Resistance Analysis of Long-Acting Lenacapavir in Highly Treatment-Experienced People with HIV after 26 Weeks of Treatment

Nicolas Margot, Laurie VanderVeen, Vidula Naik, Silvia Chang, PC Parvangada, Ross Martin, Hadas Dvory-Sobol, Martin S. Rhee, and Christian Callebaut

Gilead Sciences, Inc., Foster City, USA
Disclosures

♦ Nicolas Margot is an employee of Gilead Sciences, Inc.
Lenacapavir targets multiple stages of HIV replication cycle

EC_{50}, half-maximal effective concentration.
LEN: Long-Acting Inhibitor of HIV-1 Capsid

- Fully active against HIV with resistance to existing drug classes\(^1-3\)
  - NRTI, NNRTI, INSTI, PI
- PK of SC LEN supports its use once every 6 months\(^4\)
- Potent antiviral activity in PWH
  - In **Phase 1** proof-of-concept study:
    - Up to 2.3 log\(_{10}\) HIV-1 RNA decline after 9 days of a single-dose monotherapy\(^5\)
  - In **Phase 2** study in treatment-naïve PWH (CALIBRATE)
    - High rates of viral suppression (94%) at Week 28 when given SC or PO in combination with F/TAF\(^6\)
  - In **Phase 2/3** study in viremic, heavily treatment-experienced PWH with MDR (CAPELLA)
    - High rates of viral suppression (81%) at Week 26 in combination with an optimized background regimen\(^7,8\)

---


INSTI, integrase strand-transfer inhibitor; MDR: multidrug resistance; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor; PK: pharmacokinetics; PWH, people with HIV; SC, subcutaneous.
LEN In Vitro Resistance Characterization

- In vitro resistance selections in MT-2 cells and human PBMCs identified 7 mutations arising at 6 amino acids in capsid
  - L56I, M66I, Q67H, K70N, N74S/D, T107N
  - All mutations map to LEN binding site

- Resistance mutations correlated with low replication capacity for all mutants in vitro, except Q67H

- LEN mutations not found in analysis of 1500 HIV clinical isolates
  - Treatment-naïve or -experienced, with or without PI-treatment failure
  - Lack of pre-existing genotypic resistance to LEN

Key eligibility criteria:
- HIV-1 RNA ≥400 copies/mL
- Resistance to ≥2 agents from 3 of 4 main ARV classes

**1- Randomised cohort (Double blind)**

**Screening period**
- Pre-randomisation repeat HIV-1 RNA
  - Decline of ≥0.5 log_{10} copies/mL (vs screening) or <400 copies/mL
  - Or if Cohort 1 is fully enrolled

**2- Non-randomised cohort (Open label)**

Functional monotherapy (14-d)

- **n=24**
  - 1A-Oral LEN\(^a\)
    - Failing regimen

- **n=12**
  - 1B-Placebo
    - Failing regimen

**Maintenance**

- SC LEN\(^a\) Q6M for 52 weeks
  - OBR

- Oral LEN\(^a\)
  - SC LEN\(^a\) Q6M for 52 weeks
  - OBR

- Oral LEN\(^a\)
  - OBR

- SC LEN\(^a\) Q6M for 52 weeks
  - OBR

---


*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8 (600 mg on Days 15 and 16, 300 mg on Day 22, for placebo participants); SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15. OBR, (investigational agents, such as fostemsavir, were allowed; atazanavir (ATV), ATV/cobicistat, ATV/ritonavir, efavirenz, enetcavir, nevirapine, tipranavir were not allowed); OBR, optimised background regimen; Q6M: once every 6 months.
Efficacy at Week 26: Randomised Cohort (n=36)

HIV-1 RNA (FDA-Snapshot) and CD4 Responses

- **Participants (%):**
  - <50 cells/μL: 81%
  - ≥50 cells/μL: 19%
  - ≥200 cells/μL: 11%
  - No Virologic Data: 0%

- **HIV-1 RNA, copies/mL:**
  - <50: 29
  - ≥50: 32
  - ≥200: 7
  - No Data: 4

- **Mean Change in CD4 cells/μL (95% CI):**

- **Oral lead-in vs SC Maintenance:**
  - n = 36, 35, 35, 36, 35, 36, 34, 34
  - Median CD4 = 127, 35, 35, 36, 35, 36, 197

Resistance Analyses

Baseline Resistance Analyses

❖ Confirm Baseline resistance criteria are met
  – Resistance to ≥2 ARVs in ≥ 3 of 4 main ARV classes
    • Monogram Biosciences Assays (45 of 72)
    • Historical resistance reports (27 of 72)
❖ Test susceptibility to entry inhibitors\(^2\) (61 of 72)

Post-Baseline Resistance Analyses

❖ Suboptimal Virologic Response (SVR)
  – Confirmed HIV-1 RNA ≥ 50 c/mL and < 1 log\(_{10}\) ↓ from LEN start (assessed at Week 4)
❖ Virologic Rebound (VR)
  – After suppression, confirmed HIV-1 RNA ≥ 50 c/mL or >1 log\(_{10}\) ↑ from nadir
❖ Viremia at Last Visit

1 OSS is based on both genotypic and phenotypic data
2 Entry inhibitors are enfuvirtide, fostemsavir, ibalizumab and maraviroc.
Baseline Resistance-Associated Mutations

Main ARV Classes

% of Participants with RAMs per ARV class

<table>
<thead>
<tr>
<th>ARV</th>
<th>% Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>99%</td>
</tr>
<tr>
<td>NNRTI</td>
<td>94%</td>
</tr>
<tr>
<td>PI</td>
<td>83%</td>
</tr>
<tr>
<td>INSTI</td>
<td>65%</td>
</tr>
</tbody>
</table>

Mean # RAMs per ARV class

<table>
<thead>
<tr>
<th>ARV</th>
<th>Mean # RAMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>3.8</td>
</tr>
<tr>
<td>NNRTI</td>
<td>2.4</td>
</tr>
<tr>
<td>PI</td>
<td>4.1</td>
</tr>
<tr>
<td>INSTI</td>
<td>1.3</td>
</tr>
</tbody>
</table>

N=72

ARV = antiretroviral; INSTI = integrase strand-transfer inhibitor; NRTI = nucleoside RT inhibitor; NNRTI = non-nucleoside RT inhibitor; PI = protease inhibitor; R = resistance; RAM: resistance-associated mutation (primary); Number of RAMs tallied: NRTI = 16; NNRTI = 14; PI = 15; INSTI = 10
**Baseline Class Resistance**

**4 Main ARV Classes**

**Entry Criteria:** Resistance to ≥2 ARVs in ≥ 3 of 4 main ARV classes

<table>
<thead>
<tr>
<th>Resistance Class</th>
<th>Number (%) of Participants</th>
<th>Cohort 1 (n = 36)</th>
<th>Cohort 2 (n = 36)</th>
<th>All (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INSTI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>** Resistance to **</td>
<td>17 (47%)</td>
<td>16 (44%)</td>
<td>33 (46%)</td>
<td></td>
</tr>
<tr>
<td>**Resistance to **</td>
<td>9 (25%)</td>
<td>13 (36%)</td>
<td>22 (31%)</td>
<td></td>
</tr>
<tr>
<td>**Resistance to **</td>
<td>8 (22%)</td>
<td>5 (14%)</td>
<td>13 (18%)</td>
<td></td>
</tr>
<tr>
<td>**Resistance to **</td>
<td>2 (6%)</td>
<td>0</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>**Resistance to **</td>
<td>0</td>
<td>1 (3%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

* M184V/I alone was not sufficient to fulfill the NRTI resistance criteria in the study.

ARV = antiretroviral; INSTI = integrase strand-transfer inhibitor; NRTI = nucleoside RT inhibitor; NNRTI = non-nucleoside RT inhibitor; PI = protease inhibitor.
Baseline Resistance to Lenacapavir

- Evaluated with Gag-Pro assay (Monogram)
  - No LEN resistance mutations detected
  - Wild-type LEN phenotypic susceptibility: mean fold-change = 1.0 (0.3–1.7)

<table>
<thead>
<tr>
<th>LEN RAM&lt;sup&gt;a&lt;/sup&gt;</th>
<th>L56I</th>
<th>M66I</th>
<th>Q67H</th>
<th>K70N</th>
<th>N74D/S</th>
<th>T107N</th>
</tr>
</thead>
<tbody>
<tr>
<td># Participant with RAM&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> RAM, resistance associated mutation; mutations identified during in vitro resistance selections (Link JO, et al. Nature 2020;584:614-8).

<sup>b</sup> Data available for 62 participants

<sup>c</sup> Fold change from wild-type control
## Post-Baseline Resistance Analysis
Through Week 26

<table>
<thead>
<tr>
<th>Study Phase/Treatment</th>
<th>Cohort 1A (n = 24)</th>
<th>Cohort 1B (n = 12)</th>
<th>All (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Monotherapy</td>
<td>Oral LEN + Failing Regimen</td>
<td>Placebo + Failing Regimen</td>
<td>N/A</td>
</tr>
<tr>
<td>Maintenance Therapy</td>
<td>LEN¹ + OBR</td>
<td>LEN² + OBR</td>
<td>LEN + OBR</td>
</tr>
</tbody>
</table>

### Resistance Categories

<table>
<thead>
<tr>
<th>Resistance Categories</th>
<th>Cohort 1A (n = 24)</th>
<th>Cohort 1B (n = 12)</th>
<th>All (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance Analysis Population (RAP)</td>
<td>6 (25%)</td>
<td>5 (42%)</td>
<td>11 (31%)</td>
</tr>
<tr>
<td>With CA-R Emerging</td>
<td>1 (4%)</td>
<td>3 (25%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>M66I</td>
<td>1 (4%)</td>
<td>3 (25%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Others³</td>
<td>1 (4%)</td>
<td>2 (17%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>No CA-R Emergence</td>
<td>5 (21%)</td>
<td>2 (17%)</td>
<td>7 (19%)</td>
</tr>
</tbody>
</table>

- 11 of 36 participants were analyzed for resistance
- 4 of 36 participants had CA resistance emerging by week 26

1- Subcutaneous LEN; 2- Oral LEN followed by SC LEN; 3- Other mutations include Q67G/H, K70R/S/H, N74D, A105S/T, and T107N
CA: capsid protein; OBR: optimized background regimen; -R: resistance; RAP: resistance analysis population; SC: subcutaneous
Participant 1
Viral Response and Resistance

![Chart showing viral response over time with drug combinations and resistance markers.](chart.png)

- Incoming ARVs
- OBR
- LEN

- Poor adherence by drug levels
  - DTG<LLOQ
  - Inconsistent DRV level

- Effective LEN monotherapy

Drugs in red are not active (OSS = 0); drugs in orange are partially active (OSS = 0.5); drugs in black are fully active (OSS = 1); 3TC = lamivudine; c = cobicistat boosting; CA = Capsid protein; DRV = darunavir; DTG = dolutegravir; FC = fold-change compared to wild-type control; FTC = emtricitabine; IBA = ibalizumab; LEN = lenacapavir; LLOQ = lower limit of quantification; MVC = maraviroc; O = oral LEN; OBR = optimized background regimen; OSS = overall susceptibility score; P = placebo; PK = pharmacokinetics; r = ritonavir boosting; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ↓: SC LEN injection
Participant 2
Viral Response and Resistance

3TC DRV/c DTG-bid MVC T20

3TC DRV/c DTG-bid MVC T20 ➔ 3TC ➔ FTC/TAF

CA Emerging M66I, N74D, A105T
LEN FC >1445

CA Emerging M66I, N74D, A105T
LEN FC >884

CA Emerging M66I, Q67Q/H, N74D, A105T
LEN FC AF

3TC  DRV/c  DTG - bid  MVC  T20  ➔  3TC  ➔  FTC/TAF

HIV-1 RNA (copies/mL)

Time (weeks)

HIV-1 RNA (copies/mL)

Time (weeks)

SC LEN

SC LEN

P

50 copies/mL

No fully active ARV in OBR
Effective LEN monotherapy

Incoming ARVs
OBR
LEN

Drugs in red are not active (OSS = 0); drugs in orange are partially active (OSS = 0.5); drugs in black are fully active (OSS = 1); 3TC = lamivudine; c = cobicistat boosting; CA = Capsid protein; DRV = darunavir; DTG = dolutegravir; FC = fold-change compared to wild-type control; FTC = emtricitabine; IBA =ibalizumab; LEN = lenacapavir; LLOQ = lower limit of quantification; MVC = maraviroc; O = oral LEN; OBR = optimized background regimen; OSS = overall susceptibility score; P = placebo; PK = pharmacokinetics; r = ritonavir boosting; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ↓: SC LEN injection
Participant 3
Viral Response and Resistance

FTC  IBA  TAF

FTC  IBA  TAF  DRV/r  DTG

O
SC LEN

SC LEN

HIV-1 RNA (copies/mL)

Time (weeks)

10^6

10^5

10^4

10^3

10^2

-4 0 4 8 12 16 20 24 28 32 36 40

50 copies/mL

CA Emerging
M66M/I
LEN FC AF

CA Emerging
M66M/I, A105A/T
LEN FC = 46

50 copies/mL

-4 0 4 8 12 16 20 24 28 32 36 40

FTC = emtricitabine; IBA = ibalizumab; LEN = lenacapavir; LLOQ = lower limit of quantification; MVC = maraviroc; O = oral LEN; OBR = optimized background regimen; OSS = overall susceptibility score; P = placebo; PK = pharmacokinetics; r = ritonavir boosting; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ↓: SC LEN injection

Drugs in red are not active (OSS = 0); drugs in orange are partially active (OSS = 0.5); drugs in black are fully active (OSS = 1); 3TC = lamivudine; c = cobicistat boosting; CA = Capsid protein; DRV = darunavir; DTG = dolutegravir; FC = fold-change compared to wild-type control; FTC = emtricitabine; IBA = ibalizumab; LEN = lenacapavir; LLOQ = lower limit of quantification; MVC = maraviroc; O = oral LEN; OBR = optimized background regimen; OSS = overall susceptibility score; P = placebo; PK = pharmacokinetics; r = ritonavir boosting; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ↓: SC LEN injection

Incoming ARVs
OBR
LEN

- No fully active ARV in OBR
- Effective LEN monotherapy
Participant 4
Viral Response and Resistance

**Incoming ARVs**
- **OBR**
- **LEN**

**3TC**

<table>
<thead>
<tr>
<th><strong>DRV/r-bid</strong></th>
<th><strong>DTG-bid</strong></th>
<th><strong>TDF</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>O</strong> SC LEN</td>
<td><strong>SC LEN</strong></td>
<td></td>
</tr>
</tbody>
</table>

**CA Emerging**
- M66M/I, K70K/S
- LEN FC AF

**CA Emerging**
- M66M/I
- LEN FC AF

**HIV-1 RNA (copies/mL)**

- **10^6**
- **10^5**
- **10^4**
- **10^3**
- **10^2**
- **50 copies/mL**

**Time (weeks)**

-4 0 4 8 12 16 20 24 28 32 36 40

**50 copies/mL**

**Drugs in red** are not active (OSS = 0); **drugs in orange** are partially active (OSS = 0.5); **drugs in black** are fully active (OSS = 1); 3TC = lamivudine; c = cobicistat boosting; CA = Capsid protein; DRV = darunavir; DTG = dolutegravir; FC = fold-change compared to wild-type control; FTC = emtricitabine; IBA = ibalizumab; LEN = lenacapavir; LLOQ = lower limit of quantification; MVC = maraviroc; O = oral LEN; OBR = optimized background regimen; OSS = overall susceptibility score; P = placebo; PK = pharmacokinetics; r = ritonavir boosting; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ↓: SC LEN injection

- Poor adherence by drug levels
  - DTG<LLOQ
  - DRV<LLOQ
- Effective LEN monotherapy
Summary of Participants with CA Resistance

<table>
<thead>
<tr>
<th>Part. ID</th>
<th>1st Visit with CA-R</th>
<th>CA RAMs</th>
<th>LEN FC(^a)</th>
<th># of Fully Active Drugs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Week 26</td>
<td>M66I</td>
<td>138</td>
<td>3</td>
<td>Effective LEN monotherapy (OBR adherence issue)</td>
</tr>
<tr>
<td>2</td>
<td>Week 10</td>
<td>M66I, N74D, A105T</td>
<td>&gt;1445</td>
<td>0</td>
<td>Effective LEN monotherapy (no active ARVs in OBR)</td>
</tr>
<tr>
<td>3</td>
<td>Week 4</td>
<td>M66M/I</td>
<td>46</td>
<td>0</td>
<td>Effective LEN monotherapy (no active ARVs in OBR)</td>
</tr>
<tr>
<td>4</td>
<td>Week 4</td>
<td>M66M/I, K70K/S</td>
<td>ND</td>
<td>2</td>
<td>Effective LEN monotherapy (OBR adherence issue)</td>
</tr>
</tbody>
</table>

- Emergence of M66I (± others) in all 4 participants with CA resistance
  - LEN susceptibility ranging from 46 to >1445-fold above wild-type control
- Effective LEN monotherapy at the time of CA-R emergence
  - Inadequate OBR drug levels
  - Lack of active agents in OBR

\(^a\) Fold change from Wild-type control

ARV: antiretroviral drug; BL: baseline; CA: capsid; CA-R: capsid resistance; OBR: optimized background regimen; RB: viral load rebound; RAM: resistance associated mutation
Conclusions

- In heavily treatment-experienced PWH with multidrug resistance
  - LEN + OBR led to high rates of virologic suppression (81%) and increases in CD4 cells by Week 26
  - LEN was well tolerated with no AEs leading to discontinuation

- Overall, the level of baseline resistance to the main ARV classes was high and consistent with the enrollment criteria defined in concert with FDA

- Post-baseline Cohort 1: 4 of 36 participants with emergence of LEN-associated mutations
  - no emerging resistance to OBR

- Viral rebound cases associated with effective LEN monotherapy at the time of resistance emergence
Acknowledgments

We are grateful to all the individuals who participated in this trial, their partners, and families.

Participating study investigators and their study teams:

**Canada** J Brunetto, B Trottier; **Dominican Republic** E Koenig; **France** J-M Molina, S Ronot-Bregigeon, Y Yazdanpanah; **Germany** H-J Stellbrink; **Italy** A Antinori, A Castagna, F Castelli; **Japan** T Shirasaka, Y Yokomaku; **South Africa** M Rassool; **Spain** J Mallolas; **Taiwan** C-C Hung; **Thailand** A Avihingsanon, P Chetchotisakd, K Siripassorn, W Ratanasuwan; **United States** DS Berger, M Berhe, C Brinson, CM Creticos, GE Crofoot, E DeJesus, D Hagins, T Hodge, K Lichtenstein, JP McGowan, O Ogbuagu, O Osiyemi, GJ Richmond, MN Ramgopal, PJ Ruane, W Sanchez, S Segal-Maurer, J Sims, GI Sinclair, DA Wheeler, A Wiznia, K Workowski, C Zurawski

Monogram Biosciences for resistance analyses

Seq-IT for sequence analyses

**This study was funded by Gilead Sciences, Inc.**