Tenofovir alafenamide vs tenofovir disoproxil fumarate, each co-formulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, Phase 3, non-inferiority trials

Background

- Tenofovir disoproxil fumarate (TDF) is included in most recommended antiretroviral regimens, and although potent and generally well tolerated, has been associated with clinically significant renal and bone toxicity

- Relative to TDF 300 mg, tenofovir alafenamide (TAF) 25 mg has 90% lower circulating plasma TFV, while maintaining high antiviral activity

- In Phase 2, efficacy of elvitegravir, cobicistat, emtricitabine, and TAF (E/C/F/TAF) was comparable to E/C/F/TDF, and demonstrated significant improvements in renal and bone safety

- We sought to confirm the efficacy of E/C/F/TAF in two fully powered clinical trials

Disclosure of Interest Statement

- Study 104 and 111 are Gilead Sciences sponsored Phase IIIb studies
- Dr. Bloch has received funding from, acted as an advisor for and/or participated in clinical research for: Gilead Sciences, Janssen, Merck, Bristol Myers Squibb ViIV Healthcare, Abbvie

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Tenofor Alafenamide (TAF)

TAF is a Targeted Prodrug of TFV – Reduces Circulating TFV

- TAF is more stable in plasma compared with TDF
- Intact TAF transits directly into target cells where it is intracellularly activated to tenofovir-disphosphate (TFV-DP)
- TAF has 90% lower circulating plasma TFV levels compared to TDF 300mg

Studies 104 and 111: ART-Naive Adults, Week 48 Combined Analysis

**Study Design**

Two Phase 3, International, randomized, double-blind, active-controlled studies

- **Primary Endpoint**
  - Non-inferiority (12% margin of E/C/F/TAF to Stribild based on HIV-1 RNA <50 copies/mL at Week 48 by FDA Snapshot analysis)

- **Secondary Endpoints**
  - Efficacy safety, and bone density observed through Week 96, Week 144

- **Stratification by**
  - HIV-1 RNA ≤100,000 copies/mL
  - CD4 count ≥350 cells/µL
  - geographic region

- **Te-Novel Adults**
  - HIV-1 RNA≤5000 copies/mL
  - eGFR ≥50 mL/min

- **Week 48**
  - E/C/F/TAF QD
  - Stribild Placebo QD

- **Week 96**
  - E/C/F/TAF Placebo QD

- **Week 144**
  - E/C/F/TAF QD

- **ClinicalTrials.gov Identifier:** NCT01780506 and NCT01797445

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1. Efficacy and safety of TAF were compared with TDF based on the Week 48 snapshot analysis.
2. NDI = number of patients with no deaths or discontinuations due to AEs.
3. Tenofovir plasma concentration may be lower than 150 ng/mL due to differences in PK formulation.

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1. TDF and TAF are prodrugs that are converted into their active metabolites, TFV and TFV-DP, respectively, within cells.
2. TDF is known to be associated with renal toxicity and bone loss.
3. TAF is expected to have lower renal and bone toxicity compared to TDF.

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1. TAF is currently approved in the United States for the treatment of HIV-1 infection as part of a combination antiretroviral therapy regimen.
2. TAF is expected to be a superior option for HIV-1 treatment due to its improved safety profile.
3. The use of TAF in combination with other antiretroviral drugs is recommended to achieve an optimal therapeutic effect.
E/C/F/TAF was non-inferior to Stribild at Week 48 in each study
- 93% E/C/F/TAF vs 92% Stribild (Study 104)
- 92% E/C/F/TAF vs 89% Stribild (Study 111)
- Increase in CD4 count (cells/μL) at Week 48
  - E/C/F/TAF: +211 vs Stribild: +181 (P=0.024)

High rates of virologic success across age, sex, and race subgroups

0.8% developed treatment emergent resistance on E/C/F/TAF

Changes in Spine and Hip BMD Through Week 48

<table>
<thead>
<tr>
<th>Patients</th>
<th>Spine BMD</th>
<th>Hip BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/C/F/TAF</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Stribild</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

**Significantly less decrease in spine and hip BMD in the E/C/F/TAF group at Week 48**

*Comparison of E/C/F/TAF vs Stribild at Week 48*
Changes (%) in Quantitative Proteinuria at Week 48

**Urine Protein/Creatinine Ratio**

- **E/C/F/TAF**:
  - Protein/Creatinine (P/Cr): 3.5 to 3.2 g/g
  - Albumin/Creatinine (A/Cr): 3.3 to 3.0 g/g
  - β2-globulin/Creatinine (β2-g/Cr): 2.9 to 2.7 g/g

- **Stribild**:
  - Protein/Creatinine (P/Cr): 3.7 to 3.5 g/g
  - Albumin/Creatinine (A/Cr): 3.5 to 3.3 g/g
  - β2-globulin/Creatinine (β2-g/Cr): 3.1 to 2.9 g/g

**Changes (%) in Quantitative Proteinuria at Week 48**

- **E/C/F/TAF**:
  - Gain >3%
  - Loss >3%
  - No Change*

- **Stribild**:
  - Gain >3%
  - Loss >3%
  - No Change*

*No Change = 0% to 3%
Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Fasting Lipids at Week 48

<table>
<thead>
<tr>
<th>Median values (mmol/L)</th>
<th>E/C/F/TAF Baseline</th>
<th>Week 48</th>
<th>Stribild Baseline</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>5.00</td>
<td>4.65</td>
<td>4.92</td>
<td>4.69</td>
</tr>
<tr>
<td>LDL</td>
<td>2.96</td>
<td>2.56</td>
<td>3.02</td>
<td>2.67</td>
</tr>
<tr>
<td>HDL</td>
<td>1.32</td>
<td>1.24</td>
<td>1.29</td>
<td>1.22</td>
</tr>
<tr>
<td>triglycerides</td>
<td>1.13</td>
<td>1.13</td>
<td>1.13</td>
<td>1.13</td>
</tr>
<tr>
<td>TC:HDL Ratio</td>
<td>4.22</td>
<td>3.97</td>
<td>4.14</td>
<td>3.77</td>
</tr>
</tbody>
</table>

Subjects initiating lipid-modifying medications: 3.6% E/C/F/TAF vs 2.9% Stribild (P<0.001).

Changes in TC, LDL, TG were balanced by changes in HDL on TAF compared to TDF with no difference between the arms on the TC:HDL ratio.

Safety Summary Through Week 48

<table>
<thead>
<tr>
<th>%</th>
<th>E/C/F/TAF n=866</th>
<th>Stribild n=867</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Events (AE)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Any drug-related AE</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>Grade 3 or 4 AE</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Drug-related grade 3 or 4 AE</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Serious AE</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Drug-related serious AE</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>AE-related discontinuation, % (n)</td>
<td>0.9 (8)</td>
<td>1.5 (13)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0.2*</td>
<td>0.3†</td>
</tr>
</tbody>
</table>

*Stroke (1), alcohol intoxication (1). †Alcohol and drug intoxication (1), myocardial infarction (2).

Discontinuations due to AEs occurred in 0.9% in the E/C/F/TAF arm.

Common Adverse Events (≥5%) Through Week 48

<table>
<thead>
<tr>
<th>Adverse event (all grades), %</th>
<th>E/C/F/TAF n=866</th>
<th>Stribild n=867</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Cough</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Back pain</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Rash</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Rates and types of AEs were similar between both arms. No new safety findings.

Grade 3 or 4 Lab Abnormalities

<table>
<thead>
<tr>
<th>Grade 3 or 4 lab abnormalities* ,%</th>
<th>E/C/F/TAF n=866</th>
<th>Stribild n=867</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine kinase elevation</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>LDL elevation (fasting)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Hypercholesterolemia (fasting)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hematuria (quantitative)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ART elevation</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Serum amylase elevation</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia (&lt;1000 cells/µL)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*≥1% on E/C/F/TAF arm

Similar types and rates of grade 3 or 4 lab abnormalities.

Conclusions

Phase 3 E/C/F/TAF studies of 1,733 ART-naïve patients demonstrated:

- Non-inferior efficacy to Stribild at W48 with high and similar virologic success rates across studies (93% Study 104 & 92% Study 111) and subgroups (HIV-1 RNA, CD4 count, age, sex, and race)
- Low virologic failure rates with <1% resistance in both arms
- Well tolerated with low discontinuations due to AEs (0.9% E/C/F/TAF vs 1.6% Stribild) and similar common AEs to Stribild
- Detailed protocol-specified renal and bone endpoints confirmed the favorable safety and tolerability profile of TAF vs. TDF
  - No discontinuations due to renal AEs
  - Significantly less eGFR decline and less proteinuria, albuminuria, and tubular proteinuria
  - Significantly less impact on spine and hip BMD

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis