Evaluable Time Point for patients in TDF arm

% rtN236T at Baseline and Last Evaluable Time Point for Patients in FTC/TDF Arm

Average % N236T is from n=2 AS-PCR runs
Conclusions

• The rtN236T mutant virus showed similar early viral load kinetics of HBV DNA decline to that of WT virus

• No statistical differences in the rate of viral load decline between rtN236T and wild-type virus at W4 on either TDF or FTC/TDF

• Despite low levels of cross resistance observed in vitro, TDF equally suppresses WT and rtN236T viruses in vivo
I would like to thank my colleagues at Gilead for their contribution to and review of this presentation:

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