Bioequivalence of Two Pediatric Formulations vs Adult Tablet Formulation of Elvitegravir

JM Custodio, Y Liu, H Graham, M Hepner, L Wiser, E Quirk, BP Kearney, and S Ramanathan

Gilead Sciences, Inc., Foster City, CA, USA

Introduction

- Safe and effective pediatric antiretroviral (ARV) therapeutic options are needed
  - Perinatally infected children require lifelong ARV therapy
  - There is a need for convenient, well-tolerated pediatric therapies with activity against HIV resistant to existing classes
  - No once-daily integrase inhibitor is approved for use in HIV-infected children younger than 12 years
- Elvitegravir (EVG) is a once-daily integrase inhibitor in development as a single agent for the treatment of adults and children with HIV-1 infection
  - In regulatory review in the United States
  - Approved in the European Union for treatment of adults when coadministered as part of an antiretroviral regimen containing a boosted protease inhibitor
- EVG has also been coformulated with cobicistat (COBI), emtricitabine (FTC), and tenofovir DF (TDF) into the single tablet regimen E/C/F/TDF (Strivid; STB) approved for the treatment of HIV-1 infection in adults
- EVG pharmacokinetics (PK) well characterized and previous taste assessment of an EVG oral suspension demonstrated that flavors are unlikely to be patient-perceptible due to the lack of chalky, oily, drying, or tongue stinging in the formulation

Objectives

Primary:
- Evaluate the bioequivalence of the age-appropriate EVG pediatric tablet and suspension formulations compared with the adult EVG tablets in healthy adult subjects

Secondary:
- Evaluate the safety of the age-appropriate EVG pediatric tablet and suspension formulations and adult EVG tablets in healthy adult subjects

Methods

- All EVG treatments across all cohorts included 100 mg of RTV as a pharmacoenhancer (EVG/RTV)
  - On PK days, study treatments were administered in the morning following an overnight fast and within five minutes of the completion of a standardized meal
  - Intensive PK sampling performed over 48 hours
  - EVG PK determined using validated LC/MS/MS assays
  - PK parameters estimated using non-compartmental methods and WinNonlin® software v6.3 (Pharsight Corporation, Mountain View, CA, USA)
  - A parametric (normal theory) analysis of variance (ANOVA) using a mixed effects model was fitted to the natural logarithmic transformation of PK parameters of each analyte
  - Bioequivalence (BE) 90% confidence interval (CI) (pediatric formulation: adult tablet) about geometric mean ratio (GMR) as follows: EVG AUC_{0-24h}, C_{max} 90% to 125%
  - Cohorts 1 and 2 contained >85% power to conclude BE
  - In Cohort 3, only descriptive PK was assessed

Results (cont’d)

Table 1. Demographics

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Age (mean [range])</td>
<td>27 (18-44) yr</td>
<td>27 (20-40) yr</td>
<td>27 (18-41) yr</td>
</tr>
<tr>
<td>Weight (mean [range])</td>
<td>75.4 (65.0-109) kg</td>
<td>72.9 (55.4-99.8) kg</td>
<td>74.6 (52.7-102) kg</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>Black</td>
<td>American Indian</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 2. Cohort 3: Steady State PK of Pediatric Tablet and Suspension

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK Parameter</td>
<td>Pediatric EVG</td>
<td>Pediatric EVG</td>
<td>Adult EVG</td>
</tr>
<tr>
<td>mean (%CV)</td>
<td>3x50 mg Tablets</td>
<td>3x50 mg Tablets</td>
<td>150 mg Tablet</td>
</tr>
<tr>
<td>AUC_{0-24h} (ng*h/mL)</td>
<td>25000 (36)</td>
<td>24000 (36)</td>
<td>20900 (24)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>4700 (23)</td>
<td>4400 (18)</td>
<td>2040 (30)</td>
</tr>
<tr>
<td>C_{trough} (ng/mL)</td>
<td>440 (18)</td>
<td>410 (18)</td>
<td>377 (31)</td>
</tr>
</tbody>
</table>

Results

- EVG pediatric tablets are BE compared to adult EVG tablet
- EVG pediatric suspension is BE compared to adult EVG tablet

Conclusions

- EVG pediatric tablet and suspension formulations were each bioequivalent to adult tablets, when coadministered with RTV
- Steady state PK of both pediatric formulations were consistent with historical data of boosted EVG
- EVG pediatric formulations were well tolerated and overall safety profile consistent with previous studies with EVG adult tablets
- These study findings support evaluation of these pediatric formulations in HIV infected children in an ongoing Phase 2/3 study