Lenacapavir for Persons with Multidrug-Resistant HIV

CAPELLA
Lenacapavir in Multidrug Resistant HIV CAPELLA Study: Background

• **Background**
  – Phase 3, randomized, trial with oral and subcutaneous lenacapavir, a first-in-class capsid inhibitor, versus optimized background therapy (OBT)

• **Enrollment Criteria:**
  – Age ≥12 years
  – Virologic failure on current ART
  – HIV RNA >400 copies/mL for ≥8 wks
  – Documented HIV drug resistance to at least 2 HIV medications from at least 3 of the 4 main classes
  – At least one fully active agent available for HIV treatment

Lenacapavir in Multidrug Resistant HIV
CAPELLA Study: Study Design

**Study Cohorts**

**Cohort 1 (Randomized, Stable Viremia)**
- First 36 participants with:
  - HIV RNA decrease <0.5 log between the screening and cohort-selection visits and
  - HIV-1 RNA ≥ 400 copies/mL during screening

**Cohort 2 (Nonrandomized, Reduced Viremia)**
- Participants with:
  - HIV RNA decrease ≥0.5 log between the screening and cohort-selection visits or
  - HIV-1 RNA <400 copies/mL during screening

**Functional Monotherapy**

- *Oral Lenacapavir + failing therapy (n = 24)

- Placebo + failing therapy (n = 12)

- ^Oral Lenacapavir + OBT (n = 36)

- SC Lenacapavir Q6M + OBT for 52 weeks (n = 24)

- ^Oral Lenacapavir + OBT (n = 12)

- SC Lenacapavir Q6M + OBT for 52 weeks (n = 12)

- SC Lenacapavir Q6M + OBT for 52 weeks (n = 36)

OBT = optimized background regimen

*Oral lenacapavir = 600 mg days 1 and 2, 300 mg day 8
^Oral lenacapavir = 600 mg days 15 and 16, 300 mg day 22
SC Lenacapavir = 927 mg every 6 months

Lenacapavir in Multidrug Resistant HIV CAPELLA Study: Results

Baseline to Day 15 Change in HIV RNA Level (Functional Monotherapy in Randomized Cohort)

Median change in HIV RNA from baseline (log10 copies/mL)

P < 0.001

Lenacapavir in Multidrug Resistant HIV CAPELLA Study: Results

Decrease in HIV RNA Level of ≥0.5 log at Day 15 (Functional Monotherapy in Randomized Cohort)

Lenacapavir in Multidrug Resistant HIV CAPELLA Study: Results

Virologic Responses at 26 Weeks

Lenacapavir in Multidrug Resistant HIV CAPELLA Study: Capsid Inhibitor Resistance

Lenacapavir-related capsid substitutions developed in 8 participants

- 5 with M66I (alone)
- 1 with M66I + N74D
- 1 with Q67H + K70R
- 1 with K70H (alone)

Mutations and median change in lenacapavir susceptibility

- M66I: 234-fold decrease
- 1 with Q67H + K70R: 15-fold decrease
- 1 with K70H: 265-fold decrease

Conclusions: “In patients with multidrug-resistant HIV-1 infection, those who received lenacapavir had a greater reduction from baseline in viral load than those who received placebo.”
Lenacapavir for Treatment-Naïve Persons with HIV

CALIBRATE
Lenacapavir in Treatment-Naïve Persons with HIV

CALIBRATE: Background

• **Background**
  – Phase 2 randomized, open-label trial in United States and Dominican Republic evaluating the efficacy of lenacapavir in various combinations as initial and maintenance antiretroviral therapy in persons with HIV

• **Enrollment Criteria:**
  – Age ≥18 years
  – Antiretroviral naïve
  – HIV RNA ≥200 copies/mL
  – CD4 count ≥200 cells/mm³
  – Negative pregnancy test for women
  – Exclusions: hepatitis B, hepatitis C, or any active opportunistic infection

Lenacapavir in Treatment-Naïve Persons with HIV

CALIBRATE: Background

<table>
<thead>
<tr>
<th>Group 1* (n = 52)</th>
<th>LEN lead-in</th>
<th>LEN (SC Q6M) + TAF-FTC</th>
<th>LEN (SC Q6M) + TAF</th>
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</thead>
<tbody>
<tr>
<td>Group 2* (n = 53)</td>
<td>LEN lead-in</td>
<td>LEN (SC Q6M) + TAF-FTC</td>
<td>LEN (SC Q6M) + BIC</td>
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<tr>
<td>Group 3^ (n = 52)</td>
<td>LEN oral QD</td>
<td>LEN (oral QD) + TAF-FTC</td>
<td>BIC-TAF-FTC</td>
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<td>Group 4 (n = 25)</td>
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*Groups 1 and 2: LEN Oral lead in = 600 mg days 1 and 2, 300 mg day 8; first dose LEN SC = 927 mg on day 15; requires HIV RNA <50 copies/mL on weeks 16 and 22 to change to 2-drug regimen

^Group 3: LEN oral 600 mg days 1 and 2, followed by 50 mg daily

Primary Endpoint

Secondary Endpoint

Abbreviations: LEN = lenacapavir; SC = subcutaneous; TAF-FTC = tenofovir alafenamide-emtricitabine; TAF = tenofovir alafenamide; BIC = bictegravir; BIC-TAF-FTC = bictegravir-tenofovir alafenamide-emtricitabine

Lenacapavir in Treatment-Naïve Persons with HIV

CALIBRATE: Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEN SC + TAF-FTC to LEN SC + TAF</td>
<td>47/52</td>
<td>85/53</td>
<td>85/52</td>
<td>92/23</td>
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<tr>
<td>LEN PO + TAF-FTC</td>
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Lenacapavir in Treatment-Naïve Persons with HIV

CALIBRATE: Results

Lenacapavir in Treatment-Naïve Persons with HIV

CALIBRATE: Results

Lenacapavir-related capsid substitutions developed in 2 of 157 participants

- Group 2 participant: Q67H + K70R
- Group 3 participant: Q67H

Interpretation: “Lenacapavir warrants further investigation as a potential antiretroviral used orally and as injection in combination with other antiretroviral drugs.”

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