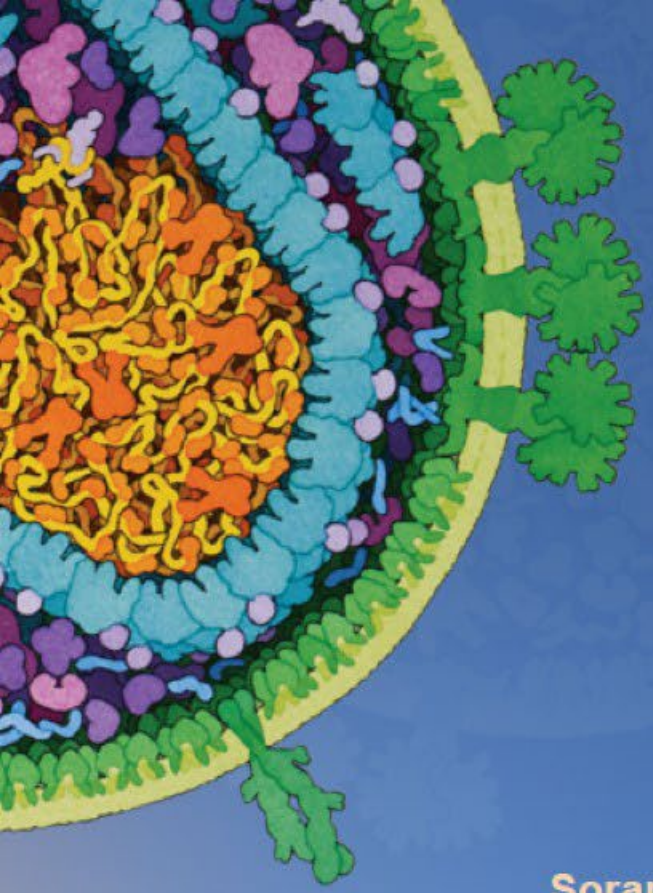

ORAL ABSTRACT

POTENT ANTIVIRAL ACTIVITY OF LENACAPAVIR IN PHASE 2/3 IN HEAVILY ART-EXPERIENCED PWH

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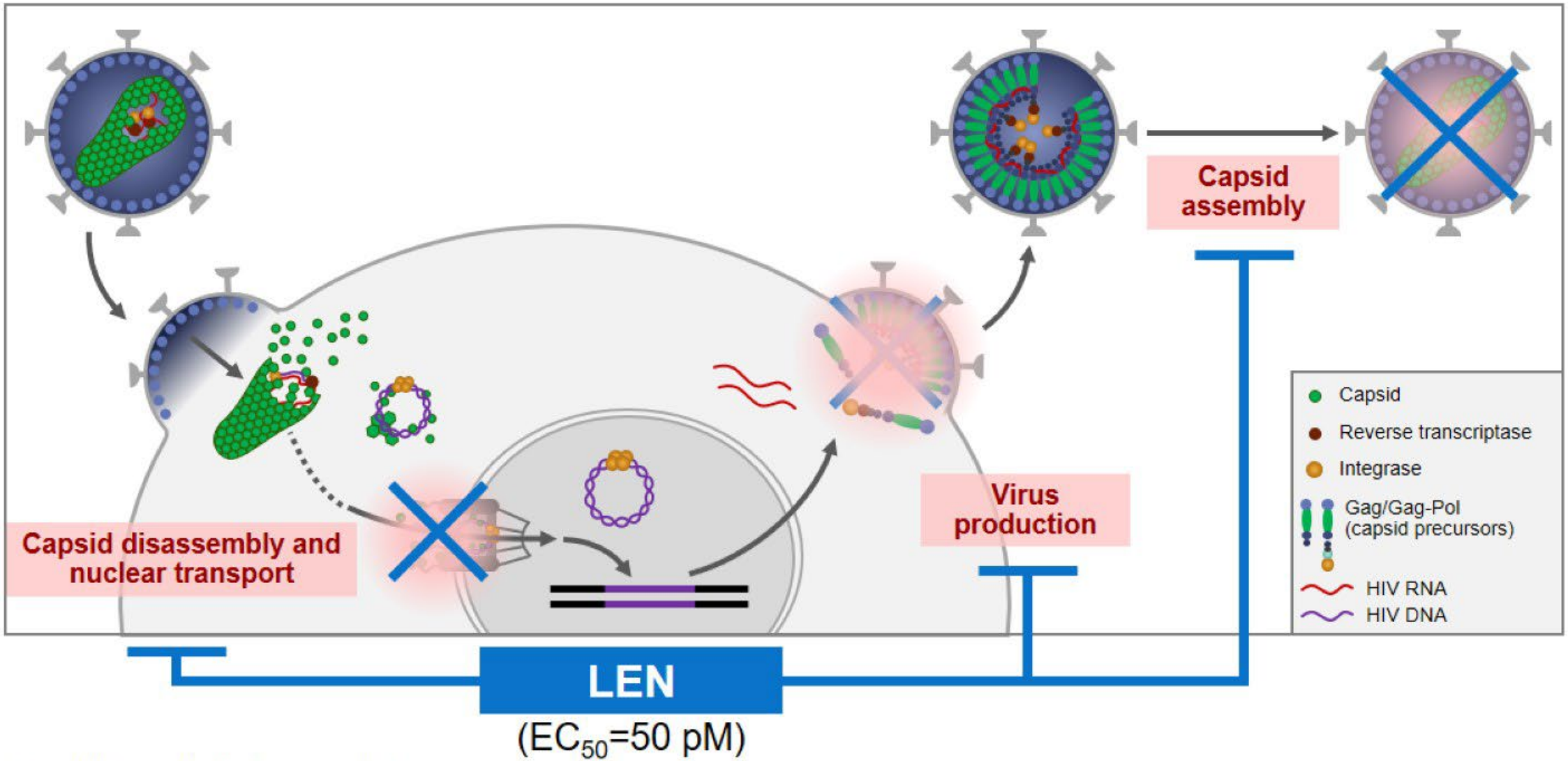
Lenacapavir (LEN): Novel, First-in-class HIV Capsid Inhibitor Highly Potent and Long-acting



EC_{50}, half maximal effective concentration.

Introduction

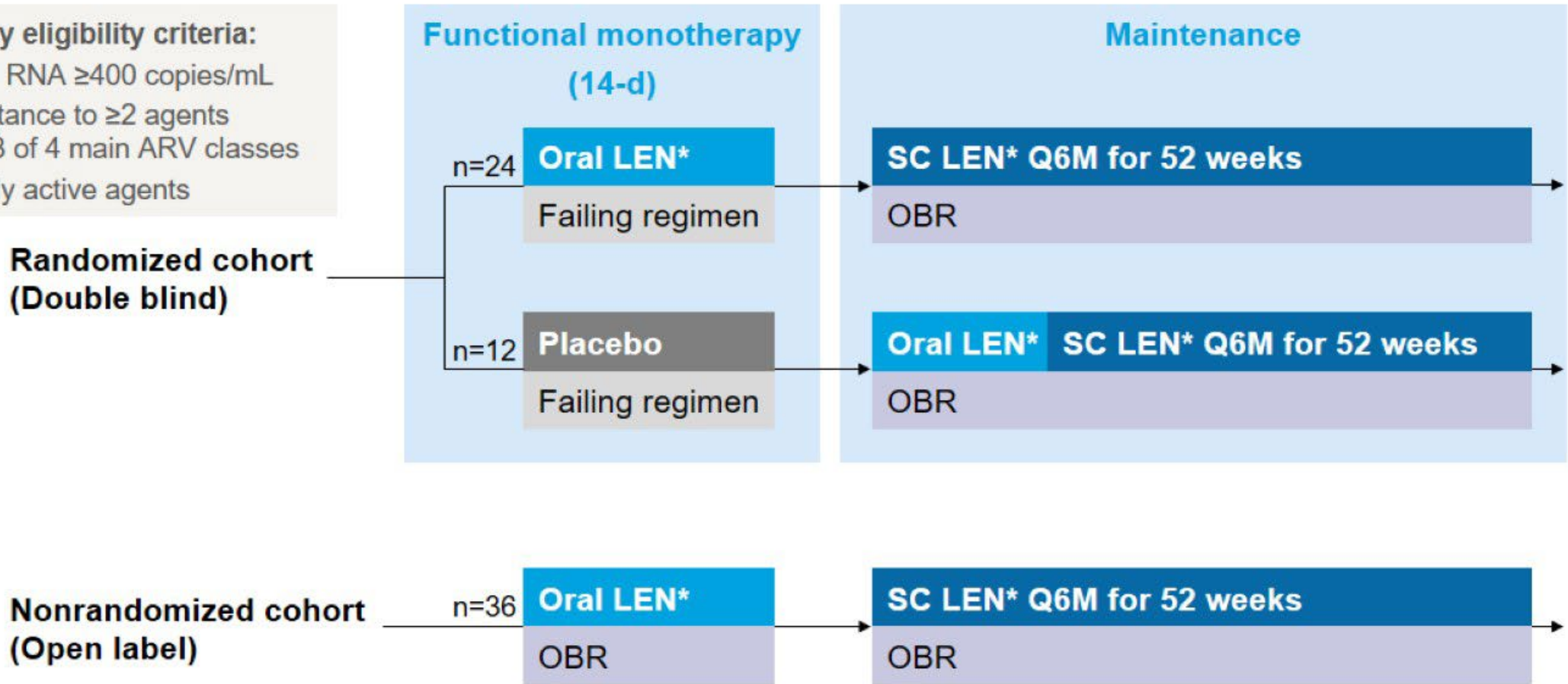
- LEN can meet significant unmet medical needs:
  - A new mechanism of action for heavily treatment-experienced people with multidrug-resistant HIV
  - Reduction of daily pill burden through less frequent dosing for treatment and prevention
- Highly desirable in vitro profile for heavily treatment-experienced people with HIV (PWH)
  - Nonoverlapping resistance profile with full activity against NRTI-, NNRTI-, INSTI-, and PI-resistance[1,2,3]
  - No observed pre-existing resistance[2]
- Single SC doses of LEN maintained target concentrations for 26 weeks, supporting its use once every 6 months[4]
- Potent antiviral activity in PWH, 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]

1. Yant SR, et al. CROI 2019, poster 480; 2. Margot N, et al. CROI 2020, poster 529; 3. VanderVeen L, et al. CROI 2021, oral 01781
4. Begley R et al. PEB0265 AIDS 2020; 5. Daar E, et al. CROI 2020, poster 3691

Study Design

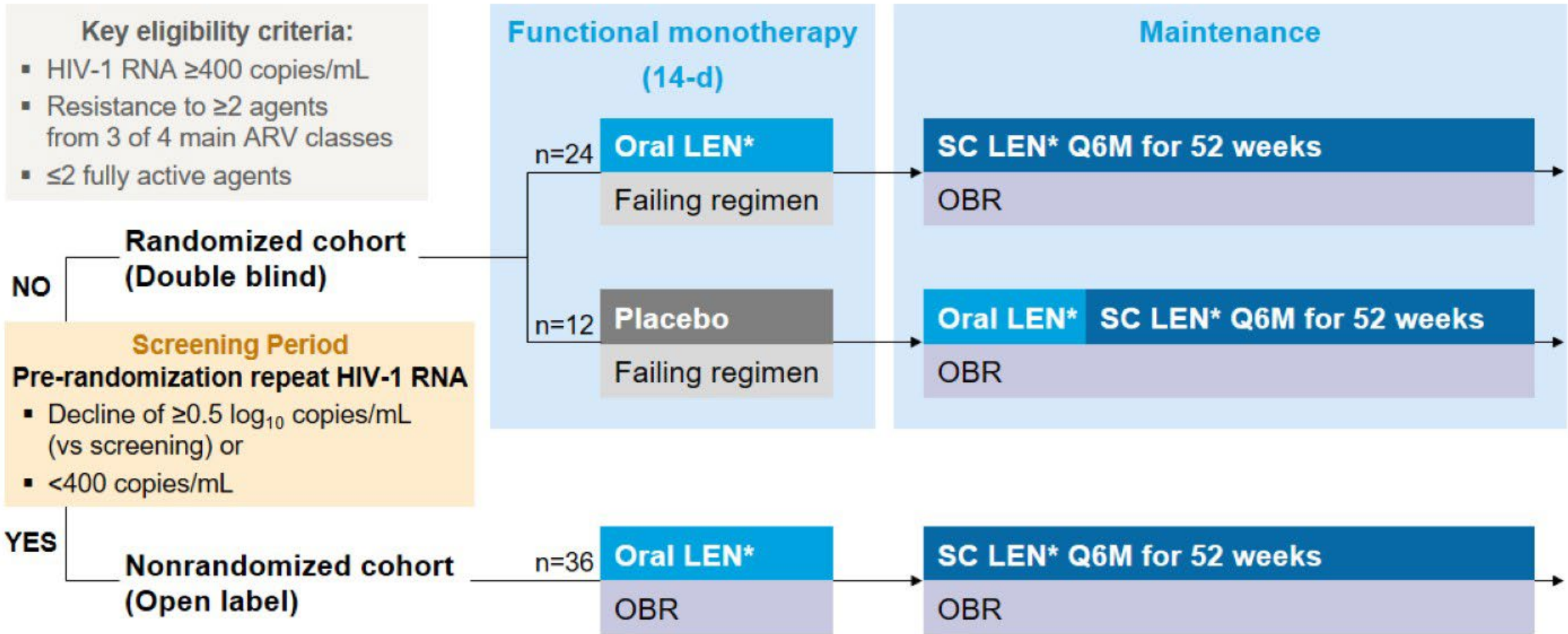
Key eligibility criteria:

- HIV-1 RNA ≥400 copies/mL
- Resistance to ≥2 agents from 3 of 4 main ARV classes
- ≤2 fully active agents



*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, optimized background regimen (investigational agents, such as fostemsavir, were allowed; ATV, ATV/co, ATV/r, EFV, ETV, NVP, TPV were not allowed).

Study Design



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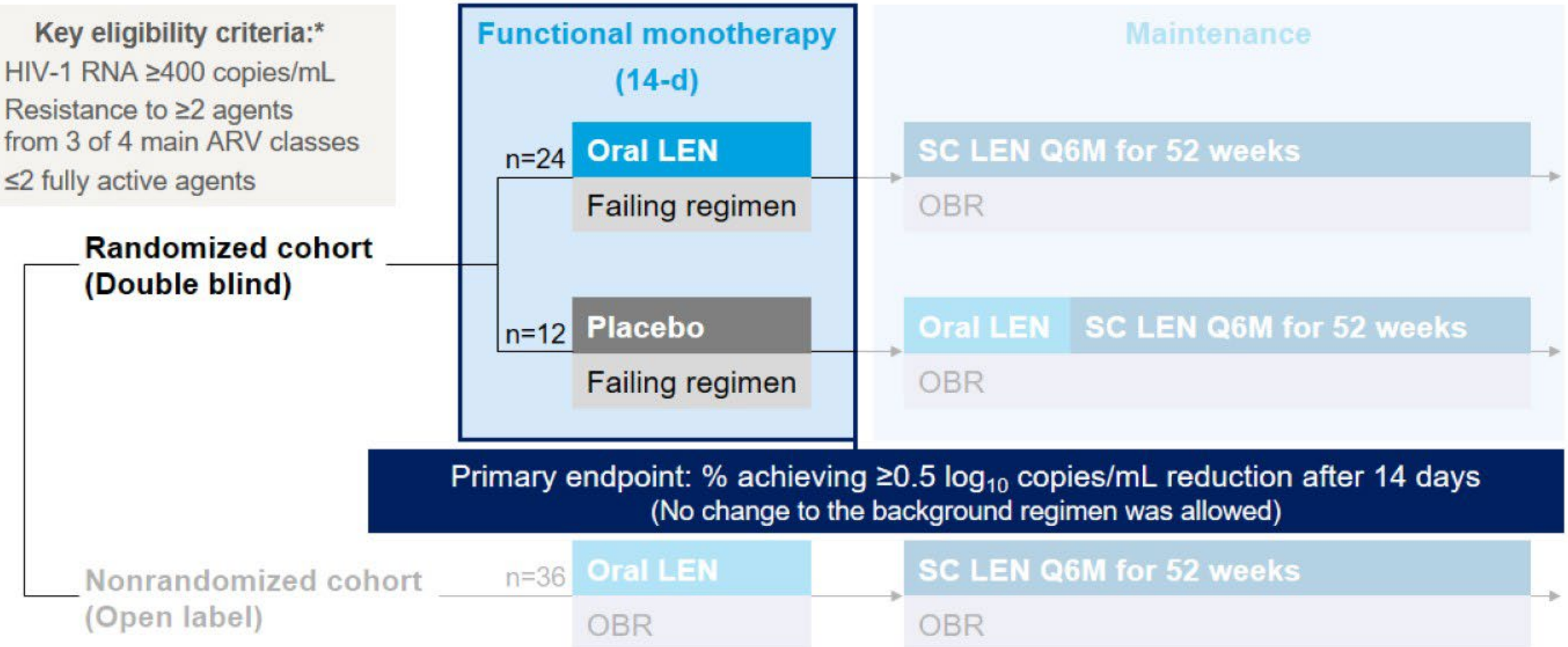
Study Design:
Primary Endpoint

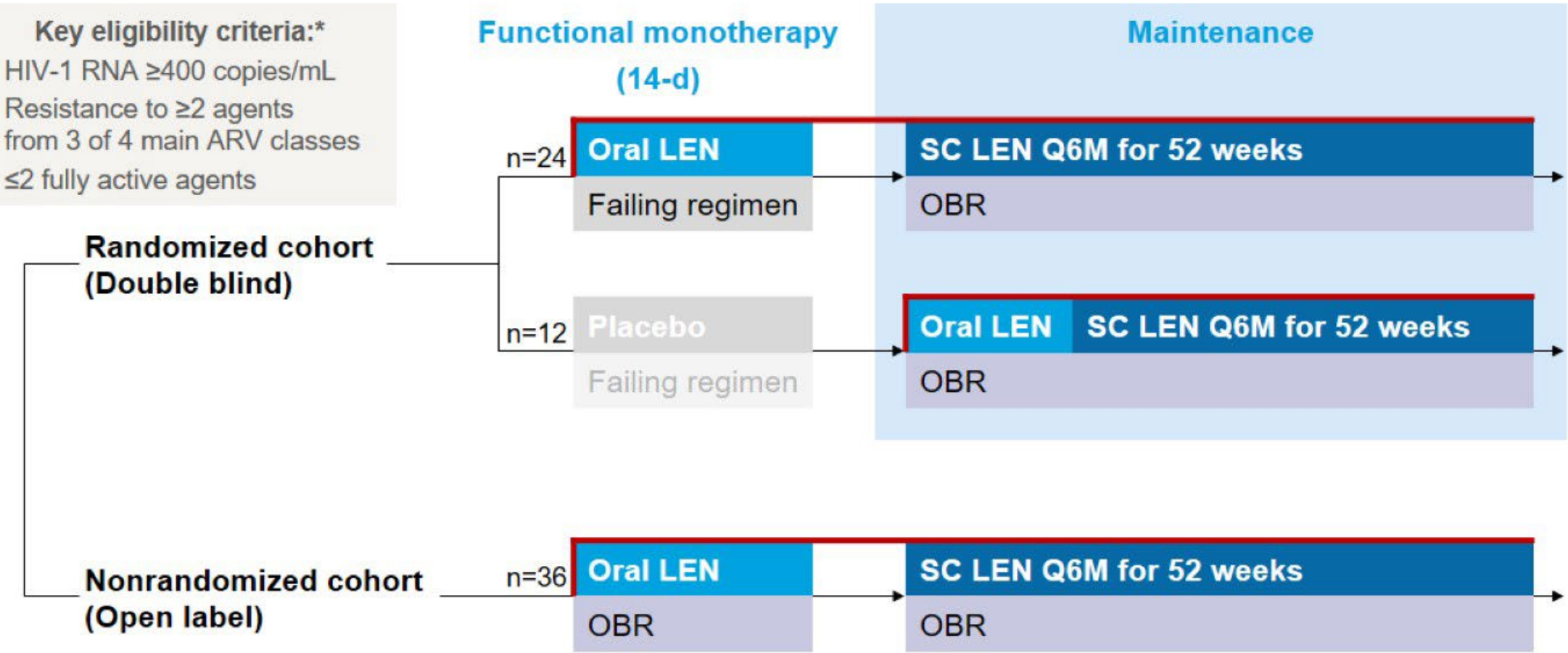
Key eligibility criteria:*
- HIV-1 RNA ≥400 copies/mL
- Resistance to ≥2 agents from 3 of 4 main ARV classes
- ≤2 fully active agents



*HIV-1 RNA was repeated prior to randomization 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.

Study Design:
Efficacy/Safety through at least Week 16

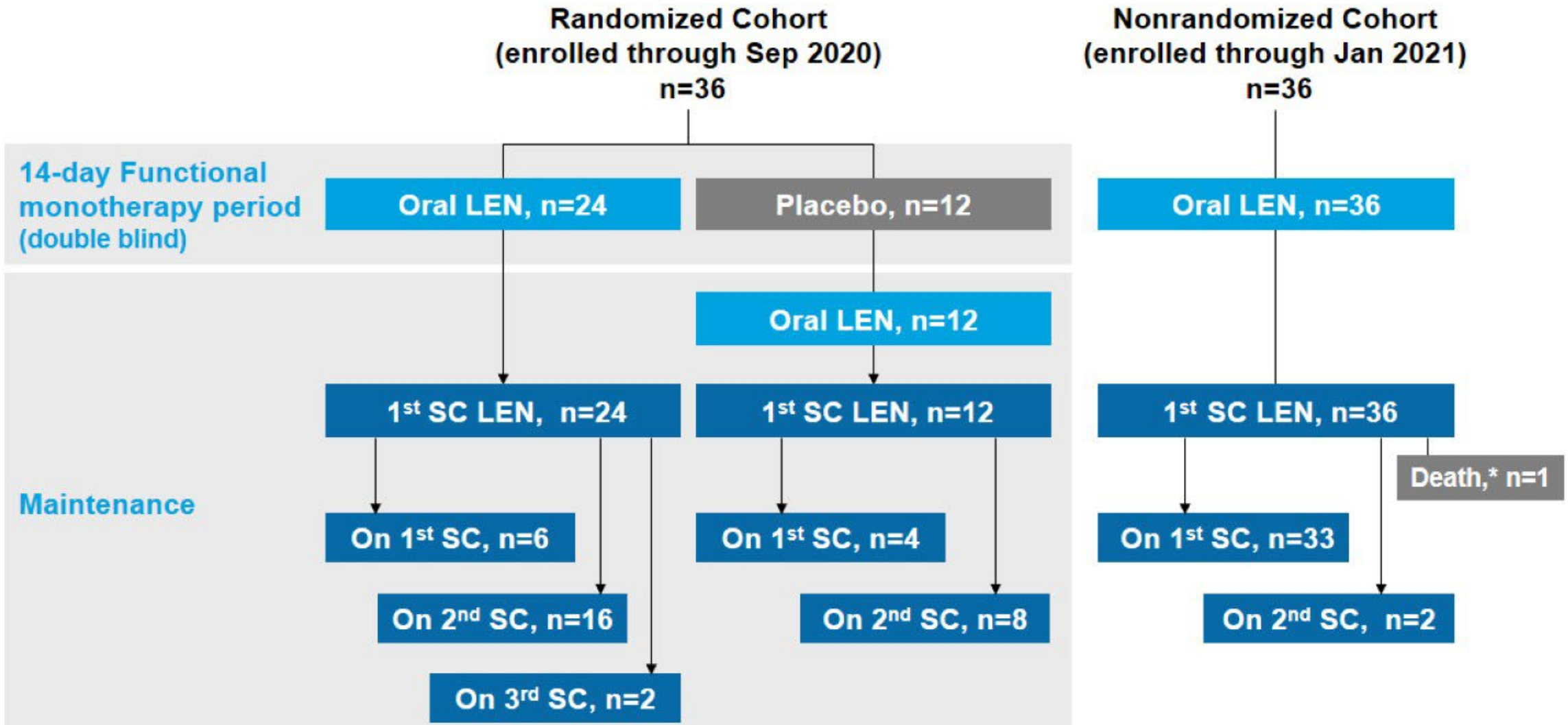
Key eligibility criteria:*
- HIV-1 RNA ≥400 copies/mL
- Resistance to ≥2 agents from 3 of 4 main ARV classes
- ≤2 fully active agents



Efficacy/safety from LEN start: randomized cohort through Wk16 and available data from nonrandomized cohort†

*HIV-1 RNA was repeated prior to randomization 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 analyzed in those who received ≥1 dose of SC LEN.

Participant Disposition (as of Feb2021)



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

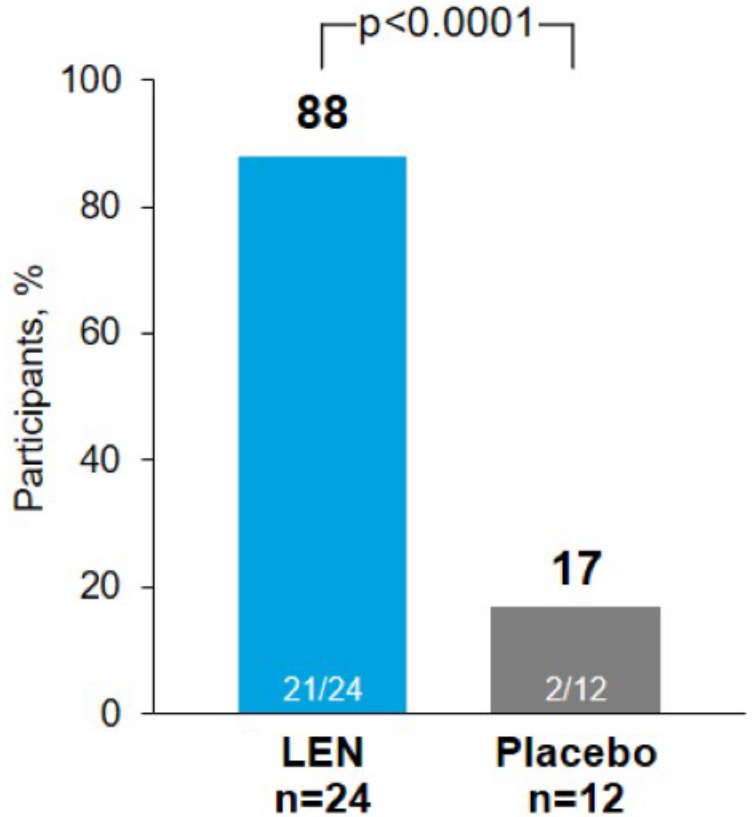
Baseline Characteristics

	Randomized		Nonrandomized	
	LEN n=24	Placebo n=12	LEN n=36	Total N=72
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

Antiviral Activity during Functional Monotherapy

Primary Endpoint

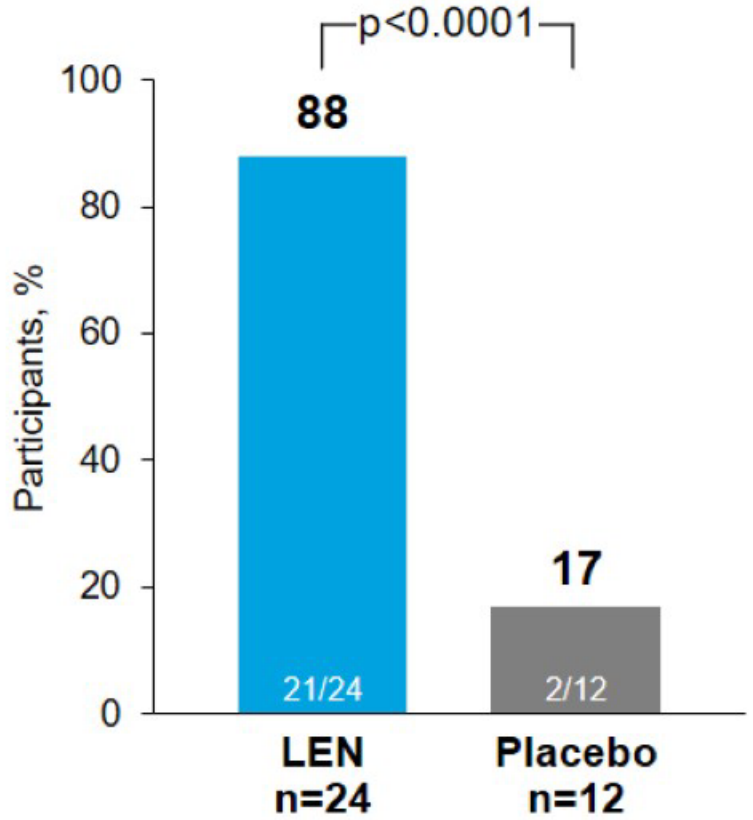
% Achieving HIV-1 RNA Decline ≥0.5 log_{10} copies/mL



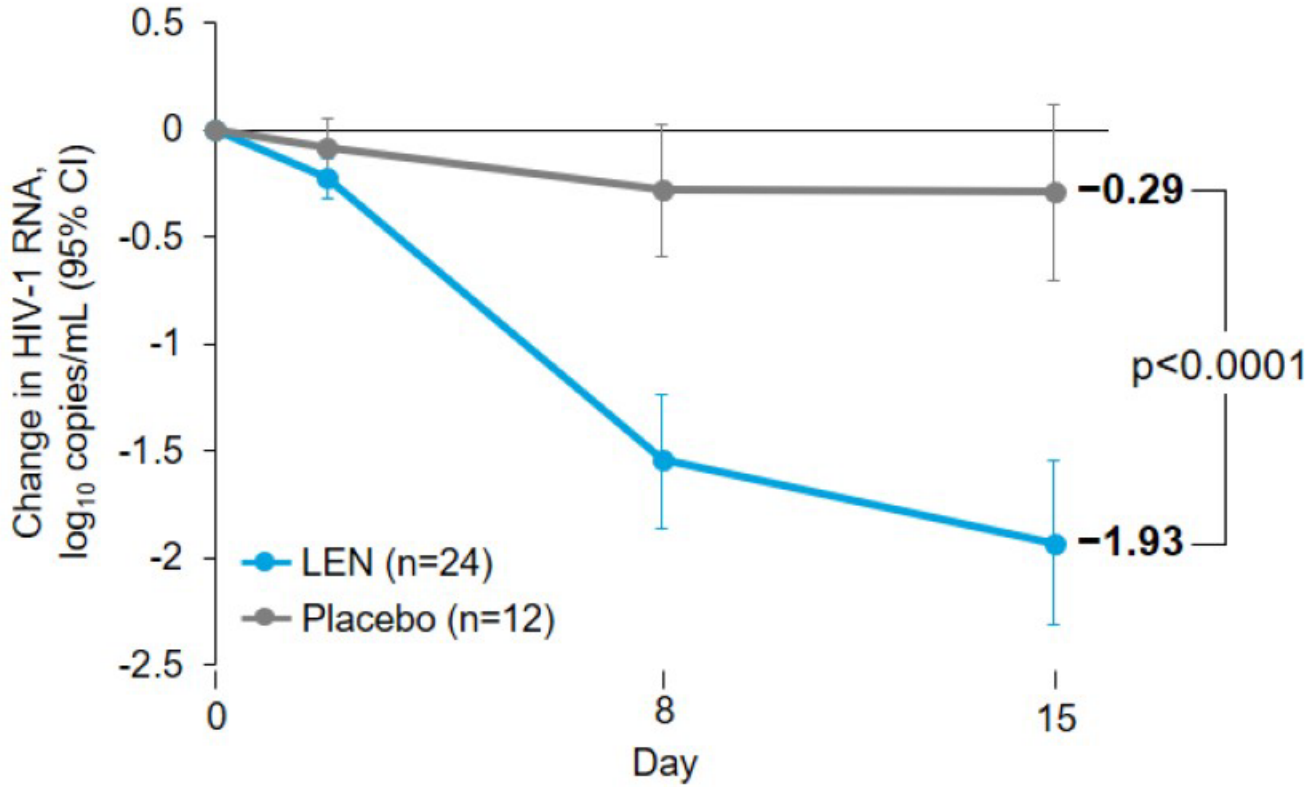
Antiviral Activity during Functional Monotherapy

Primary Endpoint

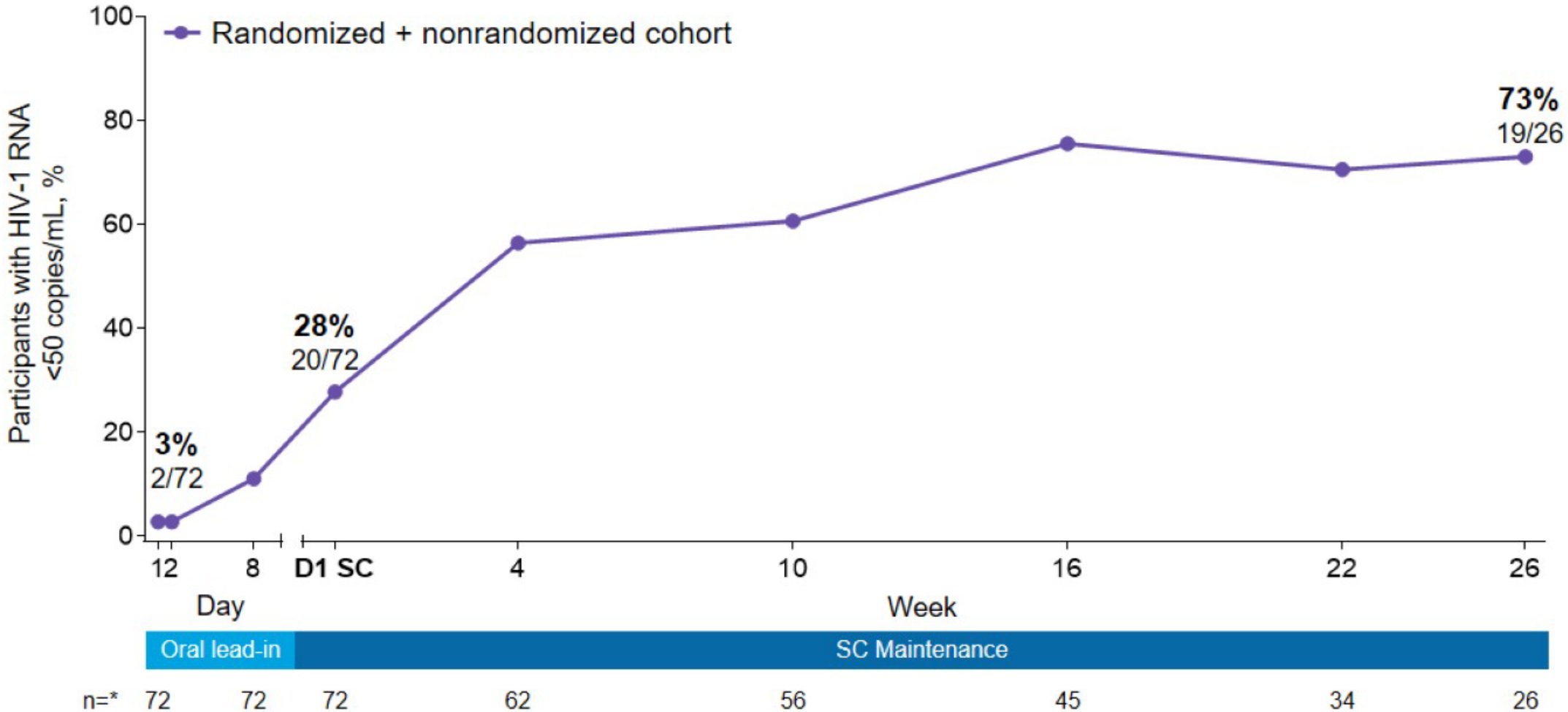
% Achieving HIV-1 RNA Decline ≥0.5 log_{10} copies/mL



Mean Change in HIV-1 RNA by visit (95% CI)

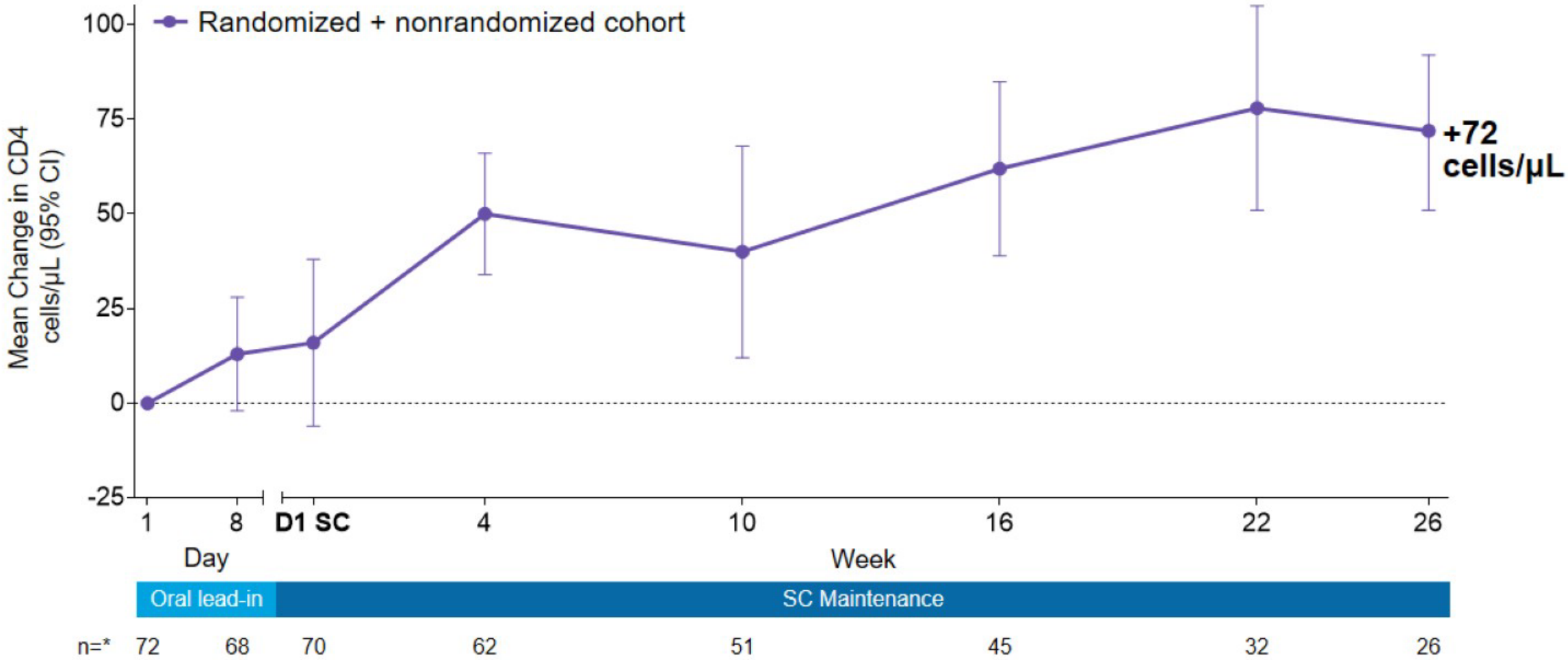


Participants with HIV-1 RNA <50 copies/mL (M=F): To date (Feb2021) in those who received SC LEN (n=72)



*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 (nonrandomized 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).

Changes in CD4



D1 SC, the first day SC LEN was administered.

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

- 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 WT)
  - M66I mutation significantly impairs viral replication (1.5% replication capacity vs WT)
    - See oral presentation 1781: VanderVeen ***et al*** for additional information
- Further analyses are ongoing

*Other agents in the OBR:
- For participant #1: MVC, T20, DTG BID, DRV/COBI, 3TC.
- For participant #2: F/TAF; DRV/COBI and DTG were dosed BID.

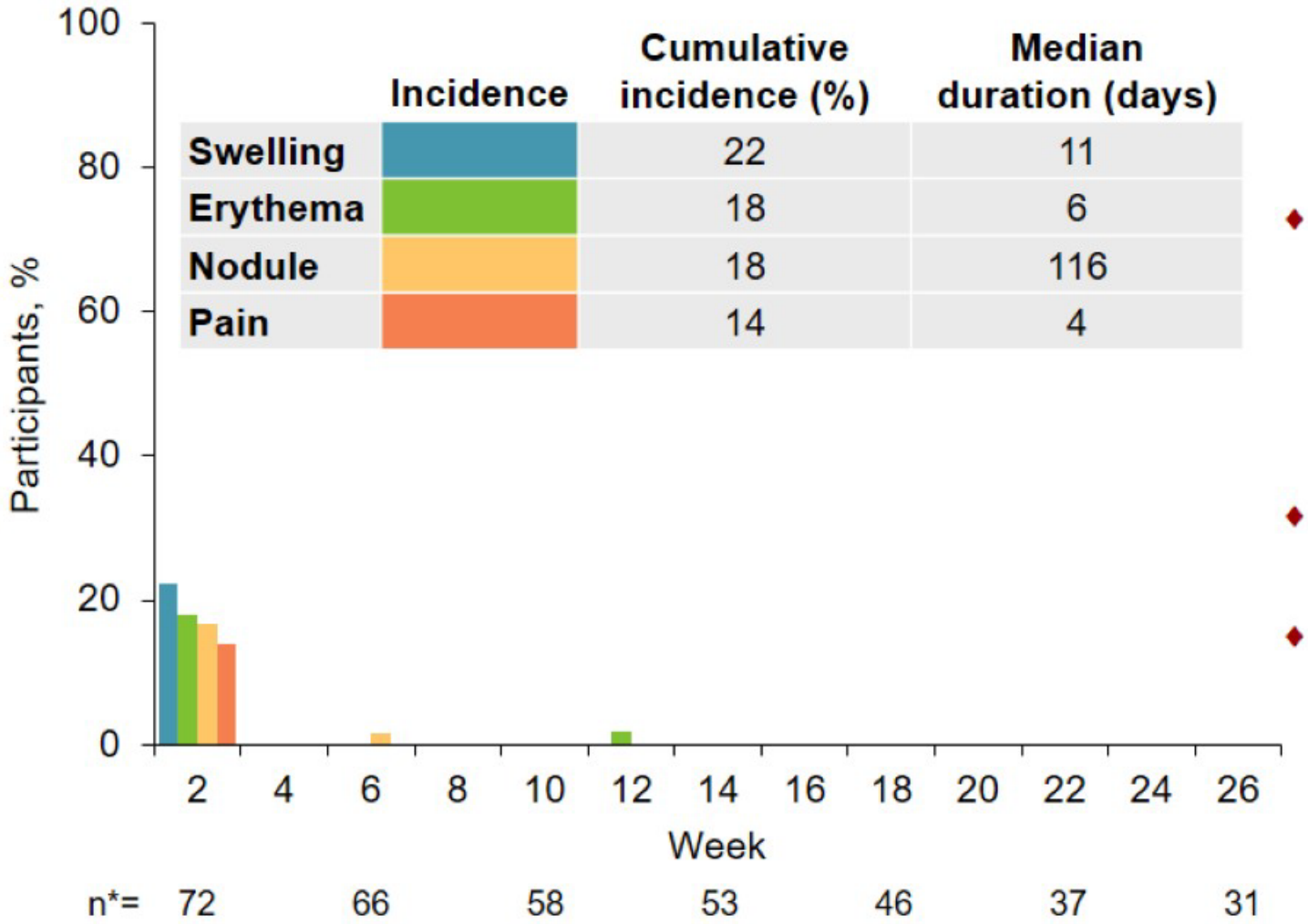
Adverse Events (excluding injection site reactions)

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

- 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

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

Injection Site Reactions to SC LEN: Incidence



	Incidence	Cumulative incidence (%)	Median duration (days)
Swelling		22	11
Erythema		18	6
Nodule		18	116
Pain		14	4

- 46% (33/72) had ≥1 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

*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).

Grade 3 or 4 Laboratory Abnormalities

≥ 5% in total, %	Randomized	Nonrandomized	
	On LEN n=36	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 hyperglycemia	12	0	7
High creatinine*	8	3	6
Glycosuria	8	3	6
Fasting hyperglycemia	11	0	6

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

*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.

Conclusions

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