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

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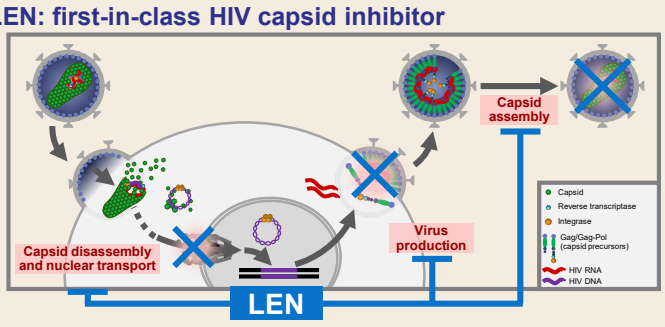
Introduction

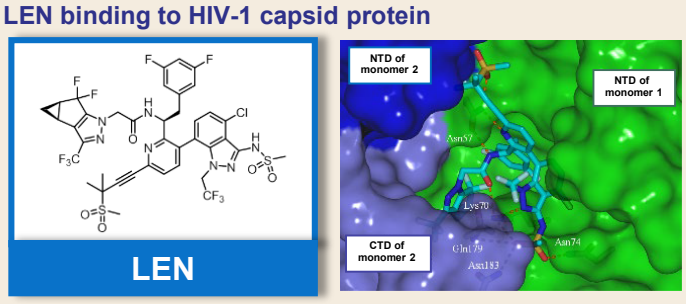
- Lenacapavir (LEN, GS-6207): first-in-class inhibitor of HIV-1 capsid function (Link 2020)
- High potency in vitro (30 – 100 pM); selectivity >140,000
- No cross-resistance against NRTI, NNRTI, PI, INSTI, MI
- In vitro resistance selections with LEN: 7 mutations identified in HIV-1 capsid protein (CA), 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)
- Active in vitro on primary viruses from TN, TE (Margot 2019)
- Administered subcutaneously (SC) Q6M as a long acting inhibitor (Begley 2020)
- Phase 1b proof-of-concept dose-finding study in people living with HIV (PLWH): single SC injection of LEN 20, 50, 150, 450, or 750 mg (Link 2020, Daar 2020)
- Potent antiviral activity: up to 2.3 $\log_{10}$ decline in HIV-1 RNA after 9 days of monotherapy (Link 2020, Daar 2020)
- Here we describe the resistance analyses for all participants

LEN: first-in-class HIV capsid inhibitor



- LEN binds between 2 adjacent CA monomers; binding alters assembly / disassembly of CA core (multi-stage effect)

LEN binding to HIV-1 capsid protein



CTD, C-terminal domain; NTD, N-terminal domain.
Yant et al, CROI 2019.

- Pocket naturally binds nuclear import factors necessary for virus replication

Phenotype of HIV-1 encoding *in vitro* emergent variants

HIV-1 CA Sequence	WT	Q67H	N74D	K70N	Q67H N74S	Q67H T107N	L56I	Q67H N74D	M66I
Fold resistance to LEN*	1	6	22	24	32	62	239	1,099	>3,200
Replication level (% WT) in primary CD4+ T-cells‡	100	100	1	ND	ND	28	3	<1	<1

*Data are mean mutant/wild-type (WT) EC_{50} ratios from triplicate cell cultures, n = 3. ‡Data are % of the WT virus from six replicate cell cultures, n = 2. Cells infected with a replication competent reporter HIV-1. EC_{50}, half maximal effective concentration. ND, not determined.
Link et al, Nature 2020

Prevalence of LEN *in vitro* RAMs in Clinical Isolates (N=1500)

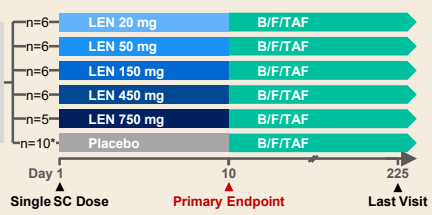
LEN RAMs (*in vitro*-selected)	ARV-naïve (n=500)	ARV-experienced (no PI use) (n=500)	ARV-experienced (PI failure history) (n=500)
L56I	0%	0%	0%
M66I	0%	0%	0%
Q67H	0%	0%	0%
K70N	0%	0%	0%
N74D	0%	0%	0%
N74S	0%	0%	0%
T107N	0%	0%	0%

Subtype B, AG, F1, CRF 06, A1, D and other non-B represented. RAM: resistance-associated mutation
Marcelin et al, JAC 2020.

- Lack of pre-existing resistance to LEN
- Failure on PI treatment does not lead to resistance to LEN

Phase 1b LEN monotherapy: Study design
Dose-Ranging Study: GS-US-200-4072

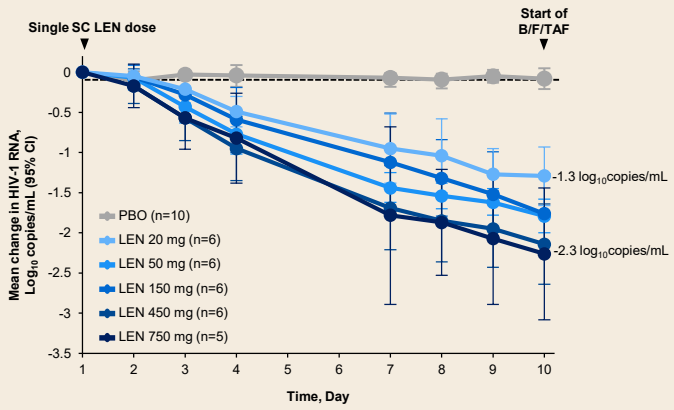
Key inclusion criteria:
- HIV-1 RNA 5000–400,000 copies/mL
- CD4+ cell count >200 cells/mm^3
- Naïve to CA and integrase inhibitors



*2 from each dose cohort. 8 participants from each dose cohort (7 for the 750 mg cohort) were randomised to receive either active treatment (n=6 and n=5 for the 750 mg cohort) or placebo (n=2).

- Phase 1b, double-blind, randomised, placebo-controlled, dose-ranging study (NCT03739866)
- 39 participants enrolled: 29 receiving LEN and 10 receiving placebo
- Primary endpoint: maximum reduction of plasma HIV-1 RNA through Day 10
- All participants required to start B/F/TAF on Day 10

Subcutaneous LEN: antiviral activity



Daar et al, EACS 2019; Daar et al, CROI 2020.

Methods

- Study 4072 is a double-blind, placebo-controlled, dose-ranging, randomized (3:1; n=8/group) study in PLWH who were capsid inhibitor-naïve
- Resistance analyses were performed for all participants prior to study entry and at the end of monotherapy using genotypic and phenotypic Gag-Pro assays
  - Monogram Biosciences: next-generation sequencing (NGS) assay reporting mutations present in >10% of reads. Gag-PR sequence from participants was cloned into gag-PR-deleted NL 4-3-based test vector for phenotypic testing (single-cycle assay)
  - Seq-IT: NGS genotyping assay (2% limit of detection).
- Samples were evaluated for the emergence of CA mutations and/or change in phenotypic susceptibility to LEN.

Results

- In the pre-treatment analysis, no participants had HIV-1 harboring resistance mutations to LEN, with all having wild-type (WT) phenotypic susceptibility to LEN
- Post-monotherapy analyses revealed the emergence of CA mutation Q67H at Day 10 in 2 participants
- One participant (20 mg group) had a Q67Q/H mixture detected in two separate NGS analyses, and another participant (50 mg group) had a Q67H mutation, detected in one of the NGS analyses
- No other substitutions were observed in the CA protein

Plasma HIV-1 RNA levels and genotype in PLHIV (GS-US-200-4072)

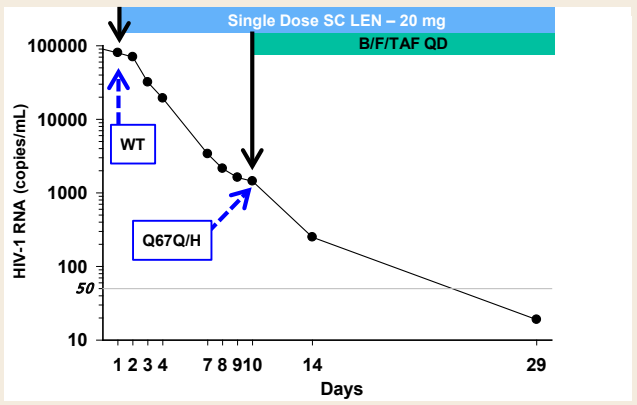
LEN Dose	Participant ID	BL HIV-1 RNA ($\log_{10}$ copies/mL)	Max. HIV-1 RNA change (day 9) ($\log_{10}$ copies/mL)	CA genotype (day 9) (Monogram; NGS>10%)*	CA genotype (day 9) (Seq-IT; NGS>2%)*
20 mg	20-1	4.84	-0.83	wild-type	wild-type
	20-2	3.86	-1.58	wild-type	wild-type
	20-3	4.90	-1.74	Q67Q/H†	Q67Q/H
	20-4	4.19	-1.43	wild-type	wild-type
	20-5	4.21	-1.33	wild-type	wild-type
	20-6	4.73	-1.21	ND	wild-type
50 mg	50-1	4.01	-2.39	ND	Q67H
	50-2	4.81	-1.55	wild-type	wild-type
	50-3	4.30	-1.61	wild-type	wild-type
	50-4	4.33	-2.32	ND	wild-type
	50-5	4.85	-1.16	wild-type	wild-type
	50-6	4.32	-1.73	ND	wild-type
150 mg	150-1	4.61	-2.06	ND	wild-type
	150-2	4.55	-1.68	wild-type	wild-type
	150-3	4.58	-1.86	wild-type	wild-type
	150-4	4.25	-1.49	ND	wild-type
	150-5	4.61	-1.87	wild-type	wild-type
	150-6	4.31	-1.62	ND	wild-type
450 mg	450-1	4.31	-2.32	ND	wild-type
	450-2	4.38	-2.86	ND	wild-type
	450-3	4.53	-2.11	ND	wild-type
	450-4	4.84	-1.83	wild-type	wild-type
	450-5	4.44	-1.58	wild-type	wild-type
	450-6	4.62	-2.52	ND	wild-type
750 mg	750-1	4.74	-2.87	wild-type	wild-type
	750-2	4.94	-1.48	wild-type	wild-type
	750-3	4.35	-3.02	ND	ND
	750-4	4.17	-1.95	wild-type	wild-type
	750-5	4.60	-1.98	wild-type	wild-type

ND, not determined.
Link et al, Nature; Daar et al CROI 2020; Margot et al HIV Glasgow 2020.
(*) Mutations from next-generation sequencing (NGS) assays found in >10% or >2% of reads were reported.
(†) Phenotypic fold-change from WT: 1.6

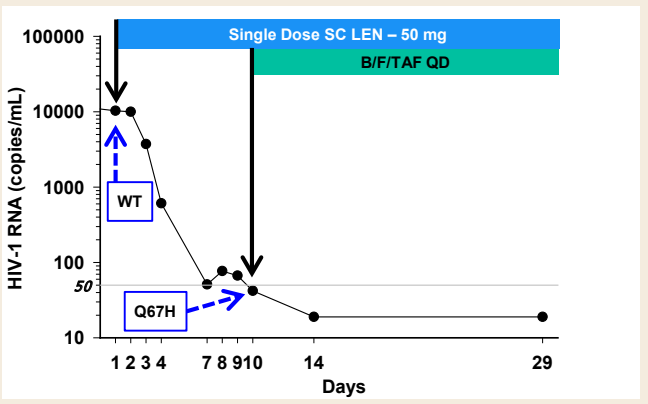
Results (Cont'd)

Participants with Emerging LEN Resistance

Participant 20-3

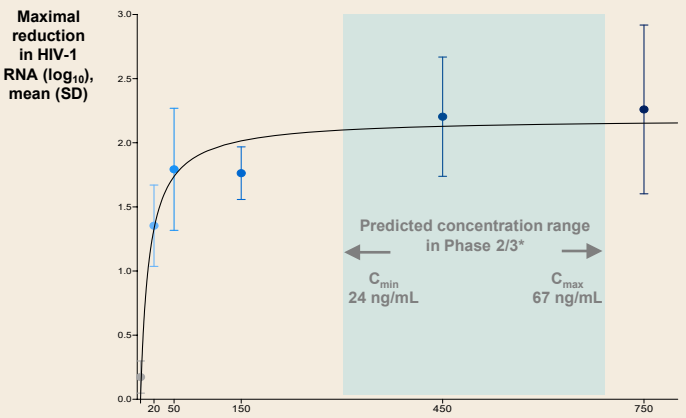


Participant 50-1



B/F/TAF: bictegravir/emtricitabine/tenofovir alafenamide; WT: Wild-type

Dose-Response Relationship
LEN SC Dose vs. Predicted IQ



Protein-adjusted EC_{95}: 2.32 ng/mL, CD4+ T cells; and 3.87 ng/mL, MT-4 cells; IQ, ratio of LEN plasma concentration/EC_{95}. Daar et al, CROI2020. (*) Begley AIDS 2020; (†) Based on MT-4 paEC95

- Maximum reduction observed between 50 and 150 mg doses
- Near maximal antiviral activity observed at mean concentrations ≥4.4 ng/mL (IQ>1.1)
- 6-month Phase 2/3 dosing: LEN C_{min} = 24 ng/mL → IQ>6, low probability of resistance emergence

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 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

References

Yant 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; Margot et al, CROI 2020; Marcelin et al, JAC 2020; Begley et al, AIDS2020

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