Introduction

- Tenofovir DF (TDF) is a nucleoside analog and obligate chain terminator
- Approved for HIV-1 in 2001: ~2 million patient-years of experience
- Approved for chronic hepatitis B (CHB) in 2008
- TDF was well tolerated through 48 weeks of treatment in the phase 3 CHB studies 102 and 103.
- Weak 48 Phase 3 data showed that TDF had superior antiviral efficacy to adefovir dipivoxil (ADV) in the ADV1 study, but not in the ADV2 study.
- 93% vs 63% (HBeAg-negative) and 76% vs 13% (HBeAg-positive) patients achieved HBV DNA <400 copies/mL (ITT).
- TDF continues to demonstrate durable, potent antiviral efficacy at Week 96.
- 91% of HBeAg-negative patients and 78% of HBeAg-positive patients had HBV DNA <400 copies/mL (ITT).

Methods

To evaluate the overall safety of 96 weeks (2 years) of treatment with TDF in both HBeAg-positive and HBeAg-negative patients enrolled in the phase 3, pivotal studies 102 and 103.

Results

Safety and tolerability

- Deaths
- Serious Adverse Events (SAEs)
- Grade 3 or 4 Adverse Events (AEs)
- (AEs) leading to study drug discontinuation
- Grade 3 or 4 laboratory abnormalities
- Renal tolerance (confirmed increase ≥ 0.5 mg/dL in creatinine, creatinine clearance <60 ml/min, phosphorus <3 mg/dL)
- Resistance Mutations

Safety Endpoints

- Overall Summary of TDF Safety

Table 1. Overall Summary of TDF Safety

<table>
<thead>
<tr>
<th>Adverse Event Category</th>
<th>Drug</th>
<th>N (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Serious AEs</td>
<td>TDF</td>
<td>5 (1.2%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Any Grade 3/4 AEs</td>
<td>TDF</td>
<td>5 (1.2%)</td>
<td>0.01</td>
</tr>
<tr>
<td>All Adverse Events</td>
<td>TDF</td>
<td>38 (9.6%)</td>
<td>0.01</td>
</tr>
<tr>
<td>All Grade 3 AEs</td>
<td>TDF</td>
<td>34 (8.5%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 2. AEs Resulting in Permanent Discontinuation of TDF

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Related to TDF</th>
<th>Week 96</th>
<th>Week 384</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>2 (0.5%)</td>
<td>1 (0.2%)</td>
<td>0.2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (0.2%)</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>1 (0.2%)</td>
<td>0.2%</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Treatment Emergent Grade 3 or 4 Clinical AEs

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Related to TDF</th>
<th>Week 96</th>
<th>Week 384</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix Carcinoma</td>
<td>1 (0.2%)</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>1 (0.2%)</td>
<td>0.2%</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- The safety and tolerability profile of tenofovir DF was good and did not show any new or unexpected adverse events in the HBV–infected population.
- The renal safety of tenofovir DF was good and confirms the profile established in patients with HIV-infection.
- The virologic safety profile of tenofovir DF remains excellent with <2% resistance at 2 years.

References


Acknowledgements

Special thanks to all the participating investigators and patients in the US-US-147101 and US-US-147110 studies.

None of the patients with a confirmed decrease in phosphorus had a concurrent and/or clinically significant increase in creatinine or decrease in creatinine clearance.

Virologic Safety

- No HBV pol/RT amino acid substitutions associated with TDF resistance were detected through 96 weeks of TDF monotherapy in HBeAg-negative and HBeAg-positive patients.