Poster # P004

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Lenacapavir as part of a Combination Regimen in Treatment-Naïve People with HIV: Week 54 Results

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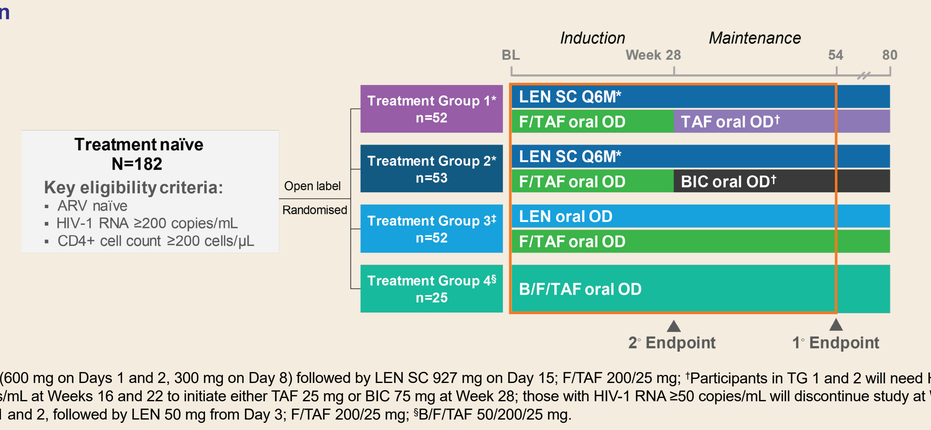
Introduction

LEN Targets Multiple Stages of HIV Replication Cycle



EC_{50}, half-maximal effective concentration.

- Lenacapavir (LEN, GS-6207) is a long-acting first-in-class inhibitor of HIV-1 capsid protein
  - In clinical development for treatment and prevention of HIV-1 infection
- Highly potent activity (EC_{50}: 50–100 pM), with a low clearance and slow release kinetics[1]
  - Can be administered orally (daily or weekly) or subcutaneously (every 6 months)[2-4]
- CALIBRATE was designed to generate exploratory clinical data to support the future development of LEN-containing regimens

Capella	Phase 2/3 in heavily Tx-experienced people with HIV[5,6]	LEN + OBR	Week 52	83% virologic suppression (CROI 2022)[7]
Calibrate	Phase 2 in Tx-naïve people with HIV[8]	LEN + F/TAF	Week 28	94% virologic suppression

F/TAF, emtricitabine/tenofovir alafenamide; OBR, optimised background regimen; Tx, treatment.

Study Design

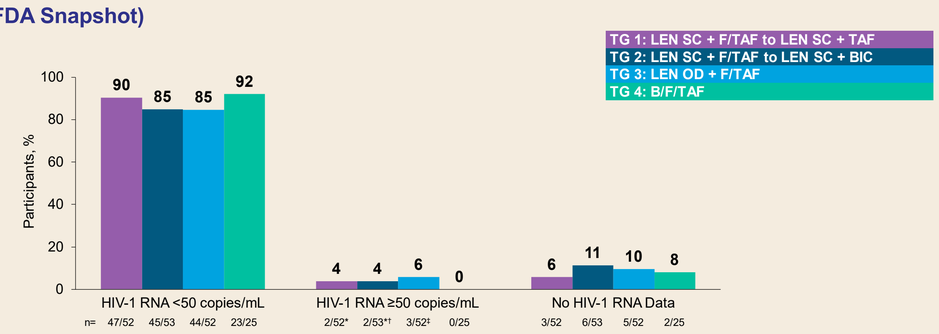
*LEN oral lead-in (600 mg on Days 1 and 2, 300 mg on Day 8) followed by LEN SC 927 mg on Day 15; F/TAF 200/25 mg; †Participants in TG 1 and 2 will need HIV-1 RNA results <50 copies/mL at Weeks 16 and 22 to initiate either TAF 25 mg or BIC 75 mg at Week 28; those with HIV-1 RNA ≥50 copies/mL will discontinue study at Week 28; ‡LEN 600 mg on Days 1 and 2, followed by LEN 50 mg from Day 3; F/TAF 200/25 mg; §B/F/TAF 50/200/25 mg.

ARV, antiretroviral; BIC, B, bictegravir; BL, baseline; OD, once daily; Q6M, every 6 months; SC, subcutaneous; TG, treatment group.

Baseline Characteristics

	LEN Total TG 1 n=52	LEN Total TG 2 n=53	LEN Total TG 3 n=52	B/F/TAF TG 4 n=25	Overall N=182
Age, median (range), years	31 (19, 61)	28 (19, 56)	28 (19, 72)	29 (21, 61)	29 (19, 72)
Sex, % female at birth	10	2	12	0	7
Race, % Black	46	45	60	64	52
Ethnicity, % Hispanic/Latinx	48	40	46	48	45
HIV-1 RNA, median log_{10} copies/mL	4.27	4.32	4.53	4.37	4.37
Q1, Q3	3.77, 4.63	3.96, 4.74	3.82, 4.83	4.09, 4.77	3.86, 4.74
>100,000 copies/mL, %	10	17	17	16	15
CD4 count, median cells/µL	404	450	409	482	437
Q1, Q3	320, 599	332, 599	301, 600	393, 527	332, 599
<200 cells/µL, %	0	2	6	0	2

Efficacy at Week 54 (FDA Snapshot)

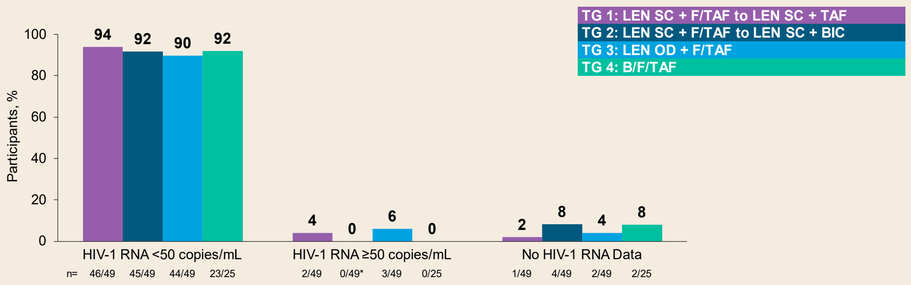


*3 participants (2 in TG 1 and 1 in TG 2) discontinued due to not meeting the protocol criteria of having HIV-1 RNA <50 copies/mL prior to Week 28;

†1 participant discontinued on Day 2; ‡2 of the 3 participants with HIV-1 RNA ≥50 copies/mL at Week 54 were suppressed in subsequent visit.

- In the pooled SC LEN group (TG 1+2: initially in combination with F/TAF, then with TAF or BIC), 88% (92/105) achieved and maintained virologic suppression at Week 54

Efficacy at Week 54 (FDA Snapshot) Among Participants who were Virologically Suppressed at Week 28



*1 participant discontinued due to not meeting the protocol criteria of having HIV-1 RNA <50 copies/mL prior to Week 28; 1 participant discontinued on Day 2.

- In the pooled SC LEN group (TG 1+2: initially in combination with F/TAF, then with TAF or BIC), among participants who were virologically suppressed at Week 28, 93% (91/98) maintained virologic suppression at Week 54

References: 1. Link JO, et al. Nature 2020;584:614-8; 2. Begley R, et al. AIDS 2020, abstr PEB0265; 3. Begley R, et al. CROI 2020, abstr 470; 4. Daar E, et al. CROI 2020, abstr 469; 5. Segal-Maurer S, et al. CROI 2021, abstr 127; 6. Molina J-M, et al. IAS 2021, abstr OALX01LB02; 7. Ogbuagu O, et al. CROI 2022, abstr 1047; 8. Gupta SK, et al. IAS 2021, abstr OALB0302; Link JO, et al. Nature 2020;584:614-8; Bester SM, et al. Science 2020;370:360-4

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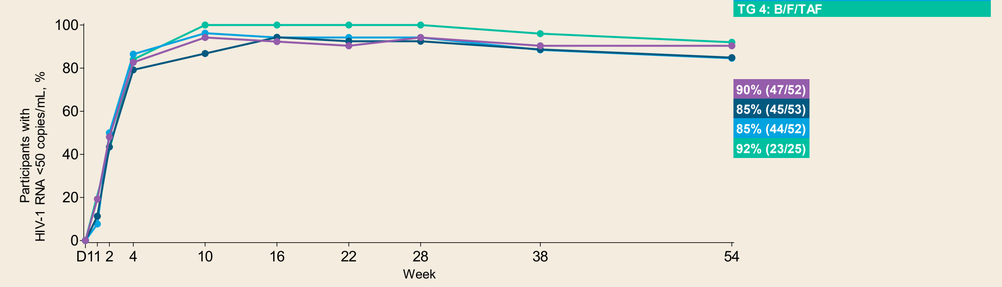
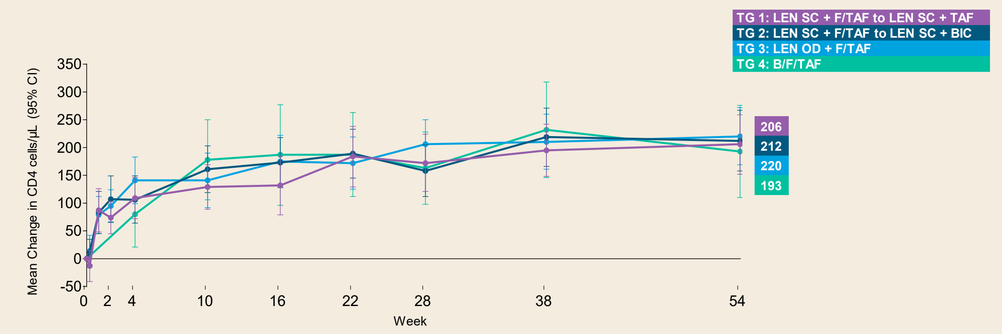
Results

Participants with HIV-1 RNA <50 copies/mL by Visit

Missing = Failure (On Treatment)



Changes in CD4



- Baseline CD4 of the overall study population: median 437 cells/µL

Resistance Analysis*

Participants, n	TG 1 n=52	TG 2 n=53	TG 3 n=52	TG 4 n=25
Participants meeting the resistance testing criteria	1	1	3	1
Emergent LEN resistance	0	1	1	0

*Genotypic and phenotypic resistance testing performed on any participants with confirmed HIV-1 RNA ≥50 copies/mL and <1 log_{10} HIV-1 RNA reduction from Day 1 at the Week 10 visit, at any visit after achieving HIV-1 RNA <50 copies/mL and a rebound to ≥50 copies/mL, and at any visit, with >1 log_{10} increase from the nadir; †Previously presented (Gupta SK, et al. IAS 2021, abstr OALB0302, VanderVeen L, et al. IDWeek 2021, oral 73).

CA, HIV capsid; INSTI, integrase strand transfer inhibitor; NRTI, nucleotide reverse transcriptase; RT, reverse transcriptase.

- Emergent LEN resistance in 2/157 (1.5%) participants
  - One participant in TG 2 developed Q67H+K70R (LEN fold change=20) in CA at Week 10, preceded by M184M/I in RT (IDWeek 2021)†
    - Pattern of mutation emergence suggests incomplete adherence to F/TAF
  - One participant in TG 3 developed Q67H (LEN fold change=7) in CA at Week 54
    - Non-adherence to F/TAF as assessed by pill count and drug levels
  - Both participants later re-suppressed on a regimen of INSTI + 2 NRTI

Adverse Events (excluding ISRs)

≥10% Participants in LEN total, %	LEN Total TG 1+2+3 n=157	B/F/TAF TG 4 n=25
Headache	13%	12%
Nausea	13%	4%
COVID-19	10%	12%

ISR, injection site reaction; SAE, serious adverse event.

- No SAEs related to study drug
- No Grade 4 AEs related to study drug
- No discontinuations due to non-ISR AEs
- Gastrointestinal AEs: SC LEN (TG 1+2) vs oral LEN (TG 3)
  - Nausea: 14% vs 12%
  - Diarrhoea: 7% vs 10%
  - Vomiting: 4% vs 8%

Injection Site Reactions

ISR Types*	After 1st SC Dose at Week 1 n=103†	After 2nd SC dose at Week 26 n=95†	Median duration (days)
Swelling	14%	12%	11
Erythema	14%	18%	5
Pain	15%	9%	4
Nodule	11%	8%	195
Induration	9%	6%	202

*Includes those >5% at both Weeks 1 and 26; †TG 1+2 (ie, those who received ≥1 dose of SC LEN and still on study or last study date in 2-week interval).

- Mostly Grade 1 or 2 ISRs
  - One Grade 3 ISR (nodule) after the second SC dose
- Three participants discontinued due to ISRs:
  - Two due to induration (both Grade 1, after the first SC dose)
  - One due to erythema and swelling (Grade 1, after the second SC dose)

Laboratory Abnormalities

Participants, %	LEN Total TG 1+2+3 n=157	B/F/TAF TG 4 n=25
Any Grade 3 or 4 lab abnormality	25%	24%
≥5% in LEN total		
Low creatinine clearance/eGFR*	8%	12%
High creatine kinase	7%	4%

*Per Division of AIDS scale, Grade 3 creatinine clearance is <60–30 mL/min or 30–<50% decrease from baseline. eGFR, estimated glomerular filtration rate.

- No clinically relevant Grade 3 or 4 lab abnormalities
- No discontinuations associated with Grade 3 or 4 lab abnormalities

Conclusions

- In treatment naive people with HIV, subcutaneous lenacapavir (LEN), initially in combination with F/TAF and later with oral TAF or BIC, achieved and maintained high rates of virologic suppression through 1 year (90% and 85%, respectively)
  - Oral LEN in combination with F/TAF had similar efficacy (85%)
- LEN was well tolerated; discontinuations due to adverse events were infrequent
- These Phase 2 data support the ongoing evaluation of LEN for treatment and prevention of HIV-1 infection
  - In heavily treatment-experienced people with HIV in the ongoing CAPELLA study
  - In treatment-naïve and -experienced people with HIV in combination with other agent(s)
  - In people who could benefit from pre-exposure prophylaxis (PrEP)

F/TAF, emtricitabine/tenofovir alafenamide; BIC, bictegravir; SC, subcutaneous.