DURABLE EFFICACY OF DOLUTEGRAVIR (DTG) PLUS LAMIVUDINE (3TC) IN ANTIRETROVIRAL TREATMENT-NAIVE ADULTS WITH HIV-1 INFECTION—3-YEAR RESULTS FROM THE GEMINI STUDIES

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Introduction

• Two-drug regimens (2DRs) have been investigated as a means for reducing the number of ARV agents taken by individuals who need lifelong ART\textsuperscript{1,2}

• In the primary analysis of the GEMINI-1 and GEMINI-2 studies at Week 48, the 2DR DTG + 3TC (DOVATO, FDC) was non-inferior to the 3-drug regimen DTG + TDF/FTC in the treatment of ART-naive adults with HIV-1\textsuperscript{3}

• DTG + 3TC maintained non-inferior efficacy over 96 weeks vs DTG + TDF/FTC in ART-naive adults, with low rates of confirmed virologic withdrawal (CVW), and no resistance development in either treatment group\textsuperscript{4}

• DTG + 3TC is recommended as an initial ART regimen for most PLWH, with exceptions for individuals with HIV-1 RNA >500,000 c/mL, HBV co-infection, or in whom therapy is started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available\textsuperscript{5,6}

• We present data from the prespecified Week 144 secondary endpoint analyses of GEMINI-1 and GEMINI-2 evaluating durability after 3 years of therapy with DTG + 3TC
Methods

• GEMINI-1 and GEMINI-2 (ClinicalTrials.gov identifiers, NCT02831673 and NCT02831764, respectively) are identically designed, randomized, double-blind, parallel-group, multicenter, phase III, non-inferiority studies

• Participants with HIV-1 RNA ≤500,000 c/mL at screening were randomized 1:1 (stratified by plasma HIV-1 RNA and CD4+ cell count) to once-daily treatment with DTG + 3TC or DTG + TDF/FTC

• The primary endpoint was proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm in the intention-to-treat–exposed [ITT-E] population)
**GEMINI-1 and GEMINI-2 Study Design**

**Screening (28 days)**
- ART-naive adults

**Double-blind phase**
- DTG + 3TC (N=716)
- DTG + TDF/FTC (N=717)

**Open-label phase**

**Continuation phase**
- DTG + 3TC

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

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

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

a~10% non-inferiority margin for individual studies.
Demographic and Baseline Characteristics of the Pooled GEMINI-1 and GEMINI-2 Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DTG + 3TC (N=716)</th>
<th>DTG + TDF/FTC (N=717)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>32 (18-72)</td>
<td>33 (18-70)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>113 (16)</td>
<td>98 (14)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American/African heritage</td>
<td>90 (13)</td>
<td>71 (10)</td>
</tr>
<tr>
<td>Asian</td>
<td>71 (10)</td>
<td>72 (10)</td>
</tr>
<tr>
<td>White</td>
<td>484 (68)</td>
<td>499 (70)</td>
</tr>
<tr>
<td>Other</td>
<td>71 (10)</td>
<td>75 (10)</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;100,000 c/mL, n (%)a</td>
<td>140 (20)</td>
<td>153 (21)</td>
</tr>
<tr>
<td>CD4+ cell count ≤200 cells/mm³, n (%)</td>
<td>63 (9)</td>
<td>55 (8)</td>
</tr>
</tbody>
</table>

*a2% of participants in each group had baseline HIV-1 RNA ≥500,000 c/mL and were included in the ITT-E analysis.

- 1433 participants in GEMINI-1 and GEMINI-2 were randomized and received ≥1 dose of study medication (DTG + 3TC, N=716; DTG + TDF/FTC, N=717)
- At baseline, 20% (n=293) of participants had HIV-1 RNA >100,000 c/mL and 8% (n=118) had CD4+ cell count ≤200 cells/mm³
• DTG + 3TC was non-inferior to DTG + TDF/FTC in Snapshot HIV-1 RNA <50 c/mL for GEMINI-1, GEMINI-2, and the pooled population at Week 144
Snapshot Analysis of the Proportion of Participants With Plasma HIV-1 RNA <50 c/mL Through Week 144 in the GEMINI-1, GEMINI-2, and Pooled ITT-E Populations

- **Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL), baseline CD4+ cell count (≤200 vs >200 cells/mm³), and study (GEMINI-1 vs GEMINI-2).**

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For Healthcare Professionals Only
Summary of Study Outcomes at Week 144: Snapshot Analysis (ITT-E Population)\(^7\)

<table>
<thead>
<tr>
<th>Snapshot outcome, n (%)</th>
<th>DTG + 3TC (N=716)</th>
<th>DTG + TDF/FTC (N=717)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt;50 c/mL</td>
<td>584 (82)</td>
<td>599 (84)</td>
</tr>
<tr>
<td>HIV-1 RNA ≥50 c/mL</td>
<td>23 (3)</td>
<td>21 (3)</td>
</tr>
<tr>
<td>Data in window and HIV-1 RNA ≥50 c/mL</td>
<td>4 (&lt;1)</td>
<td>5 (&lt;1)</td>
</tr>
<tr>
<td>Discontinued for lack of efficacy</td>
<td>10 (1)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Discontinued for other reason and HIV-1 RNA ≥50 c/mL</td>
<td>7 (1)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Change in ART</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>No virologic data</td>
<td>109 (15)</td>
<td>97 (14)</td>
</tr>
<tr>
<td>Discontinued study due to AE or death</td>
<td>29 (4)</td>
<td>32 (4)</td>
</tr>
<tr>
<td>Discontinued study for other reasons(^a)</td>
<td>78 (11)</td>
<td>64 (9)</td>
</tr>
<tr>
<td>On study but missing data in window</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

\(^a\)Other reasons for discontinuation at Week 144 included protocol deviation, lost to follow-up, physician decision, withdrawal by participant, and lack of efficacy (in 1 participant in each treatment group in GEMINI-2).

- The proportion of participants with HIV-1 RNA ≥50 c/mL was low and similar between treatment groups (3% in both groups)
- The majority of Snapshot failures were due to non-virologic reasons
At Week 144, in participants with baseline HIV-1 RNA >100,000 c/mL, 82% and 84% in the DTG + 3TC and DTG + TDF/FTC groups, respectively, achieved HIV-1 RNA <50 c/mL; among participants with baseline CD4+ cell count ≤200 cells/mm\(^3\), 67% in the DTG + 3TC group and 76% in the DTG + TDF/FTC group achieved HIV-1 RNA <50 c/mL.

The corresponding proportions were 81% and 84%, respectively, for those with baseline HIV-1 RNA ≤100,000 c/mL and 83% and 84%, respectively, for those with baseline CD4+ cell count >200 cells/mm\(^3\).
Confirmed Virologic Withdrawal\textsuperscript{7}

- Across both studies, 12 participants (2\%) in the DTG + 3TC group (1 since Week 96) and 9 participants (1\%) in the DTG + TDF/FTC group (2 since Week 96) met protocol-defined CVW criteria\textsuperscript{1} through Week 144
  - None of these participants had treatment-emergent INSTI or NRTI resistance mutations
- 1 non-CVW participant with reported non-adherence in the DTG + 3TC group developed M184V at Week 132 (HIV-1 RNA 61,927 c/mL) and R263R/K at Week 144 (HIV-1 RNA 135 c/mL), conferring a 1.8-fold change in susceptibility to DTG
  - Baseline HIV-1 RNA: 93,515 c/mL; CD4+ cell count: 393 cells/mm\textsuperscript{3}
  - Suppressed to HIV-1 RNA <50 c/mL from Week 4 through Week 120; HIV-1 RNA 61,927 c/mL detected at Week 132, with successive HIV-1 RNA of <50, 135, and 61 c/mL after Week 132
  - Withdrawn due to lack of efficacy after Week 144, switched to DTG once daily + DRV/COBI, and regained virologic suppression

\textsuperscript{1} Cahn et al. Lancet. 2019;393:143-155.
Safety

• Through Week 144, overall AE profiles were similar between treatment groups

• Participants in the DTG + 3TC group had a significantly lower risk of drug-related AEs (20%) compared with the DTG + TDF/FTC group for the pooled population (27%; relative risk, 0.76 [95% CI, 0.63-0.92])

• Overall, 4 deaths occurred (3 in the DTG + 3TC group and 1 in the DTG + TDF/FTC group), all considered unrelated to the study drug regimen

• Overall mean weight change from baseline to Week 144 was 3.7 kg with DTG + 3TC and 2.4 kg with DTG + TDF/FTC
## Summary of AEs in the Pooled Safety Population From GEMINI-1 and GEMINI-2

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>DTG + 3TC (N=716)</th>
<th>DTG + TDF/FTC (N=717)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>613 (86)</td>
<td>625 (87)</td>
</tr>
<tr>
<td><strong>AEs occurring in ≥10% of participants in either group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>99 (14)</td>
<td>106 (15)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>93 (13)</td>
<td>127 (18)</td>
</tr>
<tr>
<td>Headache</td>
<td>84 (12)</td>
<td>91 (13)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>84 (12)</td>
<td>61 (9)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>64 (9)</td>
<td>70 (10)</td>
</tr>
<tr>
<td><strong>Drug-related AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade 2-5 drug-related AE</td>
<td>146 (20)</td>
<td>192 (27)</td>
</tr>
<tr>
<td>Grade 2-5 drug-related AEs occurring in ≥1% of participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>58 (8)</td>
<td>69 (10)</td>
</tr>
<tr>
<td><strong>AEs leading to withdrawal from the study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any serious AE</td>
<td>76 (11)</td>
<td>85 (12)</td>
</tr>
</tbody>
</table>
Adjusted Mean Change From Baseline in (A) Serum or Plasma Renal Biomarkers and (B) Ratios of Urine Renal Biomarkers at Week 144

- Changes from baseline in renal biomarkers favored DTG + 3TC vs DTG + TDF/FTC through Week 144

Week 144 analysis used a mixed-effect repeated-measures model. Mean change from baseline adjusted for study, treatment, visit, baseline HIV-1 RNA, baseline CD4+ cell count, age, sex, race, presence of diabetes, presence of hypertension, baseline biomarker value, treatment-by-visit interaction, and baseline biomarker value-by-visit interaction. Estimated from geometric mean ratios for baseline and Week 144. Based on the same model as plasma/serum markers except adjusting for log-transformed baseline biomarker. *P<0.01. **P<0.001.

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Adjusted Mean Change From Baseline in Serum Bone Turnover Biomarkers at Week 144

- Increase from baseline in bone turnover markers was lower with DTG + 3TC than DTG + TDF/FTC
- Changes in lipid parameters generally favored DTG + TDF/FTC through Week 144
  - Adjusted mean change from baseline at Week 144 in the DTG + 3TC vs DTG + TDF/FTC group: total cholesterol, 0.365 vs −0.027 mmol/L, \( P<0.001 \); HDL-C, 0.180 vs 0.095 mmol/L, \( P<0.001 \); LDL-C, 0.158 vs −0.095 mmol/L, \( P<0.001 \); triglycerides, 0.100 vs −0.079 mmol/L, \( P=0.002 \); TC/HDL-C ratio, −0.237 vs −0.377, \( P=0.008 \)

- Week 144 analysis used a mixed-effect repeated-measures model. Mean change from baseline adjusted for study, treatment, visit, baseline HIV-1 RNA, baseline CD4+ cell count, age, sex, race, BMI, smoking status, current vitamin D use, baseline biomarker value, treatment-by-visit interaction, and baseline biomarker value-by-visit interaction. **\( P<0.001 \).

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Conclusions

- DTG + 3TC maintained non-inferior efficacy vs DTG + TDF/FTC in ART-naive adults and demonstrated a high barrier to resistance, with low rates of CVW through Week 144.
- 1 non-CVW participant in the DTG + 3TC group with reported non-adherence developed M184V at Week 132 (HIV-1 RNA 61,927 c/mL) and R263R/K at Week 144 (HIV-1 RNA 135 c/mL), conferring a 1.8-fold change in DTG susceptibility; the participant was withdrawn for lack of efficacy after Week 144, switched to DTG once daily + DRV/CObI, and regained virologic suppression.
- Overall safety and tolerability were comparable between groups. There was a lower risk of drug-related AEs with DTG + 3TC than with DTG + TDF/FTC.
- Changes in renal and bone biomarkers generally favored DTG + 3TC.
- These results confirm the durable efficacy, tolerability, and high barrier to resistance of DTG + 3TC, further supporting the 2DR DTG + 3TC as a first-line treatment option for PLWH.
Prescribing Information

DOVATO dolutegravir 50mg/lamivudine 300mg tablets

See Summary of Product Characteristics (SmPC) before prescribing

Presentation: Film-coated tablet containing dolutegravir sodium equivalent to 50 mg dolutegravir and 300 mg lamivudine debossed with “SV-137” on one face.

Indication: HIV-1 in adults & adolescents above 12 years of age weighing ≥40kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.

Dosing: One tablet once daily with or without food. Use an additional 50mg tablet of dolutegravir approximately 12 hours after the dose of Doxvato when co-administered with efavirenz, nevirapine, tipranavir/ritonavir, etravirine (without boosted PI), carambazine, oxcarbazepine, phenytoin, phenobarbital, St John’s Wort or rifampicin.

Elderly: Limited data in 65+ yrs. Not recommended in patients with creatinine clearance < 50 mL/min. Caution in severe hepatic impairment.

Contraindications: Hypersensitivity to any ingredient. Co-administration with substrates of OCT-2 with narrow therapeutic windows, such as fampridine.

Special warnings/precautions: Risk of hypersensitivity reactions. Discontinue dolutegravir and other suspect agents immediately. Risks of osteonecrosis, immune reactivation syndrome. Monitor LFTs in Hepatitis B/C co-infection and ensure effective Hepatitis B therapy. Caution with metformin: monitor renal function and consider metformin dose adjustment. Use with etravirine requires boosted PI or increased dose of dolutegravir. Use with Mg/Al-containing antacids requires dosage separation. Use with calcium, multivitamins or iron also requires dosage separation if not taken at the same time with food. Use with cladribine or emtricitabine not recommended. When possible, avoid chronic co-administration of sorbitol or other osmotic acting alcohols (see SmPC section 4.5). If unavoidable, consider more frequent viral load monitoring.

Fertility, pregnancy and lactation: Human fertility - no data; animal fertility - studies indicate no effects. Women of childbearing potential (WOCBP) should be counselled about the potential risk of neural tube defects including consideration of effective contraceptive measures. If a woman plans pregnancy, the benefits and risks of continuing treatment should be discussed with the patient. The safety and efficacy of a duel regime has not been studied in pregnancy. If a pregnancy is confirmed in the first trimester while on Doxvato, the benefits and risks of continuing Doxvato versus switching to another antiretroviral regimen should be discussed with the patient taking the gestational age and the critical time period of neural tube defect development into account (see SmPC section 4.6). There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues. Do not breast-feed.

Side effects: See SmPC for full details. Headache, GI disturbance, insomnia, abnormal dreams, depression, anxiety, dizziness, somnolence, rash, pruritus, alopecia, fatigue, arthralgia, myalgia, hypersensitivity, suicidal ideation or suicide attempt, hepatitis, blood dyscrasias, acute hepatic failure, pancreatitis, angioedema, rhabdomyolysis, lactic acidosis, peripheral neuropathy. Elevations of ALT, AST and CPK.


Adverse events should be reported to the Health Products Regulatory Authority (HPRA) using an Adverse Reaction Report Form obtained either from the HPRA or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to the HPRA by calling (01) 6764971. Adverse events should also be reported to GlaxoSmithKline on 1800 244 255.