Potent Antiviral Activity of Lenacapavir In Phase 2/3 In Heavily Art-Experienced PWH

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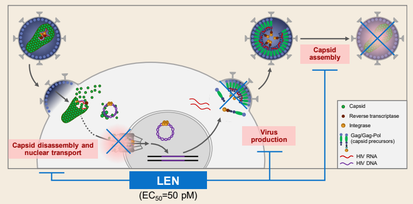
Lenacapavir (LEN): Novel, Highly Potent and Long acting, First-in-class HIV Capsid Inhibitor



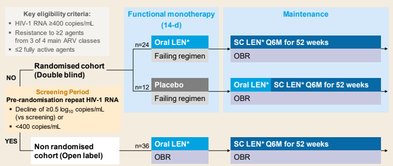
EC_{50}, half maximal effective concentration.

- Lenacapavir (LEN, GS-6207), the long-acting first-in-class HIV capsid inhibitor, is in clinical development for treatment and prevention of HIV-1 infection. With its novel mechanism of action, LEN is fully active in vitro against HIV-1 strains resistant to the major antiretroviral (ARV) classes

Introduction

- LEN has the potential to 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
  - Nonoverlapping resistance profile with full activity against NRTI-, NNRTI-, INSTI-, and PI-resistance[1,2,3]
  - No observed pre-existing resistance[2]
- Single subcutaneous (SC) doses of LEN maintained target concentrations for 26 weeks, supporting its use once every 6 months[4]
- Potent antiviral activity in people with HIV, with up to 2.3 log_{10} copies/mL decline in HIV-1 RNA[5]
  - Near maximal antiviral activity observed at IQ>1.1[5]

Study Design

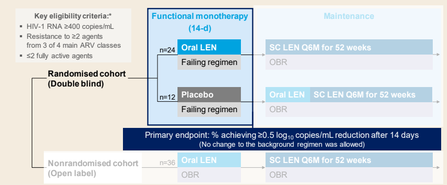


*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15.
OBR, optimised background regimen (investigational agents, such as fostemsavir, were allowed; Atazanavir; atazanavir/cobicistat; atazanavir/ritonavir; efavirenz; etravirine; nevirapine; tipranavir were not allowed

- We conducted a Phase 2/3, randomised, double-blind, placebo (PBO)-controlled study in heavily treatment-experienced (HTE) people with HIV failing their current regimen with HIV-1 RNA (VL) ≥ 400 c/mL and documented resistance to ≥ 2 agents from ≥ 3 of the 4 major ARV classes.
- Participants were randomised (2:1) to add LEN or PBO to their failing regimen for 2 weeks. During this functional monotherapy period, LEN or PBO was given orally (600 mg on Day [D] 1 and 2 and 300 mg on D8).
- The primary efficacy endpoint was the proportion of participants with at least 0.5 log_{10} copies/mL decline in viral load by D15. At D15, those on oral LEN received subcutaneous (SC) LEN 927 mg (q6month), while those on PBO started the LEN 2-week oral lead-in, followed by q6month SC.
- All participants initiated an investigator-selected, optimised background regimen (OBR) at D15.

Introduction, cont'd

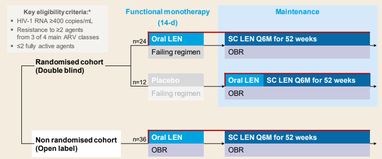
Study Design: Primary Endpoint



*HIV-1 RNA was repeated prior to randomisation to determine the cohort: only participants with <0.5-log_{10} copies/mL decline and HIV-1 RNA ≥400 copies/mL were enrolled to Cohort 1; otherwise, they were enrolled to Cohort 2.

- Primary endpoint was the percentage achieving ≥0.5 log reduction after 14 days of the functional monotherapy period

Study Design: Efficacy/Safety through at least Week 16

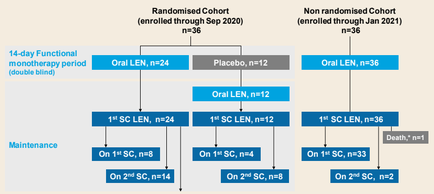


Efficacy/safety from LEN start: randomised cohort through Wk16 and available data from non randomised cohort†

*HIV-1 RNA was repeated prior to randomisation to determine the cohort: only participants with <0.5-log_{10} copies/mL decline and HIV-1 RNA ≥400 copies/mL were enrolled to Cohort 1; otherwise, they were enrolled to Cohort 2.
†Efficacy was analysed in those who received ≥1 dose of SC LEN.

- Interim efficacy and safety data from when all participants had completed at least the 16 week visit including available data from the non randomised cohort

Participant Disposition (as of Feb 2021)



*The participant had an SAE of pneumonia, not related to study drug, leading to death
SAE, serious adverse event

- Participant disposition as of 19 February 2021: 72 participants were enrolled and all received at least one dose of SC LEN, with two participants receiving their third dose
- One serious adverse event of pneumonia was reported. This was not related to study drug and led to death.
- No other discontinuations were reported

Results

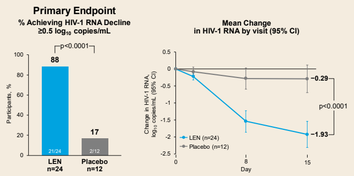
Baseline Characteristics

	Randomised		Non randomised	Total N=72
	LEN n=24	Placebo n=12	LEN n=36	
Age, median (range), years	55 (24 – 71)	54 (27 – 59)	49 (23 – 78)	52 (23 – 78)
Sex, % female at birth	29	25	22	25
Race, % Black	42	55	31	38
Ethnicity, % Hispanic or Latinx	25	36	14	21
HIV-1 RNA, median (range), log_{10} copies/mL	4.2 (2.3 – 5.4)	4.9 (4.3 – 5.3)	4.5 (1.3 – 5.7)	4.5 (1.3 – 5.7)
>75,000 copies/mL, %	17	50	28	28
CD4 count, median (range), cells/µL	172 (16 – 827)	85 (6 – 237)	195 (3 – 1296)	150 (3 – 1296)
≤200 cells/µL, %	67	92	53	64
Number of prior ARV agents, median (range)	9 (2 – 24)	9 (3 – 22)	13 (3 – 25)	11 (2 – 25)
Years since HIV diagnosis, median (range)	27 (13 – 39)	26 (14 – 35)	23 (9 – 44)	24 (9 – 44)
Prior ARV class exposure, %				
NRTI	96	92	97	96
NNRTI	92	83	92	90
PI	88	75	94	89
INSTI	100	92	83	90

INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleo(s/t)ide reverse transcriptase inhibitor; PI, protease inhibitor

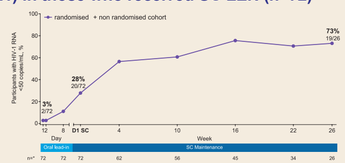
- Median age at baseline was 52 years, 25% female at birth, 38% Black and consistent with the HTE population, a median of 11 prior ARV agents had been used. The median time since diagnosis was 24 years.
- Baseline characteristics were similar across all arms except for the LEN arm in the randomised cohort, where a lower viral load and higher CD4 cell counts were noted.

Antiviral Activity during Functional Monotherapy



- The study achieved its primary endpoint, demonstrating statistically higher percentage of participants achieving ≥0.5 log decline during the functional monotherapy period. 88% of participants achieved the primary endpoint in the LEN arm compared to 17% in the placebo arm.
- During the same period, there was a statistically significant reduction in HIV RNA for those on LEN compared to placebo. LEN participants experienced a 1.93 log decline compared to only 0.29 log drop in the placebo group

Participants with HIV-1 RNA <50 copies/mL (M=F): To date (Feb2021) in those who received SC LEN (n=72)



*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 (non randomised 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).
M=F, missing=failure

- Participants with <50 copies/mL in missing=failure analysis demonstrated high rates of virologic suppression. At day 15, 20/72 participants achieved viral load <50 copies/mL and at week 26 and 19/26 participants achieved viral load <50 copies/mL

Treatment-emergent Resistance

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

*Other agents in the OBR:
For participant #1: MVC, T20, DTG BD, DRV/COBI, 3TC.
For participant #2: F/TAF; DRV/COBI and DTG were dosed BD
3TC, lamivudine; COBI, cobicistat; DTG, dolutegravir; DRV, darunavir; F, emtricitabine; MVC, maraviroc; RPV, rilpivirine;
T20, enfuvirtide; TAF, tenofovir alafenamide

- 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 wild type (WT))
  - M66I mutation significantly impairs viral replication (1.5% replication capacity vs WT)
- Further analyses are ongoing

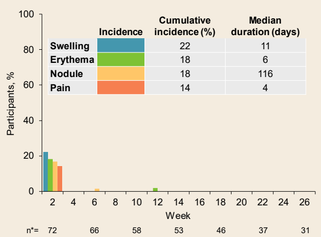
Adverse Events (excluding injection site reactions)

≥5% total in any Grade, %	Randomised On LEN n=36	Non randomised On LEN n=36	Total N=72
Headache	8	8	8
Nausea	14	3	8
Cough	11	3	7
Diarrhoea	11	3	7
Back pain	3	8	6
Pyrexia	6	6	6
Rash	8	3	6
Urinary tract infection	6	6	6

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

- 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

Injection Site Reactions to SC LEN: Incidence



*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).

- 46% (33/72) had ≥1 injection site reaction (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

Grade 3 or 4 Laboratory Abnormalities

≥5% total in any Grade, %	Randomised On LEN n=36	Non Randomised On LEN n=36	Total N=72
Any Grade 3 or 4 lab abnormality	31	11	21
Low creatinine clearance/eGFR*	11	3	7
Nonfasting hyperglycaemia	12	0	7
High creatinine*	8	3	6
Glycosuria	8	3	6
Fasting hyperglycaemia	11	0	6

*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.
DAIDS, division of AIDS; ULN, upper limit of normal

- 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)
- Hyperglycaemia/glycosuria were transient, unconfirmed, or related to underlying diabetes

Conclusions

- In heavily treatment-experienced people with HIV 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 highly treatment experienced people with HIV with MDR
- These data support the ongoing evaluation of LEN for treatment and prevention of HIV

References & Acknowledgements

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