POTENT ANTIVIRAL ACTIVITY OF LENACAPAVIR IN PHASE 2/3 IN HEAVILY ART-EXPERIENCED PWH

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Lenacapavir (LEN): Novel, First-in-class HIV Capsid Inhibitor Highly Potent and Long-acting

EC_{50}, half maximal effective concentration.

(\text{EC}_{50}=50 \text{ pM})
Introduction

- LEN can meet significant unmet medical needs:
  - A new mechanism of action for heavily treatment-experienced people with multidrug-resistant HIV
  - Reduction of daily pill burden through less frequent dosing for treatment and prevention
- Highly desirable in vitro profile for heavily treatment-experienced people with HIV (PWH)
  - Nonoverlapping resistance profile with full activity against NRTI-, NNRTI-, INSTI-, and PI-resistance\textsuperscript{1,2,3}
  - No observed pre-existing resistance\textsuperscript{2}
- Single SC doses of LEN maintained target concentrations for 26 weeks, supporting its use once every 6 months\textsuperscript{4}
- Potent antiviral activity in PWH, with up to 2.3 log\textsubscript{10} copies/mL decline in HIV-1 RNA\textsuperscript{5}
  - Near maximal antiviral activity observed at IQ>1.1\textsuperscript{5}

Study Design

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

Functional monotherapy (14-d)

Randomized cohort (Double blind)
- n=24
  - Oral LEN*
    - Failing regimen
- n=12
  - Placebo
    - Failing regimen

Maintenance
- SC LEN* Q6M for 52 weeks
  - OBR

Oral LEN*
- SC LEN* Q6M for 52 weeks
- OBR

Nonrandomized cohort (Open label)
- n=36
  - Oral LEN*
    - OBR
  - SC LEN* Q6M for 52 weeks
    - OBR

*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8. SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15. OBR, optimized background regimen (investigational agents, such as fostemsavir, were allowed; ATV, ATV/co, ATV/r, EFV, ETV, NVP, TPV were not allowed).
Study Design

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

Randomized cohort (Double blind)

Screening Period
Pre-randomization repeat HIV-1 RNA
- Decline of ≥0.5 log_{10} copies/mL (vs screening) or
- <400 copies/mL

Nonrandomized cohort (Open label)

Functional monotherapy (14-d)

- n=24 Oral LEN* Failing regimen
- n=12 Placebo Failing regimen

Maintenance

- SC LEN* Q6M for 52 weeks
  - Oral LEN* OBR
  - SC LEN* Q6M for 52 weeks
    - Oral LEN* OBR

*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8. SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15.
OBR, optimized background regimen (investigational agents, such as fostemsavir, were allowed; ATV, ATV/co, ATV/r, EFV, ETV, NVP, TPV were not allowed).
Study Design:
Primary Endpoint

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

Randomized cohort (Double blind)

N=24
- Oral LEN
  - Failing regimen

N=12
- Placebo
  - Failing regimen

Primary endpoint: % achieving ≥0.5 log10 copies/mL reduction after 14 days
(No change to the background regimen was allowed)

Nonrandomized cohort (Open label)

N=36
- Oral LEN
- OBR

SC LEN Q6M for 52 weeks
- Oral LEN
- SC LEN Q6M for 52 weeks
- OBR

Maintenance

SC LEN Q6M for 52 weeks
- OBR

OBR

*HIV-1 RNA was repeated prior to randomization to determine the cohort: only participants with <0 5-log10 copies/mL decline and HIV-1 RNA ≥400 copies/mL were enrolled to Cohort 1; otherwise, they were enrolled to Cohort 2.
Study Design: Efficacy/Safety through at least Week 16

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

Functional monotherapy (14-d)
- Oral LEN
  - Failing regimen
  - n=24
- Placebo
  - Failing regimen
  - n=12

Maintenance
- SC LEN Q6M for 52 weeks
- OBR

Randomized cohort (Double blind)

Nonrandomized cohort (Open label)
- Oral LEN
  - SC LEN Q6M for 52 weeks
  - OBR
  - n=36

Efficacy/safety from LEN start: randomized cohort through Wk16 and available data from nonrandomized cohort†

*HIV-1 RNA was repeated prior to randomization to determine the cohort: only participants with <0.5-log10 copies/mL decline and HIV-1 RNA ≥400 copies/mL were enrolled to Cohort 1; otherwise, they were enrolled to Cohort 2.
†Efficacy was analyzed in those who received ≥1 dose of SC LEN.
Participant Disposition (as of Feb 2021)

Randomized Cohort (enrolled through Sep 2020)  n=36

14-day Functional monotherapy period (double blind)

Oral LEN, n=24  Placebo, n=12

1st SC LEN, n=24  1st SC LEN, n=12

On 1st SC, n=6  On 1st SC, n=4

On 2nd SC, n=16  On 2nd SC, n=8

On 3rd SC, n=2

Nonrandomized Cohort (enrolled through Jan 2021)  n=36

Oral LEN, n=36

1st SC LEN, n=36

On 1st SC, n=33

On 2nd SC, n=2

Death,* n=1

*The participant had an SAE of pneumonia, not related to study drug, leading to death.
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Randomized</th>
<th>Nonrandomized</th>
<th>Total N=72</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LEN n=24</td>
<td>Placebo n=12</td>
<td>LEN n=36</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>55 (24 – 71)</td>
<td>54 (27 – 59)</td>
<td>49 (23 – 78)</td>
</tr>
<tr>
<td>Sex, % female at birth</td>
<td>29</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Race, % Black</td>
<td>42</td>
<td>55</td>
<td>31</td>
</tr>
<tr>
<td>Ethnicity, % Hispanic or Latinx</td>
<td>25</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>HIV-1 RNA, median (range), log&lt;sub&gt;10&lt;/sub&gt; copies/mL</td>
<td>4.2 (2.3 – 5.4)</td>
<td>4.9 (4.3 – 5.3)</td>
<td>4.5 (1.3 – 5.7)</td>
</tr>
<tr>
<td>&gt;75,000 copies/mL, %</td>
<td>17</td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>CD4 count, median (range), cells/μL</td>
<td>172 (16 – 827)</td>
<td>85 (6 – 237)</td>
<td>195 (3 – 1296)</td>
</tr>
<tr>
<td>≤200 cells/μL, %</td>
<td>67</td>
<td>92</td>
<td>53</td>
</tr>
<tr>
<td>Number of prior ARV agents, median (range)</td>
<td>9 (2 – 24)</td>
<td>9 (3 – 22)</td>
<td>13 (3 – 25)</td>
</tr>
<tr>
<td>Years since HIV diagnosis, median (range)</td>
<td>27 (13 – 39)</td>
<td>26 (14 – 35)</td>
<td>23 (9 – 44)</td>
</tr>
<tr>
<td>Prior ARV class exposure, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTI</td>
<td>96</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>NNRTI</td>
<td>92</td>
<td>83</td>
<td>92</td>
</tr>
<tr>
<td>PI</td>
<td>88</td>
<td>75</td>
<td>94</td>
</tr>
<tr>
<td>INSTI</td>
<td>100</td>
<td>92</td>
<td>83</td>
</tr>
</tbody>
</table>
Antiviral Activity during Functional Monotherapy

Primary Endpoint

% Achieving HIV-1 RNA Decline
≥0.5 log_{10} copies/mL

![Bar Chart]

- LEN (n=24): 21/24 (88%)
- Placebo (n=12): 2/12 (17%)

p<0.0001
Antiviral Activity during Functional Monotherapy

Primary Endpoint

% Achieving HIV-1 RNA Decline
≥0.5 log_{10} copies/mL

p < 0.0001

<table>
<thead>
<tr>
<th>Participants, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEN n=24</td>
</tr>
<tr>
<td>Placebo n=12</td>
</tr>
<tr>
<td>21/24</td>
</tr>
<tr>
<td>2/12</td>
</tr>
</tbody>
</table>

Mean Change in HIV-1 RNA by visit (95% CI)

<table>
<thead>
<tr>
<th>Change in HIV-1 RNA, log_{10} copies/mL (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEN (n=24)</td>
</tr>
<tr>
<td>Placebo (n=12)</td>
</tr>
<tr>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>-1.93</td>
</tr>
<tr>
<td>-0.29</td>
</tr>
</tbody>
</table>
Participants with HIV-1 RNA <50 copies/mL (M=F): To date (Feb2021) in those who received SC LEN (n=72)

- Randomized + nonrandomized cohort

<table>
<thead>
<tr>
<th>Day</th>
<th>Week</th>
<th>Participants with HIV-1 RNA &lt;50 copies/mL, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0</td>
<td>3% (2/72)</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>15% (11/72)</td>
</tr>
<tr>
<td>D1 SC</td>
<td>4</td>
<td>28% (20/72)</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>57% (42/72)</td>
</tr>
<tr>
<td>16</td>
<td>12</td>
<td>73% (53/72)</td>
</tr>
<tr>
<td>22</td>
<td>16</td>
<td>73% (53/72)</td>
</tr>
<tr>
<td>26</td>
<td>20</td>
<td>73% (53/72)</td>
</tr>
</tbody>
</table>

*Denominators are those who received ≥1 dose of SC LEN and have available HIV-1 RNA at time of data cut, while study is still ongoing; D1 SC, the first day SC LEN was administered; 2 participants in Cohort 2 (nonrandomized cohort) had HIV-1 RNA <50 copies/mL on Day 1 but also >0.5 log reduction prior to Day 1 (presumably due to improved adherence).
Changes in CD4

D1 SC, the first day SC LEN was administered.
## Treatment-emergent Resistance

<table>
<thead>
<tr>
<th>Participant</th>
<th>Fully active agents in OBR*</th>
<th>At Prior Visits while on LEN</th>
<th>Emergent Capsid Mutations</th>
<th>At Subsequent Visits while on LEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>None</td>
<td>Suppressed</td>
<td>M66I, N74D (at Wk10: 2870 copies/mL)</td>
<td>Resuppressed with change in OBR</td>
</tr>
<tr>
<td>#2</td>
<td>DRV/COBI, DTG, RPV</td>
<td>Suppressed</td>
<td>M66I (at Wk26: 561 copies/mL)</td>
<td>Resuppressed with <strong>no</strong> change in OBR</td>
</tr>
</tbody>
</table>

- Among 72 heavily treatment-experienced participants with multidrug resistance and failing therapy at baseline who received SC LEN, 2 had emergent capsid mutations
  - The mutations conferred high level LEN resistance: >884 and 138 fold-change in EC$_{50}$ (vs WT)
  - M66I mutation significantly impairs viral replication (1.5% replication capacity vs WT)
    - See oral presentation 1781: VanderVeen et al for additional information

- Further analyses are ongoing

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*Other agents in the OBR:
- For participant #1: MVC, T20, DTG BID, DRV/COBI, 3TC.
- For participant #2: F/TAF; DRV/COBI and DTG were dosed BID.
## Adverse Events (excluding injection site reactions)

<table>
<thead>
<tr>
<th></th>
<th>Randomized</th>
<th>Nonrandomized</th>
<th>Total N=72</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On LEN n=36</td>
<td>On LEN n=36</td>
<td></td>
</tr>
<tr>
<td>≥5% total in any Grade, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Cough</td>
<td>11</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Back pain</td>
<td>3</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Rash</td>
<td>8</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

- One participant had an SAE of pneumonia, not related to study drug, leading to death
- No SAEs related to study drug*
- No AEs leading to study drug discontinuation

*SAEs not related to study drug: #1: pneumonia, dizziness; #2: abdominal pain, pancreatic mass; #3 proctalgia; #4: femoral neck fracture.
Injection Site Reactions to SC LEN: Incidence

46% (33/72) had ≥1 ISR related to LEN
- Most ISRs were Grade 1 (82% [27/33]) and resolved within days
- No Grade 4 ISRs occurred; one participant had Grade 3 swelling and erythema, which resolved in 4 and 8 days, respectively
- Nodules lasted a few months and were all Grade 1
- No participant discontinued due to ISRs

* Total n of participants on study or last study date in 2-week interval; only includes AE related to LEN and excludes those not related to it (e.g., T20).
### Grade 3 or 4 Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Event</th>
<th>Randomized On LEN n=36</th>
<th>Nonrandomized On LEN n=36</th>
<th>Total N=72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade 3 or 4 lab abnormality</td>
<td>31</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Low creatinine clearance/eGFR*</td>
<td>11</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Nonfasting hyperglycemia</td>
<td>12</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>High creatinine*</td>
<td>8</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>8</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Fasting hyperglycemia</td>
<td>11</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

- Low creatinine clearance/eGFR and/or high creatinine were transient or unconfirmed abnormalities
  - One participant had a concurrent SAEs of abdominal pain and pancreatic mass (no diagnosis available)
- Hyperglycemia/glycosuria were transient, unconfirmed, or related to underlying diabetes

*Per DAIDS scale, Grade 3 creatinine clearance is <60 to 30 mL/min or 30 to <50% decrease from baseline; Grade 3 creatinine is >1.8 to <3.5 x ULN or increase to 1.5 to <2.0 x baseline.*
Conclusions

♦ In heavily treatment-experienced PWH with multi-drug resistance (MDR)
  - LEN showed potent antiviral activity, when added to a failing regimen
  - LEN led to high rates of virologic suppression, when combined with an OBR
  - LEN was well tolerated with no AE leading to discontinuation
♦ The study is ongoing and longer term data will be presented as follow-up continues
♦ LEN has the potential to become an important agent for HTE PWH with MDR
♦ These data support the ongoing evaluation of LEN for treatment and prevention of HIV