ASSESSMENTS OF VERY-LOW-LEVEL HIV REPLICATION FOR DOLUTEGRAVIR + LAMIVUDINE (DTG + 3TC) VS DOLUTEGRAVIR + TENOFOVIR DISOPROXIL/EMTRICITABINE (DTG + TDF/FTC) IN THE GEMINI-1&-2 STUDIES THROUGH WEEK 96

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Mark Underwood is an employee of ViiV Healthcare and owns GSK stock.
Introduction

• Two-drug regimens (2DRs) reduce the number of drugs for PLWHIV who need lifelong ART\(^1\)

• In the primary analysis of the GEMINI-1 and GEMINI-2 studies at Week 48, DTG + 3TC was non-inferior to DTG + TDF/FTC in the treatment of HIV-1–infected treatment-naive adults,\(^2\) with non-inferiority of the 2DR maintained in a preplanned analysis at Week 96\(^3\)

• DTG/3TC\(^a\) is currently approved as a once-daily, single-tablet 2DR by the US Food and Drug Administration and the European Medicines Agency

• The goal of this analysis is to assess differences in very-low-level viremia for DTG + 3TC 2-drug regimen vs DTG + TDF/FTC 3-drug regimen

\(^a\)DOVATO.
\(^1\) Kelly et al. Drugs. 2016;76:523-531. \(^2\) Cahn et al. Lancet. 2019;393:143-155. \(^3\) Cahn et al. IAS 2019; Mexico City, Mexico. Slides WEAB0404LB.
GEMINI-1 and GEMINI-2 Phase III Study Design

Identically designed, randomized, double-blind, parallel-group, multicenter, non-inferiority studies

Eligibility criteria
- VL 1000-500,000 c/mL at screening
- ≤10 days of prior ART
- No major RT or PI resistance mutation
- No HBV infection or need for HCV therapy

Baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm³)

Primary endpoint at Week 48: participants with HIV-1 RNA <50 c/mL (ITT-E Snapshot)²

DTG + 3TC is non-inferior to DTG + TDF/FTC with respect to proportion of participants with HIV-1 RNA <50 c/mL at Week 48 and Week 96 (Snapshot, ITT-E population) in both studies¹,²

Countries
- Argentina
- Australia
- Belgium
- Canada
- France
- Germany
- Italy
- Republic of Korea
- Japan
- Poland
- Netherlands
- Peru
- Portugal
- Romania
- Russian Federation
- South Africa
- Spain
- Switzerland
- Taiwan
- United Kingdom
- United States
- United States

¹-10% non-inferiority margin for individual studies.
DTG + 3TC Is Non-Inferior to DTG + TDF/FTC in Snapshot HIV-1 RNA <50 c/mL at Week 96

Non-inferiority criteria were met for GEMINI-1, GEMINI-2, and the pooled analysis.b

Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL), CD4+ cell count (≤200 vs >200 cells/mm³), and study (GEMINI-1 vs GEMINI-2). The upper limit of the 95% CI for the pooled analysis was 0.0007%. In GEMINI-1, HIV-1 RNA <50 c/mL (95% CI) was achieved in 300/356 participants (84.3% [80.5-88.1]) in the DTG + 3TC group and 320/358 (89.4% [86.2-92.6]) in the DTG + TDF/FTC group (adjusted treatment difference [95% CI], −4.9% [−9.8, 0.03]). In GEMINI-2, the corresponding values were 316/360 (87.8% [84.4-91.2]) and 322/359 (89.7% [86.5-92.8]), respectively (adjusted treatment difference [95% CI], −1.8% [−6.4, 2.7]).

Cahn et al. IAS 2019; Mexico City, Mexico. Slides WEAB0404LB.
HIV-1 RNA VL Data and Ad Hoc Analyses

• Abbott HIV-1 RealTime Assay
  • Generates quantitative HIV-1 RNA viral load (VL) from 40 to 10,000,000 c/mL
  • Generates qualitative data for VL <40 c/mL
    • HIV-1 RNA present → TD (target detected)
    • HIV-1 RNA not present → TND (target not detected)

• Includes Additional Virological-Focused Analyses
  • LOCF (last observation carried forward) – Includes all last on-treatment VLs up to the Week 96 analysis window while on IP
  • “Observed” – Defined as virologically suppressed at Week 96 and thereby censors earlier failures including those unrelated to efficacy
Similar Median Weeks to TND Across Groups in Observed Analysis

- Median 8 weeks to TND across groups was also seen by Snapshot analysis at Week 96 and was previously demonstrated for Week 48\(^1\)

1. Underwood et al. CROI 2019; Seattle, WA. Poster 490.

**Table:**

<table>
<thead>
<tr>
<th>N</th>
<th>Group</th>
<th>Median weeks to TND</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>616</td>
<td>DTG + 3TC</td>
<td>8</td>
<td>NE, NE</td>
</tr>
<tr>
<td>642</td>
<td>DTG + TDF/FTC</td>
<td>8</td>
<td>NE, NE</td>
</tr>
</tbody>
</table>

NE, not evaluable.

17th European AIDS Conference; November 6-9, 2019; Basel, Switzerland
Proportions With TND Were Similar Between Groups at All Visits

Proportion of Participants With TND by Visit (Snapshot Analysis, ITT-E Population)

Number at base of bars is number of participants reaching TND at week visit

Underwood et al. EACS 2019; Basel, Switzerland. Slides PS8/2.

Download Slides: Bit.ly/geminitnd
• At Week 96, median times to TND were comparable in the DTG + 3TC and DTG + TDF/FTC groups, regardless of BL VL or CD4+ cell count

### Median Time to TND in Subgroups for Observed Analysis

#### VL ≤ 100,000 c/mL

<table>
<thead>
<tr>
<th>Group</th>
<th>Weeks</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG + 3TC</td>
<td>8</td>
<td>(-8, -8)</td>
</tr>
<tr>
<td>DTG + TDF/FTC</td>
<td>8</td>
<td>(-8, -8)</td>
</tr>
</tbody>
</table>

#### CD4+ cells > 200 cells/mm³

<table>
<thead>
<tr>
<th>Group</th>
<th>Weeks</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG + 3TC</td>
<td>8</td>
<td>(NE, NE)</td>
</tr>
<tr>
<td>DTG + TDF/FTC</td>
<td>8</td>
<td>(NE, NE)</td>
</tr>
</tbody>
</table>

#### VL > 100,000 c/mL

<table>
<thead>
<tr>
<th>Group</th>
<th>Weeks</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG + 3TC</td>
<td>16</td>
<td>(~16, ~24)</td>
</tr>
<tr>
<td>DTG + TDF/FTC</td>
<td>24</td>
<td>(~24, ~36)</td>
</tr>
</tbody>
</table>

#### CD4+ cells ≤ 200 cells/mm³

<table>
<thead>
<tr>
<th>Group</th>
<th>Weeks</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG + 3TC</td>
<td>16</td>
<td>(~12, ~24)</td>
</tr>
<tr>
<td>DTG + TDF/FTC</td>
<td>12</td>
<td>(~8, ~24)</td>
</tr>
</tbody>
</table>

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Proportions With TND by Snapshot and Observed Analyses at Week 96 by BL VL and CD4+ Cell Count

- At Week 96, similar proportions\(^a\) had TND in each group regardless of BL VL, and regardless of CD4+ cell count in the observed analysis.

\(^a\)The proportion of participants with VL<40 c/mL and TND status at Week 96 was analyzed using a Cochran-Mantel-Haenszel test stratified by VL (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm\(^3\)) at BL.

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Conclusions

• Through Week 96, the proportions of participants with TND were similar at all visits in the DTG + 3TC and DTG + TDF/FTC groups

• This supports previous results based on Snapshot <50 c/mL at Week 48 and Week 96

• At Week 96, proportions of participants with TND were comparable in the DTG + 3TC and DTG + TDF/FTC groups, regardless of BL VL or CD4+ cell count in the observed analysis

• These data, utilizing a more stringent VL measure, further reinforce the efficacy and potency of DTG + 3TC in treatment-naive individuals with HIV-1 infection
Acknowledgments

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  • All study participants and their families
  • The GEMINI-1 and GEMINI-2 clinical investigators and their staff
  • ViiV Healthcare, PPD, Parexel, and GSK teams

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