**Lenacapavir Resistance Analysis in a Phase 1b Clinical Proof-Of-Concept Study**

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**Introduction**

- Lenacapavir (LEN; GS-6207): first-in-class inhibitor of HIV-1 capsid function (Link 2020)
- High potency in vitro (30 – 100 pM); selectivity >140,000
- No cross-resistance against NRTI, NNRTI, PI, INSTI, MII
- In vitro resistance selections with LEN: 7 mutations identified in HIV-1 capsid protein (CA), at L56I, M66I, Q67H, K70N, N74D, N74S and T107N; associated with reduced susceptibility to LEN, with reduced fitness (Link 2020)
- RAMs: not found in naïve/experienced PLWH (Marcelin 2020)
- No cross-resistance against NRTI, NNRTI, PI, INSTI, MII

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**Results (Cont’d)**

**Participants with Emerging LEN Resistance**

- **Participant 20-3**
  - Single SC dose: LEN 20 mg
  - B/F/TAF DD
  - Plasma HIV-1 RNA levels and genotype

- **Participant 50-1**
  - Single SC dose: LEN 30 mg
  - B/F/TAF DD
  - Plasma HIV-1 RNA levels and genotype

**Dose-Response Relationship**

- LEN SC Dose vs. Predicted IQ

**Conclusions**

- In this Phase 1 study, single SC doses of LEN resulted in potent antiviral activity over 10 days
- Rare low-level resistance to LEN via a single mutation (Q67H) emerged only at low LEN exposures below the expected exposure in Ph2/3 studies
- Previous in vitro characterization identified that Q67H mutation had the least impact on viral fitness and susceptibility to LEN, which may explain its emergence at lower LEN exposures
- These results support further evaluation of LEN as a long-acting antiretroviral agent in PLWH

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**References**

Yard et al. CROI 2019; Sager et al. CROI 2019; Margot et al. EACS 2019; Marcelin et al. EACS 2019; Daar et al. EACS 2019; Daar et al. CROI 2020; Link et al. Nature 2020; Begley et al. CROI 2020; Margot et al. JAC 2020; Begley et al. AIDS 2020

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