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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Gupta SK, Berhe M, Crofoot G, et al. Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial. *Lancet HIV* 2023; **10:** e15–23.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Gupta, et al. Lenacapavir Administered Every Six Months or Daily in Combination with Daily Oral Antiretroviral Therapy for Initial Treatment of HIV Infection: A Randomised, Open-Label, Active-Controlled, Phase 2 Trial

Lenacapavir, a Novel Capsid Inhibitor in Multidrug-Resistant HIV Infection

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Inclusion and Exclusion Criteria

To be eligible for study participation, all of the following inclusion criteria had to be met:

1) Willing and able to provide written informed consent prior to performing study procedures
2) Aged ≥18 years
3) Antiretroviral naïve with no use of any antiretroviral within one month of screening. Use of pre-exposure prophylaxis (any duration), post-exposure prophylaxis (any duration), or HIV-1 treatment (<10 days therapy total) >1 month prior to screening is permitted
4) Plasma HIV-1 RNA ≥200 copies/mL at screening
5) CD4+ cell count ≥200 cells/μL at screening
6) A negative serum pregnancy test is required for all women at screening
7) Participants of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as defined in the protocol appendix.
8) Lactating women must agree to discontinue nursing before the study drug(s) is administered

Individuals who meet any of the following exclusion criteria were not to be enrolled:

1) An opportunistic illness requiring acute therapy within 30 days prior to screening
2) Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days before screening
3) Active tuberculosis infection
4) Acute hepatitis within 30 days prior to screening
5) HBV infection, defined as screening results showing either or both of:
    a. Positive HBV surface antigen
    b. Positive HBV core antibody and negative HBV surface antibody
6) Hepatitis C virus (HCV) antibody positive and HCV RNA >lower limit of quantitation (LLOQ)
7) A history of or current clinical decompensated liver cirrhosis (eg, ascites, encephalopathy, or variceal bleeding)

8) Treatment within 3 months prior to screening, or anticipated treatment during the study period with immunosuppressant therapies, hydroxyurea, foscarnet, radiation, or cytotoxic chemotherapeutic agents without prior approval from sponsor prior to randomization. Agents disallowed in Table 5-5 of the protocol may not be considered for approval
9) Active malignancy requiring acute therapy (with the exception of local cutaneous Kaposi's sarcoma)
10) Current alcohol or substance use judged by the investigator to potentially interfere with the participant's study compliance
11) Clinically significant abnormal ECG at the screening visit
12) Any of the following laboratory values at screening
    a. Estimated glomerular filtration rate (eGFR) ≤ 50 mL/min according to the Cockcroft-Gault formula for creatinine clearance
    b. Alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN)
    c. Direct bilirubin > 1.5 x ULN
    d. Platelets < 50,000/mm^3
    e. Hemoglobin < 8.0 g/dL
13) Participation or planned participation in any other clinical trial (including observational trials) without prior approval from the sponsor throughout the study
14) Prior use of, or exposure to, GS-6207
15) Known hypersensitivity to the study drug(s), the metabolites, or formulation excipient
16) Use or planned use of exclusionary medications, refer to Section 5.4 of the protocol
17) Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the participant unsuitable for the study or unable to comply with dosing requirements

Table S1. Participants Who Discontinued Study Drug

Last Dose (Day)	Reason
SC lenacapavir +F/TAF→TAF (n=5)	
205	Lack of efficacy (Did not meet the protocol criterion of having HIV-1 RNA <50 copies/mL prior to week 28)
183	Lack of efficacy (Did not meet the protocol criterion of having HIV-1 RNA <50 copies/mL prior to week 28)
8	Investigator's discretion (Due to COVID-19, complying with study procedures was not feasible)
71	Lost to follow-up
209	Lost to follow-up
SC lenacapavir +F/TAF→BIC (n=12)	
156	Adverse event (Grade 1, injection site induration at day 15)
211	Adverse event (Grade 1, injection site induration at day 15)
399	Adverse Event (Grade 1, injection site erythema and injection site swelling at day 196)
153	Lack of efficacy (did not meet the protocol criteria of having HIV-1 RNA <50 copies/mL prior to week 28)
1	Participant decision (not able to comply with study procedures)
200	Participant decision (withdrew consent)
376	Participant decision (relocated for employment)
396	Participant decision (lives far from study site)
113	Investigator discretion (the participant's metal health was considered interfering with study procedures)
450	Investigator discretion (the participant not compliant with study drug)

273	Lost to follow-up
388	Lost to follow-up
Oral Lenacapavir + F/TAF (n=4)	
161	Participant decision (started standard of care)
205	Lost to follow-up
72	Lost to follow-up
155	Lost to follow-up
BIC/F/TAF (n=1)	
267	Participant decision (the participant's work schedule)

Table S2. Virologic Response During Treatment (Missing = Failure)

HIV-1 RNA <50 copies/mL — no. (%) Difference in % (95% CI)	Lenacapavir				BIC/F/TAF (n=25)
	Subcutaneous		Oral	Total (n=157)	
	+F/TAF→TAF (n=52)	+F/TAF→BIC (n=53)	+F/TAF (n=52)		
Week					
4	43 (83)	42 (79)	45 (87)	130 (83)	21 (84)
	-6.6 (-20.9 to 7.8)	-4.2 (-20.1 to 11.7)	3.0 (-12.6 to 18.7)	-1.9 (-15.4 to 11.6)	
10	49 (94)	46 (87)	50 (96)	145 (92)	25 (100)
	-6.3 (-17.1 to 4.4)	-13.0 (-25.1 to -1.0)	-3.9 (-13.9 to 6.2)	-7.8 (-16.6 to 1.0)	
16	48 (92)	50 (94)	49 (94)	147 (94)	25 (100)
	-8.2 (-19.4 to 3.1)	-5.5 (-15.8 to 4.7)	-5.7 (-16.3 to 4.9)	-6.5 (-15.2 to 2.1)	
22	47 (90)	49 (93)	49 (94)	145 (92)	25 (100)
	-11.7 (-22.8 to -0.5)	-7.4 (-18.3 to 3.4)	-5.8 (-16.5 to 4.8)	-7.8 (-16.6 to 1.0)	
28	49 (94)	49 (93)	49 (94)	147 (94)	25 (100)
	-5.5 (-15.9 to 4.8)	-7.4 (-18.3 to 3.4)	-5.7 (-16.3 to 4.9)	-6.5 (-15.1 to 2.2)	
38	47 (90)	47 (89)	46 (89)	140 (89)	24 (96)
	-6.7 (-20.7 to 7.3)	-7.2 (-21.3 to 6.8)	-7.6 (-21.8 to 6.7)	-7.0 (-18.8 to 4.9)	
54	47 (90)	45 (85)	44 (85)	136 (87)	23 (92)
	-2.6 (-18.4 to 13.2)	-7.1 (-23.4 to 9.3)	-7.2 (-23.5 to 9.1)	-5.6 (-19.5 to 8.4)	

BIC, bictegravir; F, emtricitabine; TAF, tenofovir alafenamide

Table S3. Virologic Response at Week 54 (Snapshot)

Response Criteria	Lenacapavir				
	Subcutaneous		Oral		
	+F/TAF→TAF (n=52)	+F/TAF→BIC (n=53)	+F/TAF (n=52)	Total (n=157)	BIC/F/TAF (n=25)
HIV-1 RNA <50 copies/mL ─ no. (%)	47 (90)	45 (85)	44 (85)	136 (87)	23 (92)
HIV-1 RNA ≥50 copies/mL ─ no. (%)	2 (4)	2 (4)	3 (6)	7 (5)	0
HIV-1 RNA ≥50 copies/mL in week 54 window	0	0	3 (6)	3 (2)	0
Discontinued study drug due to lack of efficacy	2 (4)	1 (2)	0	3 (2)	0
Discontinued study drug due to other reasons* and last available HIV-1 RNA ≥50 copies/mL	0	1 (2)	0	1 (1)	0
No virologic data in week 54 window ─ no. (%)	3 (6)	6 (11)	5 (10)	14 (9)	2 (8)
Discontinued study drug due to AE/death	0	2 (4)	0	2 (1)	0
Discontinued study drug due to other reasons* and last available HIV-1 RNA <50 copies/mL	3 (6)	4 (8)	4 (8)	11 (7)	1 (4)
Missing data during window but on study drug	0	0	1 (2)	1 (0.6)	1 (4)

AE, adverse event; BIC, bictegravir; F, emtricitabine; TAF, tenofovir alafenamide

*Other reasons include participants who discontinued study drug due to investigator's discretion, participant decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

The week 54 window is between days 323 and 413 (inclusive).

Table S4. Details for Participants with Emergent Lenacapavir Resistance

Participant	Group	Baseline Viral Load (copies/mL)	VF Visit (copies/mL)†	Emergent Resistance Mutations*			Fold-Change‡			
				CA	RT	IN	LEN	FTC	TFV§	BIC
041	SC LEN + (F/TAF→BIC)	170000	Week 10 (96700)	Q67H K70R	M184M/I	None	20	>58	0.46	ND
003	Oral LEN + F/TAF	348000	Week 54 (64000)	Q67H	None	ND	7.1	0.85	0.75	ND

BIC, bictegravir; CA, capsid; F, FTC, emtricitabine; IN, integrase; LEN, lenacapavir; ND, not determined; RT, reverse transcriptase; TAF, tenofovir alafenamide; TFV, tenofovir; VF, virologic failure; WT, wild-type.

*Compared with screening/baseline genotype.

‡Phenotypic fold change compared with WT control.

†A sample from the confirmatory virologic failure visit was used in the resistance analysis for Participant 003. Participant 041 was included in the resistance analysis due to persistent viremia.

§Phenotypic assay was performed with TFV, the parent compound of TAF.

Table S5. Adverse Events in ≥5% of Participants in Any Treatment Group

	SC LEN + F/TAF→TAF (n = 52)	SC LEN + F/TAF→BIC (n = 53)	Oral LEN + F/TAF (n = 52)	BIC/F/TAF (n = 25)	SC LEN Total (n = 105)	LEN Total (n = 157)
Number (%) of participants with an adverse event	50 (96.2%)	45 (84.9%)	43 (82.7%)	21 (84.0%)	95 (90.5%)	138 (87.9%)
Adverse events in ≥5% of participants in any treatment group						
Injection site erythema	21 (40.4%)	12 (22.6%)	0	0	33 (31.4%)	33 (21.0%)
Injection site swelling	16 (30.8%)	13 (24.5%)	0	0	29 (27.6%)	29 (18.5%)
Injection site pain	15 (28.8%)	10 (18.9%)	0	0	25 (23.8%)	25 (15.9%)
Headache	9 (17.3%)	5 (9.4%)	7 (13.5%)	3 (12.0%)	14 (13.3%)	21 (13.4%)
Nausea	10 (19.2%)	5 (9.4%)	6 (11.5%)	1 (4.0%)	15 (14.3%)	21 (13.4%)
COVID-19	5 (9.6%)	5 (9.4%)	5 (9.6%)	3 (12.0%)	10 (9.5%)	15 (9.6%)
Syphilis	5 (9.6%)	4 (7.5%)	5 (9.6%)	4 (16.0%)	9 (8.6%)	14 (8.9%)
Injection site nodule	9 (17.3%)	8 (15.1%)	0	0	17 (16.2%)	17 (10.8%)
Lymphadenopathy	4 (7.7%)	4 (7.5%)	6 (11.5%)	1 (4.0%)	8 (7.6%)	14 (8.9%)
Injection site inflammation	10 (19.2%)	4 (7.5%)	0	0	14 (13.3%)	14 (8.9%)
Diarrhoea	3 (5.8%)	4 (7.5%)	5 (9.6%)	1 (4.0%)	7 (6.7%)	12 (7.6%)
Injection site induration	8 (15.4%)	5 (9.4%)	0	0	13 (12.4%)	13 (8.3%)
Arthralgia	2 (3.8%)	4 (7.5%)	2 (3.8%)	4 (16.0%)	6 (5.7%)	8 (5.1%)
Back pain	1 (1.9%)	4 (7.5%)	4 (7.7%)	3 (12.0%)	5 (4.8%)	9 (5.7%)
Depression	1 (1.9%)	6 (11.3%)	3 (5.8%)	1 (4.0%)	7 (6.7%)	10 (6.4%)
Influenza	4 (7.7%)	2 (3.8%)	5 (9.6%)	0	6 (5.7%)	11 (7.0%)
Nasopharyngitis	4 (7.7%)	4 (7.5%)	3 (5.8%)	0	8 (7.6%)	11 (7.0%)
Anxiety	2 (3.8%)	2 (3.8%)	3 (5.8%)	2 (8.0%)	4 (3.8%)	7 (4.5%)
Fatigue	0	6 (11.3%)	2 (3.8%)	1 (4.0%)	6 (5.7%)	8 (5.1%)
Oropharyngeal pain	2 (3.8%)	4 (7.5%)	3 (5.8%)	0	6 (5.7%)	9 (5.7%)
Pyrexia	3 (5.8%)	2 (3.8%)	2 (3.8%)	2 (8.0%)	5 (4.8%)	7 (4.5%)
Dizziness	3 (5.8%)	2 (3.8%)	2 (3.8%)	1 (4.0%)	5 (4.8%)	7 (4.5%)
Gonorrhoea	2 (3.8%)	2 (3.8%)	3 (5.8%)	1 (4.0%)	4 (3.8%)	7 (4.5%)
Hypertension	3 (5.8%)	3 (5.7%)	1 (1.9%)	1 (4.0%)	6 (5.7%)	7 (4.5%)
Vitamin D deficiency	0	4 (7.5%)	3 (5.8%)	1 (4.0%)	4 (3.8%)	7 (4.5%)
Vomiting	3 (5.8%)	1 (1.9%)	4 (7.7%)	0	4 (3.8%)	8 (5.1%)
Weight increased	2 (3.8%)	1 (1.9%)	2 (3.8%)	3 (12.0%)	3 (2.9%)	5 (3.2%)

Abdominal pain	4 (7.7%)	1 (1.9%)	1 (1.9%)	1 (4.0%)	5 (4.8%)	6 (3.8%)
Upper respiratory tract infection	2 (3.8%)	0	2 (3.8%)	3 (12.0%)	2 (1.9%)	4 (2.5%)
Urinary tract infection	1 (1.9%)	1 (1.9%)	4 (7.7%)	1 (4.0%)	2 (1.9%)	6 (3.8%)
Cough	3 (5.8%)	1 (1.9%)	1 (1.9%)	1 (4.0%)	4 (3.8%)	5 (3.2%)
Insomnia	1 (1.9%)	0	2 (3.8%)	3 (12.0%)	1 (1.0%)	3 (1.9%)
Onychomycosis	3 (5.8%)	1 (1.9%)	2 (3.8%)	0	4 (3.8%)	6 (3.8%)
Oropharyngeal gonococcal infection	1 (1.9%)	1 (1.9%)	3 (5.8%)	1 (4.0%)	2 (1.9%)	5 (3.2%)
Rash	1 (1.9%)	0	3 (5.8%)	2 (8.0%)	1 (1.0%)	4 (2.5%)
Acarodermatitis	3 (5.8%)	0	1 (1.9%)	1 (4.0%)	3 (2.9%)	4 (2.5%)
Anogenital warts	0	1 (1.9%)	3 (5.8%)	1 (4.0%)	1 (1.0%)	4 (2.5%)
Abdominal pain upper	2 (3.8%)	0	0	2 (8.0%)	2 (1.9%)	2 (1.3%)
Anal chlamydia infection	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)
Proctitis gonococcal	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)
Rhinitis allergic	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)
Constipation	0	0	3 (5.8%)	0	0	3 (1.9%)
Hypertriglyceridaemia	0	3 (5.7%)	0	0	3 (2.9%)	3 (1.9%)
Otitis media	0	0	1 (1.9%)	2 (8.0%)	0	1 (0.6%)
Ligament sprain	0	0	0	2 (8.0%)	0	0

BIC = bictegravir; COVID-19 = coronavirus disease 2019; F = emtricitabine; LEN = lenacapavir; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide

Table S6. Lenacapavir-Related Injection Site Reactions

	SC LEN + F/TAF→TAF (n = 52)	SC LEN + F/TAF→BIC (n = 53)	SC LEN Total (n = 105)
Number of participants who received ≥1 SC injection	51	52	103
Number (%) of participants	32 (62.7%)	25 (48.1%)	57 (55.3%)
Study drug-related ISRs by severity			
Grade 1	26 (51.0%)	23 (44.2%)	49 (47.6%)
Grade 2	6 (11.8%)	1 (1.9%)	7 (6.8%)
Grade 3	0	1 (1.9%)	1 (1.0%)
Grade 4	0	0	0
Grade 5	0	0	0
Injection site reaction			
Erythema	18 (35.3%)	10 (19.2%)	28 (27.2%)
Swelling	13 (25.5%)	11 (21.2%)	24 (23.3%)
Pain	12 (23.5%)	8 (15.4%)	20 (19.4%)
Nodule	8 (15.7%)	7 (13.5%)	15 (14.6%)
Inflammation	10 (19.6%)	4 (7.7%)	14 (13.6%)
Induration	8 (15.7%)	5 (9.6%)	13 (12.6%)
Mass	2 (3.9%)	2 (3.8%)	4 (3.9%)
Bruising	1 (2.0%)	0	1 (1.0%)
Haematoma	0	1 (1.9%)	1 (1.0%)
Paraesthesia	1 (2.0%)	0	1 (1.0%)
Pruritus	0	1 (1.9%)	1 (1.0%)
Warmth	1 (2.0%)	0	1 (1.0%)
Number of participants who received SC injection at day 15 visit	51	52	103
Number (%) of participants			
Study drug-related ISRs following day 15 SC injection by severity	22 (43.1%)	17 (32.7%)	39 (37.9%)
Grade 1	18 (35.3%)	16 (30.8%)	34 (33.0%)
Grade 2	4 (7.8%)	1 (1.9%)	5 (4.9%)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0

Injection site reaction following day 15 SC injection			
Pain	9 (17.6%)	6 (11.5%)	15 (14.6%)
Erythema	9 (17.6%)	5 (9.6%)	14 (13.6%)
Swelling	7 (13.7%)	7 (13.5%)	14 (13.6%)
Nodule	7 (13.7%)	4 (7.7%)	11 (10.7%)
Induration	5 (9.8%)	4 (7.7%)	9 (8.7%)
Mass	2 (3.9%)	1 (1.9%)	3 (2.9%)
Bruising	1 (2.0%)	0	1 (1.0%)
Paraesthesia	1 (2.0%)	0	1 (1.0%)
Warmth	1 (2.0%)	0	1 (1.0%)
Number of participants who received SC injection at week 28 visit	48	47	95
Number (%) of participants	24 (50.0%)	18 (38.3%)	42 (44.2%)
Study drug-related ISRs following week 28 SC injection			
Grade 1	23 (47.9%)	17 (36.2%)	40 (42.1%)
Grade 2	1 (2.1%)	0	1 (1.1%)
Grade 3	0	1 (2.1%)	1 (1.1%)
Grade 4	0	0	0
Grade 5	0	0	0
Injection site reaction following week 28 SC injection			
Erythema	11 (22.9%)	6 (12.8%)	17 (17.9%)
Inflammation	10 (20.8%)	4 (8.5%)	14 (14.7%)
Swelling	6 (12.5%)	5 (10.6%)	11 (11.6%)
Pain	5 (10.4%)	4 (8.5%)	9 (9.5%)
Nodule	3 (6.3%)	5 (10.6%)	8 (8.4%)
Induration	6 (12.5%)	0	6 (6.3%)
Haematoma	0	1 (2.1%)	1 (1.1%)
Mass	0	1 (2.1%)	1 (1.1%)
Number of participants who received SC injection at week 54 visit	47	43	90
Number (%) of participants			
Study drug-related ISRs following week 54 SC injection	12 (25.5%)	11 (25.6%)	23 (25.6%)
Grade 1	11 (23.4%)	11 (25.6%)	22 (24.4%)
Grade 2	1 (2.1%)	0	1 (1.1%)
Grade 3	0	0	0
Grade 4	0	0	0

Grade 5	0	0	0
Injection site reaction following week 54 SC injection			
Swelling	9 (19.1%)	3 (7.0%)	12 (13.3%)
Nodule	4 (8.5%)	5 (11.6%)	9 (10.0%)
Erythema	5 (10.6%)	1 (2.3%)	6 (6.7%)
Pain	4 (8.5%)	2 (4.7%)	6 (6.7%)
Induration	3 (6.4%)	1 (2.3%)	4 (4.4%)
Mass	0	1 (2.3%)	1 (1.1%)
Pruritus	0	1 (2.3%)	1 (1.1%)

BIC = bictegravir; F = emtricitabine; ISR = injection site reaction; LEN = lenacapavir; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide

Table S7. Grade 3 to 4 Adverse Events

	SC LEN + F/TAF→TAF (n = 52)	SC LEN + F/TAF→BIC (n = 53)	Oral LEN + F/TAF (n = 52)	B/F/TAF (n = 25)	SC LEN Total (n = 105)	LEN Total (n = 157)
Number (%) of participants with any Grade 3 or 4 adverse events	2 (3.8%)	5 (9.4%)	6 (11.5%)	2 (8.0%)	7 (6.7%)	13 (8.3%)
Grade 3 or 4 adverse events						
Anal fissure	0	0	1 (1.9%)	0	0	1 (0.6%)
Anogenital warts	0	0	0	1 (4.0%)	0	0
Anxiety	0	0	1 (1.9%)	0	0	1 (0.6%)
Back pain	0	0	1 (1.9%)	0	0	1 (0.6%)
Bipolar disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Deep vein thrombosis	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Dyspnoea	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Hepatitis A	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Hypertriglyceridaemia	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Injection site nodule	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Insomnia	0	0	1 (1.9%)	0	0	1 (0.6%)
Lymphadenopathy mediastinal	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Major depression	0	0	1 (1.9%)	0	0	1 (0.6%)
Mental disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Metastases to central nervous system	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Nephrolithiasis	0	0	1 (1.9%)	0	0	1 (0.6%)
Non-small cell lung cancer	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pleural effusion	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pneumocystis jirovecii pneumonia	0	0	1 (1.9%)	0	0	1 (0.6%)
Pneumonia	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pneumothorax	0	0	1 (1.9%)	0	0	1 (0.6%)
Poisoning	0	0	1 (1.9%)	0	0	1 (0.6%)
Psychotic disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Substance-induced psychotic disorder	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Syncope	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Transient ischaemic attack	0	0	0	1 (4.0%)	0	0

Uterine leiomyoma	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Vomiting	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)

BIC = bictegravir; F = emtricitabine; LEN = lenacapavir; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide

Table S8. Serious Adverse Events

System Organ Class Event, No. (%)	SC LEN + F/TAF→TAF (n = 52)	SC LEN + F/TAF→BIC (n = 53)	Oral LEN + F/TAF (n = 52)	BIC/F/TAF (n = 25)	SC LEN Total (n = 105)	LEN Total (n = 157)
Number (%) of participants with any serious adverse events	3 (5.8%)	3 (5.7%)	4 (7.7%)	0	6 (5.7%)	10 (6.4%)
Blood and lymphatic system disorders	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Lymphadenopathy mediastinal	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Gastrointestinal disorders	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Vomiting	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Infections and infestations	2 (3.8%)	3 (5.7%)	1 (1.9%)	0	5 (4.8%)	6 (3.8%)
Escherichia infection	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Hepatitis A	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Perirectal abscess	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Pneumocystis jirovecii pneumonia	0	0	1 (1.9%)	0	0	1 (0.6%)
Pneumonia	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Staphylococcal infection	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Injury, poisoning and procedural complications	0	0	1 (1.9%)	0	0	1 (0.6%)
Poisoning	0	0	1 (1.9%)	0	0	1 (0.6%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (3.8%)	0	0	0	2 (1.9%)	2 (1.3%)
Metastases to central nervous system	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Non-small cell lung cancer	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Uterine leiomyoma	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Psychiatric disorders	0	1 (1.9%)	2 (3.8%)	0	1 (1.0%)	3 (1.9%)
Bipolar disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Major depression	0	0	1 (1.9%)	0	0	1 (0.6%)
Mental disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Psychotic disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Substance-induced psychotic disorder	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	1 (1.9%)	0	1 (1.9%)	0	1 (1.0%)	2 (1.3%)
Dyspnoea	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pleural effusion	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)

Pneumothorax	0	0	1 (1.9%)	0	0	1 (0.6%)

BIC = bictegravir; F = emtricitabine; LEN = lenacapavir; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide

Table S9. Grade 3 or 4 Treatment-Emergent Laboratory Abnormalities for ≥3 Participants in Any Treatment Group

Maximum Postbaseline Toxicity Grade, No. (%)	SC LEN + F/TAF→TAF (n = 52)	SC LEN + F/TAF→BIC (n = 53)	Oral LEN + F/TAF (n = 52)	BIC/F/TAF (n = 25)	SC LEN Total (n = 105)	LEN Total (n = 157)
Participants with postbaseline value	52	53	52	25	105	157
Grade 3 or 4	11 (21.2%)	15 (28.3%)	13 (25.0%)	6 (24.0%)	26 (24.8%)	39 (24.8%)
Grade 3	6 (11.5%)	11 (20.8%)	9 (17.3%)	6 (24.0%)	17 (16.2%)	26 (16.6%)
Grade 4	5 (9.6%)	4 (7.5%)	4 (7.7%)	0	9 (8.6%)	13 (8.3%)
Hematology						
Absolute neutrophil count, low	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	0	0	0	2 (1.9%)	2 (1.3%)
Grade 3	2 (3.8%)	0	0	0	2 (1.9%)	2 (1.3%)
Chemistry						
ALT (SGPT), high	52	53	52	25	105	157
Grade 3 or 4	0	2 (3.8%)	3 (5.8%)	0	2 (1.9%)	5 (3.2%)
Grade 3	0	1 (1.9%)	1 (1.9%)	0	1 (1.0%)	2 (1.3%)
Grade 4	0	1 (1.9%)	2 (3.8%)	0	1 (1.0%)	3 (1.9%)
AST (SGOT), high	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	2 (3.8%)	3 (5.8%)	0	4 (3.8%)	7 (4.5%)
Grade 3	2 (3.8%)	1 (1.9%)	3 (5.8%)	0	3 (2.9%)	6 (3.8%)
Grade 4	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Hyperbilirubinemia	52	53	52	25	105	157
Grade 3 or 4	0	1 (1.9%)	1 (1.9%)	1 (4.0%)	1 (1.0%)	2 (1.3%)
Grade 3	0	0	0	1 (4.0%)	0	0
Grade 4	0	1 (1.9%)	1 (1.9%)	0	1 (1.0%)	2 (1.3%)
Creatine kinase, high	52	53	52	25	105	157
Grade 3 or 4	6 (11.5%)	2 (3.8%)	3 (5.8%)	1 (4.0%)	8 (7.6%)	11 (7.0%)
Grade 3	2 (3.8%)	1 (1.9%)	2 (3.8%)	1 (4.0%)	3 (2.9%)	5 (3.2%)
Grade 4	4 (7.7%)	1 (1.9%)	1 (1.9%)	0	5 (4.8%)	6 (3.8%)
Creatinine, high	52	53	52	25	105	157
Grade 3 or 4	1 (1.9%)	4 (7.5%)	1 (1.9%)	2 (8.0%)	5 (4.8%)	6 (3.8%)
Grade 3	1 (1.9%)	3 (5.7%)	1 (1.9%)	2 (8.0%)	4 (3.8%)	5 (3.2%)
Grade 4	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)

Creatinine clearance or eGFR, low	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	7 (13.2%)	3 (5.8%)	3 (12.0%)	9 (8.6%)	12 (7.6%)
Grade 3	2 (3.8%)	6 (11.3%)	3 (5.8%)	3 (12.0%)	8 (7.6%)	11 (7.0%)
Grade 4	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Triglycerides (fasting)	48	51	49	23	99	148
Grade 3 or 4	0	4 (7.8%)	0	1 (4.3%)	4 (4.0%)	4 (2.7%)
Grade 3	0	3 (5.9%)	0	1 (4.3%)	3 (3.0%)	3 (2.0%)
Grade 4	0	1 (2.0%)	0	0	1 (1.0%)	1 (0.7%)
Lipase, high	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	1 (1.9%)	0	0	3 (2.9%)	3 (1.9%)
Grade 3	1 (1.9%)	1 (1.9%)	0	0	2 (1.9%)	2 (1.3%)
Grade 4	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Hyperglycemia, nonfasting	45	43	39	18	88	127
Grade 3 or 4	2 (4.4%)	1 (2.3%)	0	1 (5.6%)	3 (3.4%)	3 (2.4%)
Grade 3	2 (4.4%)	0	0	1 (5.6%)	2 (2.3%)	2 (1.6%)
Grade 4	0	1 (2.3%)	0	0	1 (1.1%)	1 (0.8%)
Urinalysis						
Glycosuria (dipstick)	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	1 (1.9%)	1 (1.9%)	1 (4.0%)	3 (2.9%)	4 (2.5%)
Grade 3	2 (3.8%)	1 (1.9%)	1 (1.9%)	1 (4.0%)	3 (2.9%)	4 (2.5%)

BIC = bictegravir; eGFR = estimated glomerular filtration rate; F = emtricitabine; LEN = lenacapavir; N = number of participants; SC = subcutaneous; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TAF = tenofovir alafenamide

Table S10. Change from Baseline in Body Weight

	Subcutaneous LEN +F/TAF→TAF (n=52)	Subcutaneous LEN +F/TAF→BIC (n=53)	Oral LEN +F/TAF (n=52)	BIC/F/TAF (n=25)
Change from baseline in body weight, kg				
Week 28, median (Q1, Q3)	1.7 (-0.7, 4.7)	1.8 (-0.7, 4.6)	3.2 (0.5, 5.0)	2.7 (0.0, 4.8)
Week 54, median (Q1, Q3)	3.6 (-0.3, 6.8)	2.5 (-0.4, 6.3)	2.2 (0.9, 7.2)	2.3 (-3.1, 7.3)

BIC, bictegravir; F, emtricitabine; LEN, lenacapavir; TAF, tenofovir alafenamide

Figure S1. Antiviral Activity Snapshot Outcome (ITT) at Week 28. BIC, bictegravir; F, emtricitabine; LEN, lenacapavir; QD, daily; SC, subcutaneous; TAF, tenofovir alafenamide TG, treatment group. *1 participant discontinued due to not meeting the protocol criteria of having HIV-1 RNA <50 copies/mL prior to week 28; 1 participant discontinued on day 2.