Resistance Analysis of Long-Acting Lenacapavir in Heavily Treatment-Experienced People with HIV after 104 Weeks of Treatment

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Disclosures

- **N Margot, V Jogiraju, L VanderVeen, V Naik, H Dvory-Sobol, MS Rhee, and C Callebaut** are all employees and shareholders of Gilead Sciences, Inc.

Lenacapavir (LEN)

- LEN is a potent (EC_{50} 50–100 pM) first-in-class, long-acting HIV-1 capsid inhibitor[1]
- LEN is active against HIV-1 with resistance against existing ARVs[2,3]
- LEN has been approved for the treatment of HTE PWH in combination with an OBR[4,5]
- Emergence of LEN RAMs at Week 52 (n=9) in the CAPELLA study were previously reported[3]

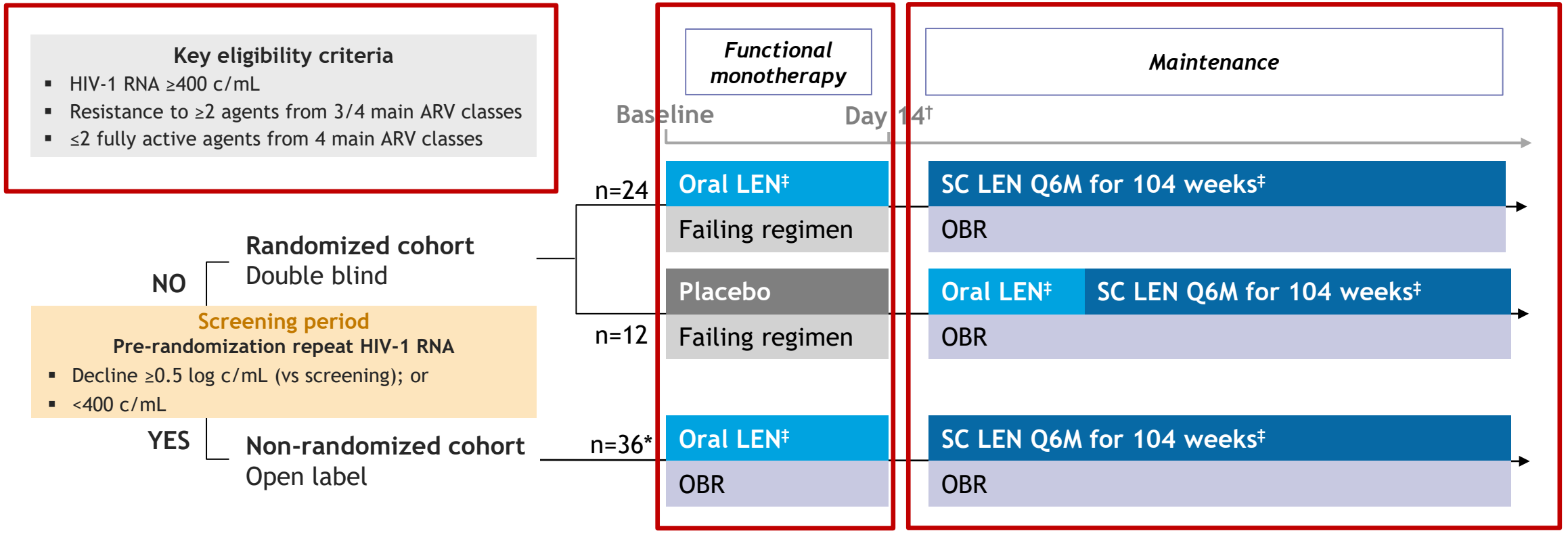
CA residue	L56	M66	Q67	K70	N74	A105	T107
In vivo	–	I	H/K/N	H/N/R/S	D/H	T/S	A/C/N/S
In vitro	I	I	H	N	D/S	–	N

Objective: To analyze the emergence of LEN RAMs through Week 104 of the CAPELLA study

1. Link JO, et al. *Nature* 2020;584:614–8. 2. Margot N, et al. *Antimicr Agents Chemother* 2021;65:e02057–20. 3. Margot N, et al. Presented at CROI 2022; Poster 508. 4. Segal-Maurer S, et al. *N Engl J Med* 2022;386:1793–803. 5. Ogbuagu O, et al. *Lancet HIV* 2023;1:e497–e505.

ARV, antiretroviral; CA, capsid; EC_{50} half maximal effective concentration; HTE, heavily treatment experienced; LEN, lenacapavir; OBR, optimized background regimen; PWH, people with HIV-1; RAM, resistance-associated mutation.

CAPELLA Study Design[1]



- 82% of participants were suppressed at Week 104 (M=E)[2]
- Mean increase in CD4 cell count of 122 cells/μL from baseline to Week 104[2]

*Enrolled after not meeting criteria for randomized cohort, n=3; enrolled after randomized cohort enrollment was completed, n=33 (of those, n=28 met the randomization criteria). †Primary endpoint: HIV-1 RNA decrease ≥0.5 $\log_{10}$ c/mL in randomized cohort. ‡Oral LEN 600 mg on Days 1 and 2, and 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in abdomen on Day 15 then Q6M.
1. Segal-Maurer S, et al. *N Engl J Med* 2022;386:1793–803. 2. Ogbuago O, et al. Presented at IDWeek 2023; Poster 1596.
ARV, antiretroviral; c/mL, copies/mL; LEN, lenacapavir; M=E, missing=excluded; OBR, optimized background regimen; Q6M, every 6 months; SC, subcutaneous.

Resistance Analysis Population and Emerging LEN RAMs at Week 104

- Genotypic/phenotypic analyses (capsid, protease, RT, integrase) performed at virologic failure*

Category, n (%)	CAPELLA (N=72)
Resistance analysis population	**27** (38)
LEN RAM emergence	**14** (19)
M66I	6 (8)
Q67H/K/N	8 (11)
K70H/N/R/S	7 (10)
N74D/H/K	3 (4)
A105T/S	4 (6)
T107A/C/N/S	3 (4)
No LEN RAM emergence	**13** (18)

- Plasma OBR drug concentrations quantification (LC-MS/MS methods)
  - DRV, DTG, TAF/TFV, FTC

*Virologic failure defined as confirmed rebound ≥50 copies/mL or <1 $\log_{10}$ decline from baseline at Week 4. Resistance assays conducted at Monogram Biosciences.
DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LEN, lenacapavir; OBR, optimized background regimen; RAM, resistance-associated mutation; RT, reverse transcriptase; TAF, tenofovir alafenamide; TFV, tenofovir.

Summary of Participants with LEN RAMs Through Week 104 (n=14)

Outcome After VF	VF participants with LEN RAMs (n=14)	
	Non-adherence to OBR (had at least 1 fully active agent)	Suboptimal OBR (had no fully active agents)
Resuppressed	1. Q67H 2. K70N N74K 3. M66I K70S 4. N74D 5. Q67H	11. M66I Q67H N74D A105T 12. M66I T107A
Did not resuppress	6. M66I N74D A105T 7. Q67H K70R A105T 8. Q67K K70H 9. Q67H K70R T107N 10. Q67H K70R	13. M66I A105T 14. M66I Q67H K70R T107C

LEN, lenacapavir; OBR, optimized background regimen; RAM, resistance-associated mutation; VF, virologic failure.

Summary of Participants with LEN RAMs Through Week 104 (n=14)

Outcome After VF	VF participants with LEN RAMs (n=14)	
	Non-adherence to OBR (had at least 1 fully active agent)	Suboptimal OBR (had no fully active agents)
Resuppressed	1. Q67H 2. K70N, N74K 3. M66I, K70S 4. N74D 5. Q67H	11. M66I, Q67H, N74D, A105T 12. M66I, T107A With OBR Change
Did not resuppress	6. M66I, N74D, A105T 7. Q67H, K70R, A105T 8. Q67K, K70H 9. Q67H, K70R, T107N 10. Q67H, K70R	13. M66I, A105T 14. M66I, Q67H, K70R, T107C

- *Post* VF, 7 of 14 participants with LEN RAMs achieved HIV-1 RNA <50 c/mL on LEN + OBR

LEN, lenacapavir; OBR, optimized background regimen; RAM, resistance-associated mutation; VF, virologic failure.

LEN Phenotypic Data

Participants with LEN RAMs

Participants with LEN RAMs						
#	Visit	Genotype				LEN FC*	Outcome after VF
1.	W88	Q67H				4.5	Resuppressed
5.	W52	Q67H				6.6	Resuppressed
14.	W4	M66I	Q67H	K70R	T107C	12.2	Not resuppressed
10.	W4	Q67H	K70R			14.8	Not resuppressed
7.	W88	Q67H	K70R	A105T		105.0	Not resuppressed
13.	W52	M66I	A105T			111.0	Not resuppressed
12.	W10	M66I	T107A			234.0	Resuppressed
2.	W78	K70N	N74K			289.0	Resuppressed
8.	W88	Q67K	K70H			342.0	Not resuppressed
9.	W78	Q67H	K70R	T107N		393.0	Not resuppressed
6.	W52	M66I	N74D	A105T		>869.0	Not resuppressed
11.	W10	M66I	Q67H	N74D	A105T	>869.0	Resuppressed
3.	W4	M66I	K70S			NA	Resuppressed
4.	W72	N74D				NA	Resuppressed

- LEN FC were not correlated with outcome
- LEN FC were not correlated with number of RAMs

*Monogram Gag-Pro PhenoSense single-cycle assay; LEN fold change compared with wild type.
FC, fold change; LEN, lenacapavir; NA, not available; RAM, resistance-associated mutation; VF, virologic failure; W, week.

LEN Phenotypic data

Patient Clones and Site-Directed Mutants

Patient Clones and Site-Directed Mutants					
#	Genotype			RC (%)[a]	LEN FC[a]
A.	M66I			0.6	>869.0
B.	M66I	A105T		1.2	>869.0
C.	M66I			1.5	>869.0
D.	M66I	Q67H	K70R	3.1	>869.0
E.	M66I			12.0	>869.0
F.	M66I	T107S		24.0	>869.0
G.	M66I	K70S		*AF*	*AF*
H.	A105T			*AF*	*AF*
I.	K70R			9.7	1.2
J.	K70H			9.8	154.2
K.	K70H			37	84.8
L.	K70S			*AF*	*AF*
M.	N74D			49.0	17.0
N.	Q67H			58.0	4.8
O.	Q67H	K70R	T107S	109.0	46.3

- Additional characterization:
  - Reasonable correlation between assays
  - Lack of replication in multicycle assays
  - High LEN FC associated with low RC

[a]Monogram Gag-Pro PhenoSense single-cycle assay; FC, fold-change compared to wild-type (WT); [b]MT-2, 5-day multicycle in-house assay.
AF, assay failure; FC, fold-change; NA, not available; RC, replication capacity; SDM, site-directed mutants;

Conclusions

- Capella participants were HTE with limited treatment options
- Virologic suppression with LEN + OBR was maintained in 82% of participants (M=E) at Week 104
- LEN RAMs occurred in 14 out of 72 participants
- LEN RAMs were associated with either inadequate OBR adherence or an OBR lacking fully-active ARVs
- Most LEN RAMs were associated with strong reduction in replication capacity
- Some participants with LEN RAMs resuppressed upon resumption of OBR or with an OBR change

ARV, antiretroviral; HTE, heavily treatment experienced; LEN, lenacapavir; M=E, missing=excluded; OBR, optimized background regimen; RAM, resistance-associated mutation.

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