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Resistance Surveillance for up to 144 Weeks in HBeAg+ and HBeAg- Hepatitis B Patients Treated with Tenofovir DF

Showed No Relationship between Virological Breakthrough and Emergence of Genotypic Changes in HBV Polymerase

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Introduction

- Tenofovir disoproxil fumarate (tenofovir DF, TDF) is a nucleoside analog with potent antiviral activity in patients mono-infected with HBV and co-infected with HIV and HBV.
- HBV pol/RT resistance mutations have been identified following first-line administration of other oral anti-HBV agents (lamivudine, adefovir dipivoxil, entecavir, and tenofovir).

Objectives

- To identify amino acid substitutions in the HBV pol/RT following up to 144 weeks of therapy with TDF 300 mg once daily.
- To evaluate the effects of these substitutions on the clinical response to TDF monotherapy in chronic hepatitis B.
- To determine whether these substitutions alter susceptibility to tenofovir by using in vitro HBV replication assays and to evaluate the cross-resistance profile of these substitutions.

Methods

Figure 1. Design of HBeAg Study 102 and HBeAg Study 103 of TDF in Chronic Hepatitis B Patients

- Patients were enrolled in one of two double-blind, randomized studies of TDF (Study 102 [HBeAg+] or Study 103 [HBeAg-]).
- Genotypic analysis by population di-deoxy sequencing of serum HBV pol/RT:
  - Covers AA 1-344 of pol/RT (AA 1-266 of HBsAg).
  - Able to detect AA substitutions present at ≤ 2% of viral quasispecies population.
- Phenotypic analyses were conducted in HepG2 cells transiently transfected with:
  - A panel of recombinant HBV plasmid DNA derived from patient serum HBV pol/RT or
  - Mutant virus created by site-directed mutagenesis in the ccr5/HBV (genotype D) or
  - pH92 (genotype A) backbone.
- Plasma HBV DNA levels were determined by Roche COBAS TaqMan assay (LLOQ = 169 copies/mL; 29 IU/mL).

Figure 2. Virology Analysis Plan for Studies 102 and 103

- All patients:
  - At baseline:
    - If HBV DNA ≥ 400 copies/mL (≥ 69 IU/mL).
    - At discontinuation of TDF monotherapy if HBV DNA ≥ 400 copies/mL.
- Any patient post-baseline with:
  - Conserved site changes in pol/RT
  - Virologic breakthrough (VB)
  - Polymorphic site changes (> 1 patient)
  - Defined as a confirmed 1 log10 increase in HBV DNA from baseline and/or confirmed HBV DNA > 400 copies/mL.

Figure 3. Genotypic Changes in HBeAg+ and HBeAg- TDF-Treated Patients During Year 3

- Patients entering Year 3: 364/426 (85%) 192/215 (89%)
- Patients on TDF monotherapy:
  - HBeAg+: 138/148 (93%)
  - HBeAg-: 9/13 (69%)
- Patients with VB:
  - HBeAg+: 6 (100%)
  - HBeAg-: 3/8 (37.5%)
- Patients on FTC/TDF combination therapy:
  - HBeAg+: 6 (100%)
  - HBeAg-: 3/5 (60%)

Figure 4. HBV DNA Profile for the TDF-TDF Treated Patients with Conserved Site Changes

- No change
- Phenotypic site change
- Conserved site change
- Unique to genotype

Figure 5. Genotypic Changes in HBeAg+ and HBeAg- ADV-TDF Treated Patients During Year 3

- Patients on TDF Monotherapy: (n=6)
  - No change
  - Phenotypic site change
  - Unique to genotype

- Patients on FTC/TDF Therapy: (n=4)
  - No change
  - Phenotypic site change
  - Unique to genotype

Results

- Table 1. HBeAg+ and HBeAg- Patients Evaluated During Year 3

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>TDF Group</th>
<th>ADV-TDF Group</th>
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<tbody>
<tr>
<td>Patients entering Year 3</td>
<td>364/426 (85%)</td>
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<td>Patients on FTC/TDF combination therapy</td>
<td>6 (100%)</td>
<td>3/5 (60%)</td>
</tr>
</tbody>
</table>

- Table 2. Development of Conserved Site Changes in HBV pol/RT that Did Not Impact Phenotypic Sensitivity to Tenofovir in vitro

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Oral Inhibitor</th>
<th>Fold Change from Baseline</th>
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<tbody>
<tr>
<td>TDF</td>
<td>ADV</td>
<td>0.7</td>
</tr>
<tr>
<td>ADV</td>
<td>FTC/TDF</td>
<td>1.4</td>
</tr>
</tbody>
</table>

- Figure 6. HBV DNA Profile for the ADV-TDF Treated Patients with Conserved Site Changes

- Figure 7. Virologic Breakthrough (VB) defined as a confirmed 1 log10 increase in HBV DNA from baseline and/or confirmed HBV DNA > 400 copies/mL.

- Figure 8. Summary of Resistance Analysis of TDF-Treated Patients Through Year 3

Conclusions

- No resistance to TDF developed following up to 3 years of TDF monotherapy in 364 patients.
- Similar data observed among the 20 patients who added FTC.
- No resistance to TDF developed among 192 ADV-treated patients following up to 2 years of TDF monotherapy.
- Similar data observed among the 14 patients who added FTC.
- Patient retention remained high, 86.7% (586/661) across both arms of Studies 102 and 103.

References & Acknowledgements

3. Jeff Sorbel – Biostatistics department GSI; Members of the Bioanalytical department GSI.