4 Year Efficacy of Tenofovir Disoproxil Fumarate (TDF) in Chronic Hepatitis B Patients with High Viral Load (HBV DNA \( \geq 9 \log_{10} \text{copies/mL} \))

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I have financial relationships within the last 12 months relevant to my presentation with Abbott, Achillion, Anadys, Bayer, Bristol-Myers Squibb, Conatus, CVS Caremark, Dynavax Technologies, Exalenz BioScience, Gilead Sciences, GlaxoSmithKline, GlobeImmune, Human Genome Sciences, Idera, Intercept, Merck, Roche, Schering Plough, SciClone, Tibotec, Valeant, Vertex, and Zymogenetics

AND

My presentation does include discussion of off-label or investigational use of FTC/TDF for the treatment of HBV
Introduction

• Tenofovir DF (TDF) approved for HIV-1 in 2001 and chronic hepatitis B (CHB) in 2008 (~3 million patient years exposure)

• Week 48 data showed significantly greater antiviral activity of TDF compared to adefovir dipivoxil (ADV)

• HBV patients with exceedingly high levels of baseline viremia (HVL) represent a clinical challenge
Objective

- Evaluate the efficacy of up to 4 years of TDF therapy in patients with HVL, i.e., HBV DNA $\geq 9 \log_{10} \text{copies/mL}$ (or $\geq 8.24 \log_{10} \text{IU/mL}$)
- HBeAg-positive and HBeAg-negative
Pre-treatment Liver Biopsy

Study Design of Phase 3 Pivotal Studies 102 (HBeAg−) and 103 (HBeAg+)

Randomization 2:1

Tenofovir DF 300 mg

Adefovir Dipivoxil 10 mg

Week 48 Liver Biopsy

Week 72 Liver Biopsy

Tenofovir DF 300 mg

Tenofovir DF 300 mg

Week 192 Liver Biopsy

Week 240

Week 384

Double Blind

Year 1

Open-label

Year 8

• 129/641 patients enrolled across the two studies had HVL at baseline
• On or after week 72 patients with a confirmed HBV DNA ≥400 copies/mL were eligible to add FTC; overall across both studies, 51 patients were eligible to add FTC (38 added and 13 did not); 35/51 had HVL

Patient Retention at Year 4: 84% (102) and 74% (103)
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Original Randomized Treatment Group</th>
<th>Patients with Baseline HBV DNA ≥9 log_{10} copies/mL</th>
<th>Patients with Baseline HBV DNA &lt;9 log_{10} copies/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TDF (N=82)</td>
<td>ADV (N=47)</td>
</tr>
<tr>
<td>Mean HBV DNA (log_{10} copies/mL)</td>
<td>9.51</td>
<td>9.59</td>
</tr>
<tr>
<td>HBeAg Positive</td>
<td>93%</td>
<td>89%</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>Mean HBsAg (log_{10} IU/mL)</td>
<td>4.87</td>
<td>4.86</td>
</tr>
<tr>
<td>Mean ALT (U/L)</td>
<td>136.9</td>
<td>168.0</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>20%</td>
<td>28%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>71%</td>
<td>60%</td>
</tr>
<tr>
<td>Male</td>
<td>74%</td>
<td>74%</td>
</tr>
<tr>
<td>Mean Knodell necroinflammatory score</td>
<td>7.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Mean Knodell fibrosis score</td>
<td>2.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Knodell fibrosis score = 4 (cirrhosis)</td>
<td>14%</td>
<td>20%</td>
</tr>
<tr>
<td>Viral Genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>B</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>C</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>D</td>
<td>53%</td>
<td>41%</td>
</tr>
</tbody>
</table>
Proportion of High Viral Load Patients with HBV DNA <400 copies/mL: ITT Analysis

Randomized Double-Blind

Open-Label

Percentage (%) vs. Weeks on Study

Treatment Group:
- TDF-TDF
- ADV-TDF

Values:
- 73%
- 71%
HBV DNA Over Time for Patients Treated with TDF for 192 Weeks: HBV DNA < 9 vs ≥ 9 log₁₀ copies/mL
Proportion of Patients with HBV DNA < 400 copies/mL Treated with TDF for 192 Weeks: On-Treatment Analysis
HBV DNA Profiles for Patients with HBV DNA \( \geq 400 \) copies/mL at Week 192

Subject 1664

Subject 7102

HBV DNA (log_{10} copies/mL)

Week
HBV DNA Profiles for Patients with HBV DNA ≥ 400 copies/mL at Week 192 (cont’d)

Subject 6002

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>108</th>
<th>120</th>
<th>132</th>
<th>144</th>
<th>156</th>
<th>168</th>
<th>180</th>
<th>192</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA (log_{10} copies/mL)</td>
<td>10</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

TDF FTC/TDF

Unable to genotype

WT

400 copies/mL
The Majority of Patients who remained on TDF Monotherapy or added FTC to TDF Between Weeks 72-192 Achieved HBV DNA < 400 copies/mL

35/129 were eligible to add FTC to TDF at / after Week 72*

6/35 (17%) remained on TDF monotherapy (2 TDF-TDF and 4 ADV-TDF)

5/6 (83%) HBV DNA < 400 c/mL (1 TDF-TDF and 4 ADV-TDF) At Week 192 / last visit

29/35 (83%) added FTC to TDF* (14 TDF-TDF and 15 ADV-TDF)

20/29 (69%) HBV DNA < 400 c/mL (8 TDF-TDF and 12 ADV-TDF) At Week 192 / last visit

*Most patients (N=26) added FTC to TDF on or before the week 96
29 High Viral Load Patients Who Added FTC
ALT Over Time by Baseline

HBV DNA $\geq 9$ vs $< 9 \log_{10}$ copies/mL (TDF-TDF)

Overall 77% normalized ALT
% High Viral Load Patients with HBeAg Loss and HBeAg Seroconversion*

*On-Treatment-Data for year 1 is for double-blind TDF only and thereafter includes all patients on open-label TDF
Cumulative probability of seroconversion to anti-HBs: 11.8% TDF-TDF and 10.0% ADV-TDF

A total of 17 HVL patients lost HBsAg, 12 of whom seroconverted to anti-HBs
Surveillance for Resistance Results

• No HBV pol/RT amino acid substitutions associated with tenofovir resistance were detected through 192 weeks of TDF in patients with high viral load.

For complete details on the Week 192 Resistance Surveillance see Poster #1365 by Snow-Lampart et al. No Resistance to Tenofovir Disoproxil Fumarate (TDF) Detected Following up to 192 Weeks of Treatment in Subjects Mono-Infected with Chronic Hepatitis B Virus.
Patients with high viral load, i.e., HBV DNA $\geq 9 \log_{10}$ copies/mL enrolled in the pivotal studies 102 and 103 achieved:

- Potent and durable antiviral activity: > 95% of patients on treatment at week 192 had HBV DNA < 400 copies/mL
- Increasing percentage of patients with HBeAg loss
- Increasing percentage of patients with HBsAg loss
- No resistance to TDF

TDF is an effective treatment option for patients with high viral load
Backup
Proportion of Patients with HBV DNA <400 copies/mL Treated with TDF for 192 Weeks: ITT Analysis

Higher retention rate in study 102 contributes significantly to the observed difference between groups since only 7% of the patients in the high viral load group were from study 102.
Proportion of High Viral Load Patients with HBV DNA <400 copies/mL: On-Treatment Analysis

![Graph showing the proportion of high viral load patients with HBV DNA <400 copies/mL over weeks on study, with percentage (%) and weeks on study as the axes. The graph includes two treatment groups: TDF-TDF and ADV-TDF. The graph also displays 100% and 95% confidence intervals.](image)
Overall Virological Response in Studies 102 and 103: HBV DNA <400 copies/mL at Week 192

Study 102: HBeAg-Negative* (Poster 476, Marcellin et al)

Study 103: HBeAg-Positive* (Poster 477, Heathcote et al)

*LTE-TDF