Weight and Metabolic Changes with Long-Acting Lenacapavir in a Combination Regimen in Treatment-Naïve People with HIV-1 at Week 80

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Key Findings

- In CALIBRATE, participants receiving subcutaneous (SC) or oral lenacapavir (LEN) experienced an increase in body weight from baseline to Week 80 (2.6–4.7 kg across LEN treatment groups). This increase in body weight is consistent with other trials of antiretrovirals (ARVs) in treatment-naïve people with HIV-1 (PWH), and may be due to the return-to-health phenomenon
- Changes from baseline to Week 80 in fasting lipid parameters in participants receiving LEN, although limited by small sample size, did not appear to be clinically relevant

Conclusions

- In the Phase 2 CALIBRATE study, treatment regimens that included SC or oral LEN in combination with other ARVs led to weight gain and increase in body mass index (BMI) through Week 80 in treatment-naïve PWH, consistent with other trials of ARVs in PWH newly initiating treatment
  - This weight gain may be attributable to the return-to-health phenomenon
- The increase in body weight was most rapid during the first few weeks–months of treatment, consistent with other trials of ARVs in treatment-naïve PWH
- The increase in body weight was not associated with clinically-relevant increases in fasting lipid parameters

Introduction

- LEN is a first-in-class, long-acting HIV-1 capsid inhibitor approved for the treatment of multidrug-resistant HIV-1 in heavily treatment-experienced PWH, in combination with other ARVs, in the EU, US, and other countries[1–6]
  - The approval of LEN was based on the results of the Phase 2/3 CAPELLA trial (NCT04150068)[7]
- LEN efficacy and safety in treatment-naïve PWH is being investigated in the ongoing Phase 2 CALIBRATE trial (NCT04143594)[8]
  - At Week 80, 75–87% of participants receiving LEN in combination with other ARVs had virologic suppression (HIV-1 RNA <50 copies/mL per FDA Snapshot analysis)[9]
- PWH newly initiating treatment may experience weight gain after commencing ARV therapy[10]
  - This weight gain may be a function of the return-to-health phenomenon, wherein ARV-induced virologic suppression and reduced inflammation leads to resolution of a catabolic state, and subsequent restoration of body weight[11]
  - Weight gain after initiation of ARVs is associated with decreased mortality amongst PWH who were not initially overweight[12]

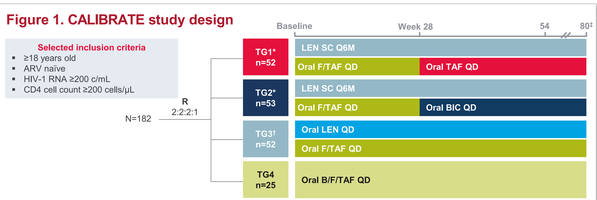
Objective

- To characterize weight and metabolic changes through Week 80 in treatment-naïve PWH enrolled in CALIBRATE

Methods

- CALIBRATE is an ongoing randomized, open-label, active-controlled, multicenter Phase 2 trial
- ARV-naïve participants were randomized to receive SC LEN every six months (treatment groups [TGs] 1 and 2) or oral LEN daily (TG3) in combination with other ARVs, or the active control group (TG4 [**Figure 1**])
- Weight, BMI, and fasting lipid parameters (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides, and total cholesterol to HDL ratio) were assessed
  - No statistical testing was performed due to the small sample size

Figure 1. CALIBRATE study design



*Participants received LEN oral loading prior to initiating LEN SC (Day 1 and 2: 600 mg; Day 8, 300 mg). †Participants received oral LEN 600 mg on Days 1 and 2, followed by QD LEN 50 mg from Day 3. ‡At Week 80, participants in TG4 complete the study, and participants in TGs 1–3 may continue beyond Week 80
BIC/B, bictegravir; c/mL, copies/mL; F, emtricitabine; LEN, lenacapavir; PWH, people with HIV; Q6M, every six months; QD, daily; R, randomized; SC, subcutaneous; TAF, tenofovir alafenamide; TG, treatment group; W, week

Results

- Overall, 182 participants were randomized and received ≥1 dose of study drug
- Baseline characteristics are shown in **Table 1**
  - Mean body weight at baseline was 80.4–88.1 kg across the four TGs (**Table 1**)

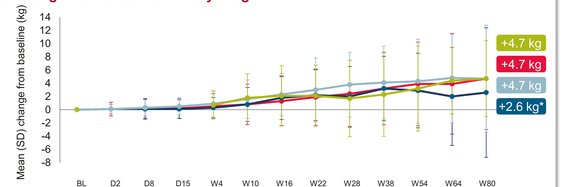
Table 1: Baseline demographic and disease characteristics

	TG1 SC LEN + F/TAF→TAF (n=52)	TG2 SC LEN + F/TAF→BIC (n=53)	TG3 Oral LEN + F/TAF (n=52)	TG4 B/F/TAF (n=25)
Median (range) age, years	31 (19–61)	28 (19–56)	28 (19–72)	29 (21–61)
Sex at birth, male, n (%)	47 (90.4)	52 (98.1)	46 (88.5)	25 (100)
Race, n (%)				
Asian	1 (1.9)	0	1 (1.9)	0
Black	24 (46.2)	24 (45.3)	31 (59.6)	16 (64.0)
White	23 (44.2)	28 (52.8)	19 (36.5)	8 (32.0)
Other	4 (7.7)	1 (1.9)	1 (1.9)	1 (4.0)
Mean (SD) weight, kg	82.4 (22.8)	80.5 (20.3)	80.4 (19.1)	88.1 (26.6)
Mean (SD) BMI, kg/m²	27.3 (7.8)	26.2 (5.9)	26.6 (5.7)	27.1 (6.1)
HIV-1 RNA				
Median (range), $\log_{10}$ c/mL	4.3 (2.3–5.6)	4.3 (2.5–5.8)	4.5 (2.4–5.5)	4.4 (2.1–5.9)
>100,000 c/mL, n (%)	5 (9.6)	9 (17.0)	9 (17.3)	4 (16.0)
Median (range) CD4 cell count, cells/µL	404 (213–1846)	450 (187–991)	409 (175–1091)	482 (232–1443)
Mean (SD) fasting lipids*	n=28	n=23	n=22	n=9
Total cholesterol, (mg/dL)	164 (32)	157 (27)	170 (38)	165 (29)
LDL cholesterol, (mg/dL)	102 (28)	91 (23)	105 (29)	100 (26)
HDL cholesterol, (mg/dL)	41 (8)	42 (12)	41 (14)	45 (9)
Triglycerides, (mg/dL)	106 (51)	123 (94)	117 (45)	102 (34)
Total cholesterol:HDL ratio	4.1 (1.0)	4.1 (1.4)	4.4 (1.1)	3.8 (0.9)

*Baseline value was the last available value collected on or prior to first dose of study drug; only fasting values were evaluated
BIC/B, bictegravir; BMI, body mass index; c/mL, copies/mL; F, emtricitabine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LEN, lenacapavir; SC, subcutaneous; SD, standard deviation; TAF, tenofovir alafenamide; TG, treatment group

- Mean baseline fasting lipid values largely consistent across TGs (**Table 1**)
- At baseline, 5 (10%), 2 (4%), 7 (14%), and 2 (8%) participants in TGs 1–4, respectively, were receiving lipid-modifying agents
- From baseline to Week 80, mean increase in body weight was 4.7 kg in TGs 1, 3, and 4, and 2.6 kg in TG2 (**Figure 2**)
  - This corresponds to a mean BMI increase of 1.6, 0.9, 1.5, and 1.5 kg/m² in TGs 1–4, respectively
- A substantial proportion of the increase in body weight had occurred by Week 28, followed by a slower rate of increase up to Week 80

Figure 2: Change from baseline in body weight



n	BL	D2	D8	D15	W4	W10	W16	W22	W28	W38	W54	W64	W80
TG1 SC LEN + F/TAF→TAF	52	52	52	51	51	49	49	50	49	49	49	49	48
TG2 SC LEN + F/TAF→BIC*	53	52	52	52	52	52	51	51	51	51	47	43	42
TG3 Oral LEN + F/TAF	52	52	51	51	51	52	51	50	50	47	48	47	46
TG4 B/F/TAF	25	–	–	–	25	25	25	25	25	25	23	24	24

Baseline value was the last available value collected on or prior to first dose of study drug.
*One participant had planned gastric sleeve surgery, leading to weight loss.
BIC/B, bictegravir; BL, baseline; D, day; F, emtricitabine; LEN, lenacapavir; SC, subcutaneous; SD, standard deviation; TAF, tenofovir alafenamide; TG, treatment group; W, week.

- One participant (baseline weight 148 kg) in TG2 underwent planned gastric sleeve surgery, which led to weight loss of 44 kg by Week 80
- Fasting lipid parameters were predominantly stable through Week 80 (**Figure 3 A–E**), with changes from baseline similar across TGs (**Table 2**)
- Grade 3/4 treatment-emergent fasting lipid laboratory abnormalities were infrequent and not clinically significant (**Table 3**), with the following rates observed in TGs 1–4, respectively:
  - Hypercholesterolemia: 2%, 2%, 0%, and 0%
  - Elevated LDL: 2%, 2%, 6%, and 0%
  - Elevated triglycerides: 0%, 8%, 0%, and 4%
- In TGs 1–4, respectively, 6%, 4%, 10%, and 16% of participants initiated lipid-modifying agents during the study

Table 2: Change from baseline in fasting lipid parameters

Mean (SD) change from baseline, mg/dL	TG1 SC LEN + F/TAF→TAF			TG2 SC LEN + F/TAF→BIC			TG3 Oral LEN + F/TAF			TG4 BIC/F/TAF		
	W28 (n=24)	W54 (n=22)	W80 (n=23)	W28 (n=22)	W54 (n=19)	W80 (n=17)	W28 (n=17)	W54 (n=17)	W80 (n=16)	W28 (n=8)	W54 (n=7)	W80 (n=9)
Total cholesterol	–6 (21)	–5 (20)	+5 (16)	+4 (21)	+14 (24)	+20 (19)	+5 (29)	+6 (35)	+8 (41)	–5 (19)	–22 (28)	+3 (25)
LDL	–7 (22)	–6 (20)	+3 (14)	–1 (18)	+11 (19)	+15 (18)	+2 (27)	+1 (24)	+1 (31)	–9 (19)	–18 (24)	+1 (21)
HDL	+4 (8)	+3 (7)	+3 (9)	+1 (7)	+3 (9)	+5 (8)	+2 (9)	+1 (11)	0 (10)	+6 (13)	+1 (7)	+6 (5)
Triglycerides	–17 (48)	–8 (45)	–6 (52)	+18 (70)	+3 (61)	–1 (70)	+6 (45)	+20 (59)	+35 (56)	–10 (35)	–26 (39)	–20 (39)
Total cholesterol to HDL ratio	–0.5 (0.6)	–0.3 (0.6)	–0.1 (0.7)	–0.1 (1.0)	+0.1 (0.8)	–0.1 (0.6)	–0.1 (0.7)	+0.1 (1.2)	+0.2 (0.9)	–0.4 (0.8)	–0.6 (0.7)	–0.4 (0.7)

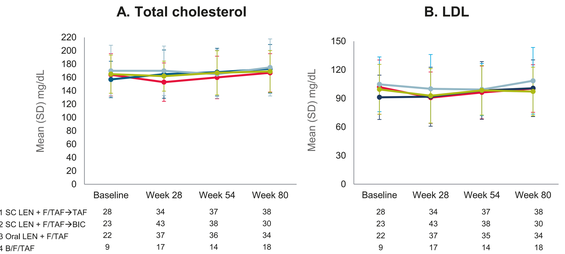
Baseline value was the last available value collected on or prior to first dose of study drug.
BIC, bictegravir; F, emtricitabine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LEN, lenacapavir; SC, subcutaneous; SD, standard deviation; TAF, tenofovir alafenamide; TG, treatment group

Table 3: Grade 3/4 treatment-emergent fasting lipid laboratory abnormalities

n (%)	TG1 SC LEN + F/TAF→TAF (n=52)		TG2 SC LEN + F/TAF→BIC (n=53)		TG3 Oral LEN + F/TAF (n=52)		TG4 B/F/TAF (n=25)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Elevated total cholesterol	1 (2.0)	0	1 (2.0)	0	0	0	0	0
Elevated LDL*	1 (2.0)	0	1 (2.0)	0	3 (6.1)	0	0	0
Elevated triglycerides	0	0	3 (5.9)	1 (2.0)	0	0	1 (4.3)	0

Treatment-emergent laboratory abnormalities were defined as an increase of at least 1 toxicity grade from baseline at any time post-baseline up to and including the date of last exposure date. Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
*LDL derived from Friedewald formula: total cholesterol–HDL– triglyceride/5.
BIC/B, bictegravir; F, emtricitabine; LDL, low-density lipoprotein; LEN, lenacapavir; SC, subcutaneous; TAF, tenofovir alafenamide; TG, treatment group

Figure 3: Mean (SD) fasting lipid values through Week 80



n	Baseline	Week 28	Week 54	Week 80
TG1 SC LEN + F/TAF→TAF	28	34	37	38
TG2 SC LEN + F/TAF→BIC	23	43	38	30
TG3 Oral LEN + F/TAF	22	37	36	34
TG4 B/F/TAF	9	17	14	18

Baseline value was the last available value collected on or prior to first dose of study drug.
BIC/B, bictegravir; F, emtricitabine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LEN, lenacapavir; SC, subcutaneous; SD, standard deviation; TAF, tenofovir alafenamide; TG, treatment group

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