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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: Rockstroh JK, Kassim S, Paredes R, et al. Fixed-dose daily doravirine (100 mg) with islatravir (0·25 mg) versus bictegravir, emtricitabine, and tenofovir alafenamide for initial HIV-1 therapy: 48-week results of a phase 3, randomised, controlled, double-blind, non-inferiority trial. *Lancet HIV* 2026; published online Feb 25. https://doi.org/10.1016/S2352-3018(26)00033-0.

Supplementary appendix

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Supplement to: Rockstroh JK, Sheetal K, Paredes R, Bettacchi C, Sinclair G, Avihingsanon A, Mugo N, Molina J-M, Ramírez BC, Gatanaga H, Xu Y, Klopfer SO, Diamond TL, Vesnesky M, Stamm LM, Fox MC, Pisculli ML. Fixed-dose daily doravirine (100 mg) with islatravir (0·25 mg) versus bictegravir, emtricitabine, and tenofovir alafenamide for initial HIV-1 therapy: 48-week results of a phase 3, randomised, controlled, double-blind, non-inferiority trial. *Lancet HIV* 2026; published online X XX. https://doi.org/.....

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Table 1. Protocol-specified discontinuation criteria for total lymphocyte and CD4+ T-cell count declines A.) and European Union specific criteria B.)

A.

Protocol-specified study intervention discontinuation criteria	Total lymphocyte count (x 10^9 cells/L)	CD4+ T-cell count (cells/µL)				
Time point of evaluation	After week 24	≥500 at week 24	≥350 to ≤499 at week 24	≥200 to ≤349 at week 24	≤199 at week 24	<50 at week 48
New on-treatment count	<1	<350	<350	<200	-	-
Percent decline	≥30% ↓ from week 24	-	≥30% ↓ from week 24	≥30% ↓ from week 24	≥30% ↓ from week 24	-
Laboratory confirmation (2 measurements)	Repeat 10 – 14 weeks later					Repeat within 4 weeks

B.

Protocol-specified study intervention discontinuation criteria	Total lymphocyte count (x 10^9 cells/L)	CD4+ T-cell count (cells/µL)				
Time point of evaluation	After week 24	≥500 at week 24	≥350 to ≤499 at week 24	≥200 to ≤349 at week 24	≤199 at week 24	<50 at week 48
New on-treatment count	<1	<350	<350	<200	-	-
Percent decline	≥30% ↓ from week 24	-	≥30% ↓ from week 24	≥30% ↓ from week 24	≥30% ↓ from week 24	-
Laboratory confirmation (2 measurements)	Repeat 10 – 14 weeks later				Repeat within 4 weeks	

Table 2. Preexisting resistance-associated mutations at baseline

	Doravirine and islatravir (100/0·25 mg) n=269	Bictegravir, emtricitabine, and tenofovir alafenamide n=267
Any NRTI	36 (13·4)	38 (14.2)
V118V/I	17 (6·3)	25 (9·4)
V118I	14 (5·2)	21 (7·9)
V118V/I	4 (1·5)	4 (1·5)
T215T/A/E/N/S	10 (3·7)	5 (1·9)
T215S	4 (1·5)	4 (1·5)
T215E	3 (1·1)	1 (0·4)
T215A	1 (0·4)	0 (0·0)
T215N	1 (0·4)	0 (0·0)
T215T/A	1 (0·4)	0 (0·0)
M41M/L	7 (2·6)	3 (1·1)
M41L	4 (1·5)	3 (1·1)
M41M/L	3 (1·1)	0 (0·0)
T69T/A/D/N	4 (1·5)	3 (1·1)
T69T/N	3 (1·1)	0 (0·0)
T69A/D	1 (0·4)	0 (0·0)
T69N	0 (0·0)	2 (0·7)
T69N/T	0 (0·0)	1 (0·4)
V75V/I	4 (1·5)	0 (0·0)
V75I	3 (1·1)	0 (0·0)
V75V/I	1 (0·4)	0 (0·0)
K219K/E/Q/R	2 (0·7)	2 (0·7)
K219K/R	1 (0·4)	1 (0·4)
K219Q	1 (0·4)	0 (0·0)
K219E	0 (0·0)	1 (0·4)
A62V	1 (0·4)	2 (0·7)
D67D/N	1 (0·4)	1 (0·4)
E44D	1 (0·4)	1 (0·4)
K70R	1 (0·4)	0 (0·0)

	Doravirine and islatravir (100/0·25 mg) n=269	Bictegravir, emtricitabine, and tenofovir alafenamide n=267
Any NNRTI	49 (18·2)	65 (24·3)
K103K/N/R/S	22 (8·2)	36 (13·5)
K103N	15 (5·6)	23 (8·6)
K103R	5 (1·9)	8 (3·0)
K103S	2 (0·7)	3 (1·1)
K103K/R	0 (0·0)	1 (0·4)
K103KN	0 (0·0)	1 (0·4)
E138A/G/K/Q/R/S	11 (4·1)	12 (4·5)
E138A	6 (2·2)	10 (3·7)
E138K	2 (0·7)	1 (0.4)
E138G	1 (0.4)	1 (0.4)
E138Q	1 (0.4)	0 (0.0)
E138R/S	1 (0.4)	0 (0.0)
V179V/D/T	8 (3.0)	11 (4.1)
V179D	6 (2.2)	8 (3.0)
V179T	2 (0.7)	1 (0.4)
V179V/D	0 (0.0)	2 (0.7)
V90V/I	6 (2.2)	4 (1.5)
V90I	4 (1.5)	4 (1.5)
V90V/I	2 (0.7)	0 (0.0)
K101E	4 (1.5)	2 (0.7)
G190A/S	3 (1.1)	1 (0.4)
G190A	2 (0·7)	1 (0·4)
G190S	1 (0·4)	0 (0·0)
V106V/I/M	3 (1·1)	4 (1·5)
V106I	2 (0·7)	2 (0·7)
V106V/I	1 (0·4)	1 (0·4)
V106V/I/M	0 (0·0)	1 (0·4)

	Doravirine and islatravir (100/0·25 mg) n=269	Bictegravir, emtricitabine, and tenofovir alafenamide n=267
Any NNRTI	49 (18·2)	65 (24·3)
Y181Y/C	1 (0·4)	0 (0·0)
A98G	0 (0·0)	2 (0·7)
F227F/I	0 (0·0)	1 (0·4)
Any INSTI	65 (24·2)	61 (22·8)
M50M/I/L/T/V	46 (17·1)	43 (16·1)
M50I	36 (13·4)	33 (12·4)
M50M/I	6 (2·2)	8 (3·0)
M50I/M	1 (0·4)	1 (0·4)
M50I/T	1 (0·4)	0 (0·0)
M50M/I/L	1 (0·4)	0 (0·0)
M50M/I/V	1 (0·4)	1 (0·4)
E157E/K/Q	12 (4·5)	10 (3·7)
E157Q	10 (3·7)	7 (2·6)
E157E/K	1 (0·4)	1 (0·4)
E157E/Q	1 (0·4)	2 (0·7)
L74L/I/M	5 (1·9)	0 (0·0)
L74M	3 (1·1)	0 (0·0)
L74L/I/M	1 (0·4)	0 (0·0)
L74LM	1 (0·4)	0 (0·0)
T97T/A	4 (1·5)	4 (1·5)
T97A	4 (1·5)	2 (0·7)
T97A/T	0 (0·0)	1 (0·4)
T97T/A	0 (0·0)	1 (0·4)
G163G/K/R	2 (0·7)	4 (1.5)
G163K	1 (0·4)	3 (1·1)
G163R	1 (0·4)	0 (0·0)
G163G/R	0 (0·0)	1 (0·4)

	Doravirine and islatravir (100/0·25 mg) n=269	Bictegravir, emtricitabine, and tenofovir alafenamide n=267
Any INSTI	65 (24·2)	61 (22·8)
S153A	1 (0·4)	4 (1·5)
E138E/K	0 (0·0)	1 (0·4)

One doravirine and islatravir participant had both V118I and V118V/I mutations reported at baseline. Baseline HIV-1 RNA was obtained from samples collected on day 1 for each participant. If data for this visit were missing, the RNA data was obtained from the most recent screening visit, when available. Screening genotype results were obtained from the local or central laboratory.

Preexisting resistance was evaluated using the following list of major and minor resistance-associated mutations:
NRTI: M41L, E44D, A62V, K65E/N/R, D67N, T69D/N, 69ins, K70E/R, L74V, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184I/V, L210W, T215A/C/D/E/F/G/H/I/L/N/S/V/Y, K219E/N/Q/R.
NNRTI: V90I, A98G, L100I, K101E/H/P, K103N/R/S, V106A/I/M/T, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/S, H221Y, P225H, F227C/H/I/L/R/V, M230I/L, L234I, P236L, Y318F.
INSTI: M50I, H51Y, T66A/I/K, L74M, E92G/Q, T97A, G118R, F121Y, E138A/K/T, G140A/C/R/S, Y143C/H/R, S147G, Q148H/K/R, S153A/F/Y, N155H/S, E157K/Q, G163K/R, R263K.
Major resistance-associated mutations that confer larger reductions in susceptibility are underlined. Minor resistance associated mutations that occur after emergence of a major RAM, confer smaller reductions in susceptibility, or may be accessory mutations that increase fitness are shown in standard font.

INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

Amino acid abbreviations: A (Ala), C (Cys), D (Asp), E (Glu), F (Phe), G (Gly), H (His), I (Ile), K (Lys), L(Leu), M (Met), N (Asn), P (Pro), Q (Gln), R (Arg), S (Ser), T (Thr), V (Val), W (Trp), Y (Tyr).

Table 3. Adherence to active study intervention

	Doravirine and islatravir (100/0·25 mg) n=269	Bictegravir, emtricitabine, and tenofovir alafenamide n=267
≥99%	139 (51·7)	151 (56·6)
≥95% to <99%	100 (37·2)	86 (32·2)
≥90% to <95%	21 (7·8)	18 (6·7)
≥80% to <90%	9 (3·3)	12 (4·5)
≥70% to <80%	0 (0·0)	0 (0·0)
<70%	0 (0·0)	0 (0·0)

Data are n (%).
Active treatment adherence: [number of days on therapy ÷ number of days should be on therapy] x 100. A day within the study was considered an "On-Therapy" day if the participant took at least 1 tablet from the bottle containing the active study intervention on that day provided for this study.

Table 4. Participants with treatment-emergent resistance-associated mutations

Treatment group	CD4+ T cell count at baseline (cells/μL)	HIV-1 RNA at screening/ baseline (copies/mL)	HIV-1 RNA at discontinuation (copies/mL)	Mutations observed at baseline[a]	Mutations observed at discontinuation[a]	Treatment-emergent mutations[b]	Phenotypic fold-shift (assessment)[c]
DOR/ISL	31	2,260,000/ 801,000	951,000 (week 16)	RT: V90I, Y181Y/C, G190S	RT: V90I, M184I, Y188L, G190S	RT: M184I, Y188L	DOR >max (Resistant) ISL 2.42 (Sensitive)
DOR/ISL	171	1,580,000/ 1,690,000	228,000 (week 24)	RT: T69T/N, *V179E*, T215T/A	RT: *L74I*, V106A, *V179E* M184V, F227L	RT: *L741*, V106A, M184V, F227L	DOR >max (Resistant) ISL 6.69 (Sensitive)
BIC/FTC/TAF	171	5,210,000/ 2,180,000	893 (week 24)[d]	IN: *M50M/T*	RT: *E44E/K* IN: M50M/I/*T*[d]	RT: *E44K* IN: M50I	BIC 0.71 (Sensitive) FTC 0.57 (Sensitive) TFV 0.80 (Sensitive)

[a]Genotypic resistance was evaluated using the GenoSure PRIme® next-generation sequencing assay and the following list of resistance-associated mutations:
NRTI: M41L, E44D, A62V, K65E/N/R, D67N, T69D/N, 69ins, K70E/R, L74V, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184I/V, L210W, T215A/C/D/E/F/G/H/I/L/N/S/V/Y, K219E/N/Q/R.
NNRTI: V90I, A98G, L100I, K101E/H/P, K103N/R/S, V106A/I/M/T, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/S, H221Y, P225H, F227C/H/I/L/R/V, M230I/L, L234I, P236L, Y318F.
INSTI: M50I, H51Y, T66A/I/K, L74M, E92G/Q, T97A, G118R, F121Y, E138A/K/T, G140A/C/R/S, Y143C/H/R, S147G, Q148H/K/R, S153A/F/Y, N155H/S, E157K/Q, G163K/R, R263K.
Any other mutation occurring at a resistance-associated position was also reported and shown in *italics*.

[b]Treatment-emergent mutations were not detected at baseline but were detected at discontinuation or viremia confirmation.

[c]Phenotypic fold-shift was calculated by dividing the IC_{50} value determined with the participant's virus by that determined with the reference virus. Assessment of susceptibility for DOR, BIC, FTC, and TFV was determined using clinical cutoffs defined by Monogram Biosciences in the PhenoSense® and PhenoSense® Integrase assays. A clinical cutoff of 20 fold-shift was used for islatravir susceptibility as the model-predicted steady state islatravir-triphosphate concentration 24h after the 0·25 mg daily dose is approximately 20-fold above the target for efficacy (defined as an inhibitory quotient of 5).

[d]Analysis was performed at viremia confirmation visit.

An additional three participants in the doravirine and islatravir group and five participants in the bictegravir, emtricitabine, tenofovir alafenamide group met the criteria for resistance testing and did not have treatment-emergent resistance-associated mutations.

BIC, bictegravir; DOR, doravirine; FTC, emtricitabine; IN, integrase; INSTI, integrase strand transfer inhibitor; ISL, islatravir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; RT, reverse transcriptase; TAF, tenofovir alafenamide; TFV, tenofovir.

Amino acid abbreviations: A (Ala), C (Cys), D (Asp), E (Glu), F (Phe), G (Gly), H (His), I (Ile), K (Lys), L(Leu), M (Met), N (Asn), P (Pro), Q (Gln), R (Arg), S (Ser), T (Thr), V (Val), W (Trp), Y (Tyr).

Table 5. Adverse events (2 or more participants in both treatment groups)

	Doravirine and islatravir (100/0·25 mg) (N=269) n (%)	Bictegravir, emtricitabine, and tenofovir alafenamide (N=267) n (%)
Upper respiratory tract infection	30 (11·2)	29 (10·9)
Nasopharyngitis	29 (10·8)	33 (12·4)
Headache	23 (8·6)	29 (10·9)
Weight increased	17 (6·3)	17 (6·4)
Diarrhoea	16 (5·9)	20 (7·5)
Urinary tract infection	16 (5·9)	10 (3·7)
Influenza	15 (5·6)	10 (3·7)
Insomnia	15 (5·6)	11 (4·1)
Anxiety	12 (4·5)	10 (3·7)
Dizziness	12 (4·5)	8 (3·0)
Gastroenteritis	12 (4·5)	15 (5·6)
Hypertension	10 (3·7)	5 (1·9)
Pyrexia	9 (3·3)	6 (2·2)
Arthralgia	8 (3·0)	13 (4·9)
Back pain	8 (3·0)	11 (4·1)
Cough	8 (3·0)	10 (3·7)
Rash	8 (3·0)	6 (2·2)
Syphilis	8 (3·0)	3 (1·1)
Alopecia	7 (2·6)	6 (2·2)
Bronchitis	7 (2·6)	7 (2·6)
Dry skin	7 (2·6)	3 (1·1)
Abdominal distention	6 (2·2)	7 (2·6)
Anogenital warts	6 (2·2)	4 (1·5)
Aspartate aminotransferase increased	6 (2·2)	2 (0·7)
Depression	6 (2·2)	8 (3·0)
Gastroesophageal reflux disease	6 (2·2)	9 (3·4)
Herpes zoster	6 (2·2)	4 (1·5)
Paraesthesia	6 (2·2)	7 (2·6)
Proctitis gonococcal	6 (2·2)	3 (1·1)
Pruritis	6 (2·2)	6 (2·2)
Asthenia	5 (1·9)	3 (1·1)
COVID-19	5 (1·9)	3 (1·1)
Creatinine renal clearance decreased	5 (1·9)	4 (1·5)
Fatigue	5 (1·9)	6 (2·2)
Influenza like illness	5 (1·9)	4 (1·5)
Pain in extremity	5 (1·9)	6 (2·2)
Toothache	5 (1·9)	4 (1·5)
Tonsillitis	5 (1·9)	5 (1·9)
Abnormal loss of weight	4 (1·5)	6 (2·2)
Constipation	4 (1·5)	3 (1·1)
Depressed mood	4 (1·5)	3 (1·1)
Memory impairment	4 (1·5)	3 (1·1)
Myalgia	4 (1·5)	4 (1·5)
Nausea	4 (1·5)	9 (3·4)
Oropharyngeal pain	4 (1·5)	2 (0·7)
Pharyngitis	4 (1·5)	5 (1·9)
Rash pruritic	4 (1·5)	3 (1·1)
Rhinitis	4 (1·5)	3 (1·1)
Abdominal pain	3 (1·1)	5 (1·9)

	Doravirine and islatravir (100/0·25 mg) (N=269) n (%)	Bictegravir, emtricitabine, and tenofovir alafenamide (N=267) n (%)
Bone density increased	3 (1·1)	2 (0·7)
Decreased appetite	3 (1·1)	5 (1·9)
Dermatitis allergic	3 (1·1)	2 (0·7)
Flatulence	3 (1·1)	5 (1·9)
Ligament sprain	3 (1·1)	2 (0·7)
Lower respiratory tract infection	3 (1·1)	4 (1·5)
Nasal congestion	3 (1·1)	2 (0·7)
Onychomycosis	3 (1·1)	3 (1·1)
Overweight	3 (1·1)	2 (0·7)
Rectal haemorrhage	3 (1·1)	2 (0·7)
Sinusitis	3 (1·1)	2 (0·7)
Viral upper respiratory tract infection	3 (1·1)	4 (1·5)
Vomiting	3 (1·1)	12 (4·5)
Abdominal pain upper	2 (0·7)	3 (1·1)
Anaemia	2 (0·7)	2 (0·7)
Anal chlamydia infection	2 (0·7)	2 (0·7)
CD4 lymphocytes decreased	2 (0·7)	2 (0·7)
Chest pain	2 (0·7)	3 (1·1)
Conjunctivitis	2 (0·7)	4 (1·5)
Dyspepsia	2 (0·7)	2 (0·7)
Food poisoning	2 (0·7)	2 (0·7)
Glomerular filtration rate decreased	2 (0·7)	11 (4·1)
Hyperhidrosis	2 (0·7)	3 (1·1)
Hypoaesthesia	2 (0·7)	3 (1·1)
Malaria	2 (0·7)	2 (0·7)
Nightmare	2 (0·7)	2 (0·7)
Osteopenia	2 (0·7)	6 (2·2)
Pneumonia	2 (0·7)	2 (0·7)
Respiratory tract infection	2 (0·7)	4 (1·5)
Seborrhoeic dermatitis	2 (0·7)	3 (1·1)
Skin laceration	2 (0·7)	2 (0·7)
Sleep disorder	2 (0·7)	4 (1·5)
Urethritis	2 (0·7)	2 (0·7)

Every participant was counted a single time for each applicable row and column.
Medical Dictionary for Regulatory Activities (MedDRA) version 28.1 was used in the reporting of this study.

Table 6. Centers for Disease Control and Prevention AIDS-Defining Category C events

Candidiasis of bronchi, trachea, or lungs	Lymphoma, Burkitt's (or equivalent term)
Candidiasis, esophageal	Lymphoma, immunoblastic (or equivalent term)
Cervical cancer, invasive	Lymphoma, primary, of brain
Coccidioidomycosis, disseminated or extrapulmonary	*Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary	*Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
Cryptosporidiosis, chronic intestinal (>1 month's duration)	Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Cytomegalovirus disease (other than liver, spleen, or nodes)	*Pneumocystis carinii* pneumonia
Cytomegalovirus retinitis (with loss of vision)	Pneumonia, recurrent
Encephalopathy, HIV-related	Progressive multifocal leukoencephalopathy
Herpes simplex: chronic ulcer(s) (>1 month's duration); or bronchitis, pneumonitis, or esophagitis	Salmonella septicemia, recurrent
Histoplasmosis, disseminated or extrapulmonary	Toxoplasmosis of brain
Isosporiasis, chronic intestinal (>1 month's duration)	Wasting syndrome due to HIV
Kaposi's sarcoma	

Category C condition according to the CDC 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults [Centers for Disease Control (CDC) 1992].

Table 7. Grade 3 or 4 laboratory abnormalities (4 or more participants in either treatment group)

Laboratory Test (Unit)	Criterion[a]	Doravirine/islatravir (100/0·25 mg)	Bictegravir/emtricitabine/ tenofovir alafenamide	Treatment difference (95% CI)[b]
Alanine aminotransferase (IU/L)	Grade 3: 5·0 to <10·0 x ULN	4/265 (1·5)	2/267 (0·7)	0·8 (−1·4, 3·2)
	Grade 4: ≥10·0 x ULN	2/265 (0·8)	0/267 (0·0)	-
Creatinine (mg/dL)	Grade 3: >1·8 to <3·5 x ULN, or 1·5 to <2·0 x baseline	3/265 (1·1)	10/267 (3·7)	−2·6 (−5·8, 0·02)
	Grade 4: ≥3·5 x ULN or increase of ≥2·0 x above baseline	0/265 (0·0)	0/267 (0·0)	-
Creatinine clearance (mL/min)	Grade 3: <60 to 30, or 30% to <50% decrease from baseline	7/265 (2·6)	24/267 (9·0)	−6·3 (−10·7, −2·5)[c]
	Grade 4: <30 or ≥50% decrease from baseline	0/265 (0·0)	0/267 (0·0)	-
Creatinine kinase (IU/L)	Grade 3: 10·0 - <20·0 x ULN	2/265 (0·8)	3/267 (1·1)	-
	Grade 4: ≥20·0 x ULN	6/265 (2·3)	4/267 (1·5)	0·8 (−1·8, 3·5)
Creatinine-based eGFR (mL/min/1·73 m^2)	Grade 3: <60 to 30, or 30% to <50% decrease from baseline	13/264 (4·9)	60/267 (22·5)	−17·6 (−23·4, −12·0)[c]
	Grade 4: <30 or ≥50% decrease from baseline	2/265 (0·8)	1/267 (0·4)	-
Fasting LDL-C (mg/dL)	Grade 3: ≥190	2/249 (0·8)	5/244 (2·0)	−1·2 (−4·0, 1·1)
Neutrophils (x 10^9 cells/L)	Grade 3: 0·400 - 0·599	4/265 (1·5)	3/267 (1·1)	0·4 (−1·9, 2·8)
	Grade 4: <0·400	0/265 (0·0)	0/267 (0·0)	-

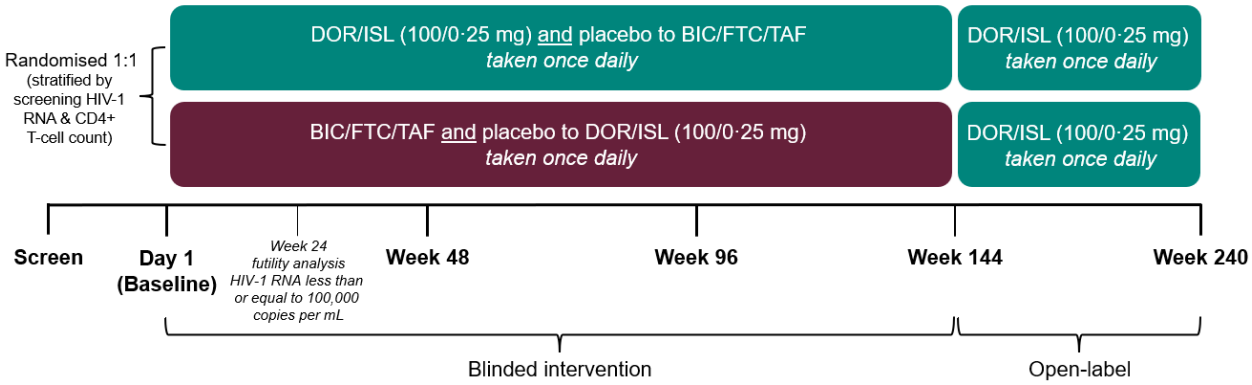
Data are n/m (%), where m = number of participants with a baseline and at least one post-baseline test result.
[a]For graded criteria, participants were counted once per test in the highest grade reported. Only participants with a worsened grade from baseline were included.
[b]Treatment difference was calculated for incidence of at least 4 participants in one or more treatment groups.
[C]Higher incidence of grade 3 changes in the bictegravir/emtricitabine/tenofovir alafenamide group is an artifact from the inhibitory effect of bictegravir on tubular secretion of creatinine.
CI, confidence interval; GFR, glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; ULN, upper limit of normal range.

Table 8. Mean change in laboratory measurements

	n	Doravirine/islatravir (100/0·25 mg)[a]	n	Bictegravir/emtricitabine/ tenofovir alafenamide[a]	Treatment difference (95% CI)[b]
Fasting LDL-C (mg/dL), mean (95% CI)[c]					
Baseline	251	94·98	252	98·12	-
Week 48 change from baseline	228	6·31 (3·55, 9·06)	227	6·89 (3·69, 10·09)	−1·30 (−5·26, 2·67)
Fasting HDL-C (mg/dL), mean (95% CI)[c]					
Baseline	251	42·13	252	40·73	-
Week 48 change from baseline	228	5·16 (4·01, 6·31)	227	3·47 (2·24, 4·69)	1·89 (0·30, 3·48)
Fasting non-HDL-C (mg/dL), mean (95% CI)[c]					
Baseline	251	118·22	252	123·28	-
Week 48 change from baseline	228	6·25 (3·20, 9·29)	227	6·65 (3·11, 10·37)	−1·08 (−5·56, 3·41)
Fasting total cholesterol to HDL ratio[c]					
Baseline	251	4·01	252	4·27	-
Week 48 change from baseline	228	−0·14 (−0·24, −0·05)	227	−0·08 (−0·19, 0·03)	−0·08 (−0·22, 0·06)
Creatinine-based eGFR (mL/min/1.73 m^2), mean (95% CI)					
Baseline	268	110·53	267	111·18	-
Week 48 change from baseline	249	7·57 (6·30, 8·84)	244	0·56 (−1·24, 2·35)	7·00 (4·83, 9·16)
Cystatin C-based eGFR (mL/min/1.73 m^2), mean (95% CI)					
Baseline	268	90·80	267	89·78	-
Week 48 change from baseline	247	10·81 (9·28, 12·34)	243	11·37 (9·82, 12·91)	−0·61 (−2·52, 1·30)
Total lymphocyte count (x 10^9 cells/L), mean (95% CI)					
Baseline	269	1·66	267	1·75	-
Week 48 change from baseline	250	0·14 (0·06, 0·22)	244	0·10 (0·04, 0·17)	−0·01 (−0·09, 0·07)
CD4+ T-cell count (cells/μL), mean (95% CI)					
Baseline	269	399	267	410	-
Week 48 change from baseline	250	217 (197, 238)	244	226 (204, 247)	−9.98 (−39.74, 19.79)

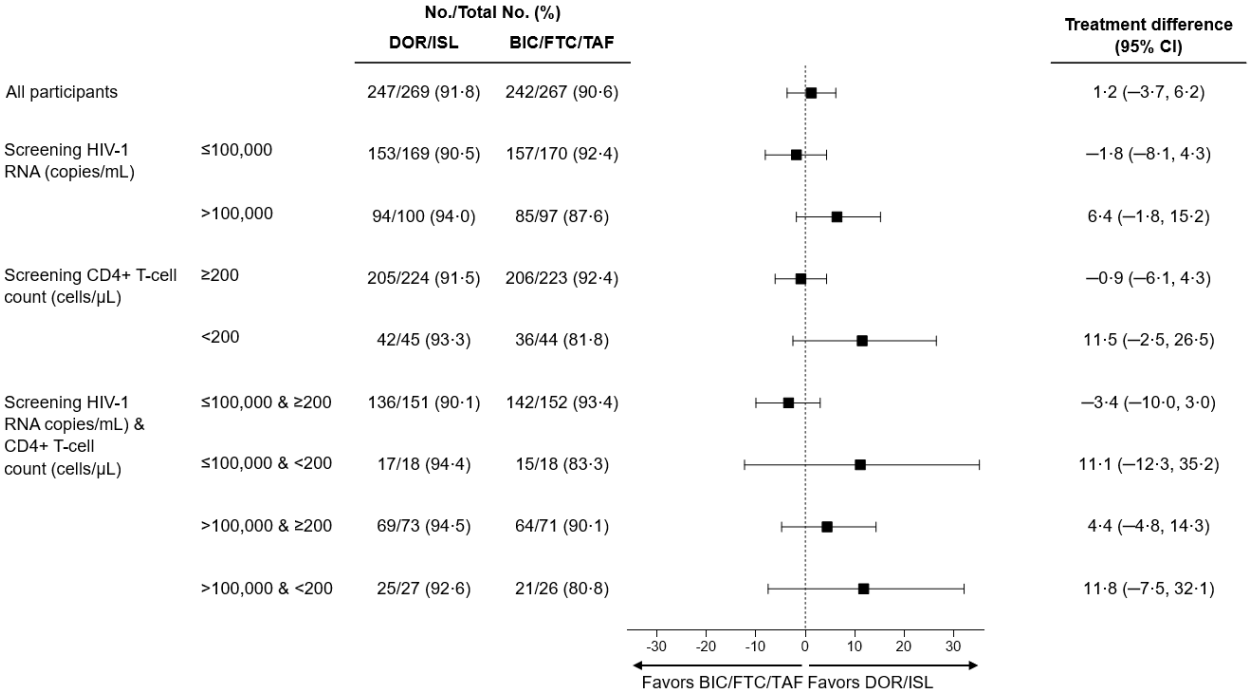
[a]Within-group 95% confidence intervals were based on the t-distribution.
[b]The 95% confidence intervals for the treatment difference were calculated from ANCOVA models with terms for baseline measurement and treatment.
[c]Participants on lipid-lowering therapy were excluded.

Figure 1. Study design



BIC/FTC/TAF, bictegravir, emtricitabine, and tenofovir alafenamide; DOR/ISL, doravirine and islatravir.

Figure 2. HIV-1 RNA <50 copies per mL at week 48 by screening HIV-1 RNA and CD4+ T-cell count (FDA snapshot approach)



MK-8591A-053 investigators who randomised participants by country

Argentina**:* Ezequiel Cordova, Gonzalo Corral, Maria Figueroa, Sergio Lupo, Marcelo Martins; ***Canada: Shariq Haider, Bertrand Lebouche, Jason Szabo, Sharon Walmsley; ***Chile**:* Alejandro Afani, Maria Campos Barker, Carolina Eugenia Chahin, Jose Martinez, Alfonso Moraga; ***Colombia***: Juan Diego Velez, Dinno Fernandez Chica, Shirley Iglesias Pertuz, Carlos Saavedra Trujillo, Sandra Valderrama-Beltrán; ***Dominican Republic***: Yeycy Donastorg Cabral; ***France***: Eric Cua, Jade Ghosn, Karine Lacombe, Jean-Michel Molina, Romain Palich, Olivier Robineau, Nicolas Vignier; ***Germany***: Johannes Bogner, Olaf Degen, Christian Hoffmann, Matthias Muller, Juergen Rockstroh; ***Guatemala***: Eduardo Arathoon, Rudy Lopez y Lopez, Johanna Samayoa; ***Israel***: Hila Elinav, Eynat Kedem, Itzchak Levy, Dan Turner; ***Japan***: Hiroyuki Gatanaga, Ei Kinai, Takuma Shirasaka, Yoshiyuki Yokomaku; ***Kenya***: Elizabeth Bukusi, Nelly Mugo; ***Malaysia***: Yasmin Gani, Hock Hin Chua, Raja Iskandar Raja Azwa, Lee Lee Low, Chee Loon Leong, Anuradha Radhakrishnan, Ting Soo Chow; ***Mexico***: Brenda Crabtree Ramírez; ***Puerto Rico***: Lizette Colon Santiago, Rafael Mendoza-Rodriguez; ***South Africa***: Shannon Bosman, Sheetal Kassim, Sharne Foulkes, Elizabeth Hellstrom, Cheryl Louw, Rosie Mngqibisa, Lerato Mohapi, Noluthando Mwelase, Gracie Nicole, Simiso Sokhela, Marije Van Schalkwyk; ***Spain***: Alfonso Cabello Ubeda, Felix Gutierrez Rodero, Arkaitz Imaz Vacas, Josep Mallolas Masferrer, Rafael Mican Rivera, Santiago Moreno Guillen, Palacios Munoz Rosario, Jordi Navarro Mercade, Roger Paredes, Leire Perez Latorre, Frederico Pulido Ortega; ***Switzerland***: Alexandra Calmy, Marcel Stoeckle; ***Thailand***: Anchalee Avihingsanon, Winai Ratanasuwan, Khuanchai Supparatpinyo; ***Turkey***: Hatice Guner, Serhat Unal; ***United Kingdom**:* Alejandro Arenas-Pinto, Philip Bright, Chloe Orkin, Frank Post, Gabriel Schembri; ***United States***: Paul Benson, Christopher Bettacchi, Indira Brar, Douglas Cunningham, Craig Dietz, Alexandra Dretler, Alireza Farabi, Carl Fichtenbaum, Cynthia Firnhaber, Bryan Gaudio, Federico Hinestrosa, Marc Johnson, Harold Katner, Cheryl McDonald, Ronald Nahass, Olayemi Osiyemi, Moti Ramgopal, Peter Ruane, Tanya Schreibman, Anita Scribner, Shivanjali Shankaran, Elliot Shin, James Sims, Gary Sinclair, Jihad Slim, Cornelius Van Dam

Institutional review board approvals

Country	Site #	IEC Name and Address	Approval of Protocol	Date of Approval of Protocol	IRB/EC Approval Number
Argentina	5850	Comité de Bioética de Fundación Huésped 3932 Doutor Carlos A. Gianantonio Buenos Aires, CABA, C1202ABB Argentina Comité de Bioética de Fundación Huésped Avenida Forest 345, Chacarita Comuna 15 CABA, Buenos Aires, C1427CEA Argentina	IRB/IEC Approval of Protocol	30-Aug-2023	Código de registro: 10495
Argentina	5851	Comité de bioética en investigación clínica. Fundación IDEAA 677 Neuquén Buenos Aires, CABA, C1405CKC Argentina	IRB/IEC Approval of Protocol	1-Sep-23	Ref: Protocolo MK-8591A-053
Argentina	5852	Comité de Etica CAICI-CIAP Rodriguez 1198 Rosario, Santa Fe, 2000 Argentina	IRB/IEC Approval of Protocol	08-Aug-2023	Ref: Protocolo MK-8591A-053
Argentina	5853	CIEIS OULTON Av, Velez sarafield 562 2 floor Córdoba, Cordoba, X5000JJS Argentina CIEIS OULTON Av, Velez sarsfield 56 2 floor Córdoba, Cordoba, X5000JJS Argentina	IRB/IEC Approval of Protocol	1-Nov-24	Nombre del Protocolo: MK-8591A-053
Argentina	5854	Comité de Ética en Investigación Instituto de Investigaciones Clínicas Av. Colón 3456 Mar del Plata, Buenos Aires, B7600FZO Argentina	IRB/IEC Approval of Protocol	25-Aug-2023	Protocolo: MK-8591A-053
Canada	5750	Hamilton Integrated Research Ethics Board - HiREB 237 Barton Street East C1-205 Hamilton, ON, L8L 2X2 Canada	Site Specific IRB/IEC Approval of Protocol	26-Jun-2024	Project ID #: 17153
Canada	5751	MUHC REB 5100, boul. de Maisonneuve Ouest 5th floor Montréal, QC, H4A 3T2 Canada	Site Specific IRB/IEC Approval of Protocol	07-Oct-2024	Project ID 2024-10545
Canada	5752	Advarra 372 Hollandview Trail Suite 300 Aurora, ON, L4G 0A5 Canada Advarra 125 Don Hillock Drive Unit 18 Aurora, ON, L4G 0H8 Canada	Site Specific IRB/IEC Approval of Protocol	07-May-2024	Project ID#:Pro00075977, Ref # Initial/01: SSU00247908

Canada	5753	Advarra 372 Hollandview Trail Suite 300 Aurora, ON, L4G 0A5 Canada Veritas IRB 3551 Street Charles Boulevard Suite 501 Kirkland, QC, H9H 3C4 Canada	Site Specific IRB/IEC Approval of Protocol	14-Jun-2024	Project ID#: 3512, Ref # Initial/01: 2025-3512-20340-1
Chile	5950	Comite de Ética de Investigación del Servicio de Salud Metropolitano Norte 1053 San José Santiago, Region M. de Santiago, 7560994 Chile Comite de Ética de Investigación del Servicio de Salud Metropolitano Norte Avda Recoleta Santiago, Region M. de Santiago, 7560994 Chile Comité Ético Científico Hospital Clínico Universidad de Chile Av. Carlos Lorca Tobar # 999 Sector D, piso 4 Santiago, Region M. de Santiago Chile	IRB/IEC Approval of Protocol	05-Apr-2023	ACTA DE APROBACIÓN Nº 020
Chile	5951	Comité Ético Científico CEIC Av. Ricardo Lyon 2911 Ñuñoa, Region M. de Santiago, 7770086 Chile	IRB/IEC Approval of Protocol	16-Mar-2023	Nº 74/23
Chile	5952	Comite de Etica del Centro de Investigaciones Clinicas Ricardo Lyon 2911. Ñuñoa Santiago, Region M. de Santiago, 7770086 Chile	IRB/IEC Approval of Protocol	14-Mar-2023	Acta: CEC-129
Chile	5954	Comite de Etica Cientifico del Servicio de Salud Metropolitano Oriente Avenida Salvador 364 Providencia Santiago, Region M. de Santiago, 7500922 Chile	IRB/IECApproval of Protocol	06-Jun-2023	Santiago, 06 de junio de 2023
Chile	5955	Comite Etico Cientifico del Servicio de Salud Araucania Sur Andres Bello 636 Temuco, Araucania, 4791301 Chile	IRB/IEC Approval of Protocol	19-Apr-2023	N° 94 / N° 95
Colombia	6050	Comité de Ética en Investigacion VITA. Calle 24 No 3 -02 Chia, Cundinamarca, 111611 Colombia	IRB/IEC Approval of Protocol	10-Feb-2023	N° CEIV-00259-23

Colombia	6051	Comité de Ética en Investigación de la Fundación Universitaria Sanitas Calle 23 # 66-46sede salitre- 2 pisobogota, Distrito Capital de Bogota, 111321 Colombia COMITÉ DE ÉTICA EN INVESTIGACIÓN Calle 23 #66-46 Oficina 903 Bogota, Distrito Capital de Bogota, 111321 Colombia Comisión de Investigación Clinica 66-46 Calle 23 Ciudad Salitre Oriental Bogotá, Distrito Capital de Bogota, 111321 Colombia	IRB/IEC Approval of Protocol	14-Feb-2023	CEIFUS 467-23
Colombia	6052	Comité de Ética en Investigación Biomédica IRB 18-73 Carrera 94c Cali, Valle del Cauca, 760032 Colombia	IRB/IEC Approval of Protocol	08-Feb-2023	No. 085 - 2023
Colombia	6053	Comité de Investigaciones y Ética Institucional Calle 42 No. 4-49 Piso 5, oficina 507 Edificio Bienestar-Facultad de Medicina Pontificia Universidad Javeriana-Hospita Bogota, Distrito Capital de Bogota, 110311 Colombia	IRB/IEC Approval of Protocol	09-Mar-2023	No. 001 - 2024
Colombia	6055	Comité de Ética en Investigación Clínica de la Costa SAS Carrera 50 n 80-144 Alto Prado Barranquilla, Atlantico, 080020 Colombia	IRB/IEC Approval of Protocol	03-Feb-2023	MK-8591A-053
Dominican Republic	8250	Comite de Etica IDCP AV. FEDERICO VELASQUEZ ESQ. AV. ALBERT THOMAS, BARRIO MARIA AUXILIADORA SANTO DOMINGO, Distrito Nacional, 10306 Dominican Republic Consejo Nacional de Bioetica en Salud (CONABIOS) Av Simón Bolívar No. 902 Universidad Catolica de Santo Domingo Santo Domingo, Distrito Nacional, 10108 Dominican Republic	IRB/IEC Approval of Protocol	11-Jan-2024	Referencia: Protocolo MK-8591A-053
France	6150, 6153, 6156, 6158, 6159, 6160, 6162	National Agency for the Safety of Medicine and Health Products 143/147 Bd Anatole France Saint-Denis, Paris, 93285 France	EU CTR Country Decision	25-Mar-2024	2022-502099-22-01

Germany	6250, 6254, 6256, 6259, 6260	Bundesinstitut fuer Arzneimittel und Medizinprodukte (BfArM) Kurt-Georg-Kiesinger Allee 3 Bonn, Nordrhein-Westfalen, 53175 Germany Paul Ehrlich Institute Paul-Ehrlich-Strasse 51-59 Langen, Hessen, 63225 Germany	EU CTR Country Decision	26-Mar-2024	2022-502099-22-01
Guatemala	8350	Comité de Ética Independiente en Investigación Zugueme 3ª calle 11-36 zona 15 Colonia Tecun Uman Guatemala, Guatemala, 01015 Guatemala	IRB/IEC Approval of Protocol	13-Dec-2023	MK8591A-053-CG-2025-0005
Guatemala	8351	Zugueme Comité Etica Independiente 3ª calle 11-36 zona 15 Colonia Tecun Uman Guatemala, Guatemala, 01015 Guatemala	IRB/IEC Approval of Protocol	13-Dec-2023	OFZU2536-23
Guatemala	8352	Comité de ética independiente ZUGUEME 3ª Calle 11-36 zona 15 Colonia Tecun Uman Guatemala, Guatemala, 01015 Guatemala	IRB/IEC Approval of Protocol	20-Mar-2024	OFZU744-24
Israel	6751	Rambam MC - ERC 8 Haaliya St. Ethical Committee Haifa, N/A, 3109601 Israel	IRB/IEC Approval of Protocol	13-Feb-2023	0625-22-RMB
Israel	6752	Hadassah EC Committee Yerushalayim str. Jerusalem, N/A, 9112001 Israel	IRB/IEC Approval of Protocol	30-Jan-2023	0701-22-HMO
Israel	6753	Chaim Sheba Medical Center Ethical Committee Derech Sheba Tel Hashomer Helsinki Committee Ramat Gan, N/A, 5265601 Israel	IRB/IEC Approval of Protocol	09-Feb-2023	0011-22-SMC
Israel	6754	IRB Tel Aviv Sourasky Medical Center 6 Weizman St. Arison, second floor, room 200 Tel Aviv, N/A, 6423906 Israel	IRB/IEC Approval of Protocol	02-Mar-2023	0782-22-TLV
Japan	6951	Clinical trial review committee 1-21-1 Toyama Radiotherapy Bldg. 3F Shinjuku-ku, Tokyo, 162-8655 Japan National Center for Global Health and Medicine IRB 1-21-1 Toyama, Shinjuku, Tokyo, 162-8655 Japan	IRB/IEC Approval of Protocol	20-Mar-2023	A-367-22a
Japan	6952	National Hospital Organization Osaka National Hospital Institutional Review BoardI 2-1-14 Hoenzaka Osaka, Osaka, 540-0006 Japan	IRB/IEC Approval of Protocol	24-Apr-2023	2023-0002

Japan	6953	National Hospital Organization Nagoya Medical Center Institutional Review Board 4-1-1, Sannomaru, Naka-ku Nagoya-shi, Aichi, 460-0001 Japan	IRB/IEC Approval of Protocol	15-May-2023	M365-7
Japan	6954	Tokyo Medical University Hospital Institutional Review Board 6-7-1, Nishishinjuku, Shinjuku-ku Tokyo, Tokyo, 160-0023 Japan	IRB/IEC Approval of Protocol	14-Mar-2023	C2022-029-I
Kenya	8650	Kenya Medical Research Institute, Scientific and Ethics Review Unit P.O.Box 54840-00200 Off. Mbagathi Road Nairobi House Number 8, KEMRI Headquaters. Nairobi, Nairobi City, 00200 Kenya KEMRI, SERU Off Raila Odinga Highway P0 BOX 54840 KEMRI Headquarters Nairobi, Nairobi City, 00200 Kenya	IRB/IEC Approval of Protocol	03-Mar-2024	KEMRI/RD/22
Kenya	8651	Kenya Medical Research Institute - Scientific Ethics Review Committee P.O.Box 54840-00200 Off. Mbagathi Road, Nairobi, House Number 8, KEMRI Headquaters. Nairobi, Nairobi City, 00200 Kenya	IRB/IEC Approval of Protocol	19-Feb-2024	KEMRI/RD/22
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Malaysia	7777	UMMC Medical Research Ethics Committee University Malaya Medical Centre 2nd floor, Kompleks Pendidikan Sains Kejururawatan Lembah Pantai, Kuala Lumpur, 59100 Malaysia	IRB/IECApproval of Protocol	22-Dec-2023	2023419-12375

Mexico	7251	Comité de Investigación del Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán 15 Vasco de Quiroga 5to piso de la UPA Ciudad de México, Distrito Federal, 14080 Mexico Comite de Etica en Investigacion del Instituto Nacional de Ciencias Medicas y Nutricion Vasco de Quiroga No. 15 Ciudad de Mexico, Mexico, 14080 Mexico Comite de Etica en Investigacion del Instituto Nacional de Ciencias Medicas y Nutricion 15 Vasco de Quiroga Ciudad de México, Distrito Federal, 14080 Mexico Comisión Federal para la Protección contra Riesgos Sanitarios 14 Oklahoma Ciudad de México, Distrito Federal, 03810 Mexico Comité de Bioseguridad del Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán 15 Vasco de Quiroga Ciudad de México, Distrito Federal, 14080 Mexico	IRB/IEC Approval of Protocol	12-Jul-2023	Protocolo: MK-8591A-053 Ref. 4488
Puerto Rico	7451	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	IRB/IEC Approval of Protocol	12-Jan-2023	Pro00066890
Puerto Rico	7452	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	IRB/IEC Approval of Protocol	16-Feb-2023	Pro00066890
South Africa	6650, 6652, 6653, 6654	University of the Witwatersrand Human Research Ethics Committee (Medical) 31 Princess Of Wales Road Johannesburg, Gauteng, 2193 South Africa	IRB/IEC Approval of Protocol	12-May-2023	230219
South Africa	6651	UCT Human Research Ethics Committee Main Road, Observatory G50 Old Main Building Cape Town, Western Cape South Africa	IRB/IEC Approval of Protocol	04-Aug-2023	107/2023
South Africa	6656, 6661	University of the Witwatersrand Human Research Ethics Committee (Medical) 31 Princess Of Wales Road Johannesburg, Gauteng, 2193 South Africa	IRB/IEC Approval of Protocol	11-May-2023	230219
South Africa	6657	Health Research Ethics Committee HREC 1 & HREC 2 Research Development and Support Faculty of Medicine and Health Sciences Cape Town, Western Cape, 7505 South Africa	IRB/IEC Approval of Protocol	26-Jun-2023	M23/02/005

South Africa	6659, 6660	University of the Witwatersrand Human Research Ethics Committee (Medical) 31 Princess Of Wales Road Johannesburg, Gauteng, 2193 South Africa KZN Department of Health 330 Langalibalele Street Pietermaritzburg, Kwazulu-Natal, 3201 South Africa	IRB/IEC Approval of Protocol	18-May-2023	230219
South Africa	6664	University of the Witwatersrand Human Research Ethics Committee (Medical) 31 Princess Of Wales Road Johannesburg, Gauteng, 2193 South Africa	IRB/IEC Approval of Protocol	06-Sep-2023	230219
Spain	6350, 6351, 6352, 6353, 6354, 6355, 6357, 6358, 6359, 6360, 6361	AEMPS - Agencia Espanyola de Medicamentos y Productos Sanitarios Parque Empresarial, Las Mercedes Edificio 8 C Campezo 1Madrid, Madrid, 28022 Spain AEMPS - Agencia Espanyola de Medicamentos y Productos Sanitarios C/Campezo 1Madrid, Madrid, 28022 Spain	EU CTR Country Decision	01-Apr-2024	2022-502099-22-01
Switzerland	8150, 8151	Commission centrale d ethique Rue Gabrielle-Perret-Gentil 4 Geneve, Geneve, 1211 Switzerland	Central IRB/IEC Approval of Protocol	29-Apr-2024	2024-00066
Thailand	7850	Human Research Protection Unit. Faculty of Medicine Siriraj Hospital, Mahidol University 2 Wang Lang Road Room 210, 2nd Floor, His Majesty the King's 80th Birthday Anniversary 5th December 2007 Building Bangkoknoi, Krung Thep Maha Nakhon, 10700 Thailand	IRB/IEC Approval of Protocol	31-Mar-2023	139/2566(IRB2)
Thailand	7851	Office of Research Ethics, Faculty of Medicine, Chulalongkorn University 1873 Rama IV road Anandamahidol Building, 3rd floor Pathumwan, Krung Thep Maha Nakhon, 10330 Thailand	IRB/IEC Approval of Protocol	11-Apr-2023	MK-8591A-053
Thailand	7852	The Human Experimentation Committee 110 Intavaroros Rd Research Institute for Health Sciences, Building 1, Chiang Mai University Chiang Mai, Chiang Mai, 50200 Thailand	IRB/IEC Approval of Protocol	27-Apr-2023	8393(27)
Türkiye	7650, 7659	Hacettepe University Clinical Trials Ethics Committee Hacettepe Universitesi Klinik Arastirmalar Etik Kurulu Sihhiye Ankara, Ankara, 6100 Türkiye Ankara Bilkent Sehir Hastanesi Klinik Arastirmalar Etik Kurulu Universiteler mah. Bilkent cad. N1 Cankaya Ankara, Ankara, 06800 Türkiye	Central IRB/IEC Approval of Protocol	29-Nov-2023	E1/4367/2023

United Kingdom	7950, 7951, 7952, 7953, 7954	Wales Research Ethics Committee 1 Cardiff Health and Care Research Wales Castlebridge 4 Cardiff, Cardiff, CF11 9AB United Kingdom of Great Britain and Northern Ireland	Central IRB/IEC Approval of Protocol	07-Jul-2023	23/WA/0055
United States of America	5650, 5659, 5668	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	11-Jan-23	Pro00066890
United States of America	5651, 5660, 5666, 5672	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	13-Jan-23	Pro00066890
United States of America	5653	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	16-Jan-23	Pro00066890
United States of America	5654	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	23-Jan-23	Pro00066890
United States of America	5655	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	14-Feb-23	Pro00066890
United States of America	5656, 5664	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	24-Jan-23	Pro00066890
United States of America	5657	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	9-Jan-23	Pro00066890
United States of America	5658	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	16-Feb-23	Pro00066890
United States of America	5662	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	8-Mar-23	Pro00066890
United States of America	5667	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	30-Mar-23	Pro00066890
United States of America	5670	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	19-Jan-23	Pro00066890
United States of America	5671, 5675	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	2-Mar-23	Pro00066890
United States of America	5674	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	26-Jan-23	Pro00066890
United States of America	5676	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	7-Feb-23	Pro00066890

United States of America	5679	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	17-Feb-23	Pro00066890
United States of America	5682	Saint Michael's Medical Center IRB- 111 Central Avenue Newark, NJ 07102	Site Specific IRB/IEC Approval of Protocol	21-Feb-23	#02/23
United States of America	5687	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	3-Mar-23	Pro00066890
United States of America	5691	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	10-May-23	Pro00066890
United States of America	5694	Advarra 6100 Merriwather Drive Suite 600 Columbia, MD 21044	Central IRB/IEC Approval of Protocol	11-Apr-24	Pro00066890

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TITLE PAGE

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Protocol Title: A Phase 3, Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate the Antiretroviral Activity, Safety, and Tolerability of Doravirine/Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in HIV-1 Infected Treatment-Naïve Participants

Protocol Number: 053-05

Compound Number: MK-8591A

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	NCT05705349
EU CT	2022-502099-22
EudraCT	Not applicable
JRCT	jRCT2031220720
WHO	Not applicable
UTN	Not applicable
IND	134,036

Approval Date: 07 March 2025

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 5	07-MAR-2025	To add ECIs requiring expedited reporting to the Sponsor at the request of a health authority.
Amendment 4	08-AUG-2024	To extend the blinded comparison period from Week 96 to Week 144 (base study) to provide additional safety and efficacy data, and to add an optional open-label extension (OLE) with access to DOR/ISL up to Week 240 or until commercially accessible (whichever comes first).
Amendment 3	01-APR-2024	**This is an amendment only for participants in Guatemala and the Dominican Republic** to require participants who become pregnant to discontinue study intervention.
Amendment 2	07-MAR-2024	**This is an amendment only for participating EU countries** CCI [redacted]
Amendment 1	24-OCT-2023	To provide for increased HIV-1 RNA monitoring during pregnancy (if recommended in local guidelines) and to clarify the management of participants with decreases in total lymphocyte and CD4+ T-cell counts and the management of participants with HIV-1 viremia.
Original Protocol	22-NOV-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendment:

To add ECIs requiring expedited reporting to the Sponsor at the request of a health authority.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 8.4.7 Events of Clinical Interest	Added 2 study-specific ECIs for elevated liver-related laboratory values during the first 48 weeks of study intervention that are to be reported to the Sponsor within 24 hours of learning of the event.	Health Authority/Agency feedback requiring these changes.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Table 5: Updated table to reflect that potential or confirmed DILI events would be reported as SAE with OME criteria in the absence of other serious criteria.	To maintain continued regulatory reporting compliance in alignment with new Health Authority DILI reporting requirements.
Section 8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information	Specified that reportable safety events include potential or confirmed DILI.	See rationale for Section 8.4.1.
Section 8.4.7 Events of Clinical Interest	Initial ECI updated to potential or confirmed DILI events, with associated reporting requirements.	See rationale for Section 8.4.1.
Section 10.1.6 Compliance with Study Registration and Results Posting Requirements	Added statement that a summary of the study results will be submitted.	For compliance with the EU Clinical Trials Regulation 536/2014.
Section 10.3.3 Definition of SAE	Added potential or confirmed DILI events to definition of SAE with OME criteria in the absence of other serious criteria.	See rationale for Section 8.4.1.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate the Antiretroviral Activity, Safety, and Tolerability of Doravirine/Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in HIV-1 Infected Treatment-Naïve Participants

Short Title: DOR/ISL 100 mg/0.25 mg QD in HIV-1 antiretroviral treatment-naïve

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

The following objectives will be evaluated in participants ≥18 years of age who are infected with HIV-1 and naïve to antiretroviral therapy.

Primary Objective	**Primary Endpoint**
To evaluate the antiretroviral activity of DOR/ISL compared to BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48 **Hypothesis (H1):** DOR/ISL is non-inferior to BIC/FTC/TAF, as assessed by the percentage of participants with HIV 1 RNA <50 copies/mL at Week 48. A margin of 10 percentage points is used to define non-inferiority	HIV-1 RNA
To evaluate the safety and tolerability of DOR/ISL compared with BIC/FTC/TAF as assessed by review of the accumulated safety data through Week 48	Adverse events Adverse events leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
To evaluate the antiretroviral activity of DOR/ISL compared with BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA <50 copies/mL at Week 96 and Week 144	HIV-1 RNA

To evaluate the antiretroviral activity of DOR/ISL compared with BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA <200 copies/mL at Week 48, Week 96, and Week 144	HIV-1 RNA
To evaluate the immunologic effect of DOR/ISL compared with BIC/FTC/TAF, as assessed by the mean change from baseline in CD4+ T-cell count at Week 48, Week 96, and Week 144	CD4+ T-cell count
To evaluate the development of viral drug resistance in participants who receive DOR/ISL and in those who receive BIC/FTC/TAF	Viral resistance-associated substitutions
To evaluate the effect of DOR/ISL compared with BIC/FTC/TAF on weight, as assessed by the mean change from baseline to Week 48, Week 96, and Week 144 Hypothesis (H2): DOR/ISL is superior to BIC/FTC/TAF as assessed by lower mean increase from baseline in weight at Week 48 Hypothesis (H3): DOR/ISL is superior to BIC/FTC/TAF as assessed by lower mean increase from baseline in weight at Week 96	Weight
To evaluate the safety and tolerability of DOR/ISL compared with BIC/FTC/TAF as assessed by review of the accumulated safety data through Week 144	Adverse events Adverse events leading to discontinuation of study intervention

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	HIV infection
Population	Participants ≥18 years of age with HIV-1 who are naïve to antiretroviral therapy
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.

Type of Control	ACTIVE CONTROL
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Sponsor Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 6 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 500 participants will be randomized.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use
Group 1	doravirine/ islatravir	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Day1 to Week 144	Test Product
Group 1	Placebo to bictegravir/ emtricitabine/ tenofovir alafenamide	0 mg	0 mg QD	Oral	Day 1 to Week 144	Placebo
Group 1	doravirine/ islatravir	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Week 144 up to Week 240	Test Product
Group 2	bictegravir/ emtricitabine/ tenofovir alafenamide	50 mg/ 200 mg/ 25 mg	50 mg/ 200 mg/ 25 mg QD	Oral	Day 1 to Week 144	Comparator
Group 2	Placebo to doravirine/ islatravir	0 mg	0 mg QD	Oral	Day 1 to Week 144	Placebo
Group 2	doravirine/ islatravir	100 mg/ 0.25 mg	100 mg/ 0.25 mg	Oral	Week 144 up to Week 240	Test Product

QD=once-daily

Study intervention will be extended open-label for participants who become pregnant on treatment and provide documented informed consent to continue their assigned study intervention (DOR/ISL or BIC/FTC/TAF) as specified in Sections 1.3.4 and 8.11.6.

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the blinded base study for approximately 3 years from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 45 days, each participant will receive the assigned blinded study intervention for approximately 144 weeks in the base study. After Week 144, participants will be given the option to continue in an OLE and receive DOR/ISL for up to 96 weeks or until DOR/ISL is commercially accessible (whichever comes first). Participants who discontinue study intervention or who become pregnant will be followed up as described in the protocol.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No

Study governance considerations are outlined in Appendix 1.

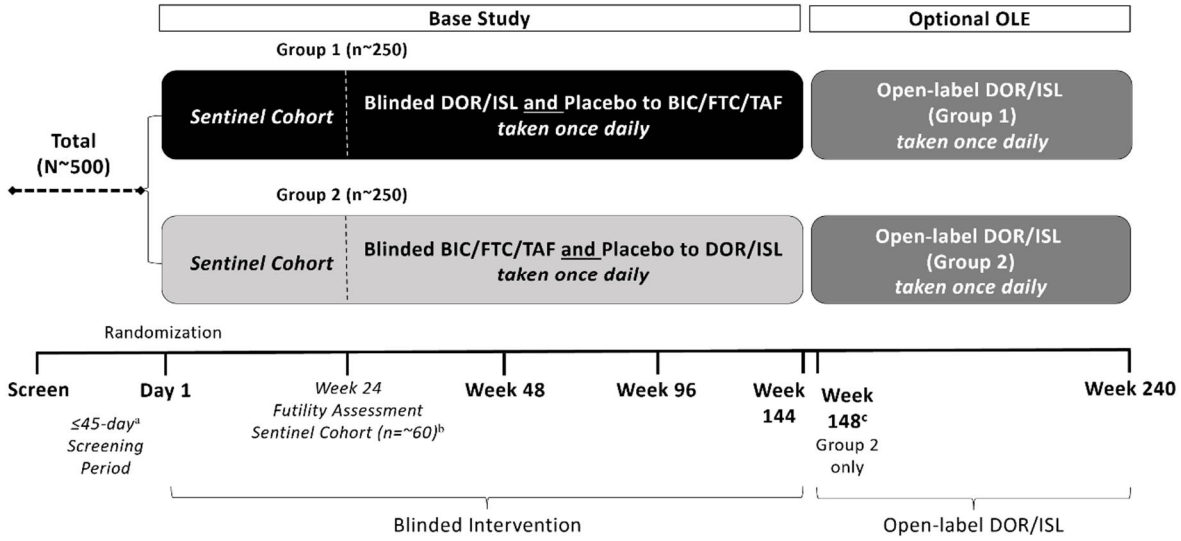
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema and Treatment Plan



BIC=bictegravir; DOR=doravirine; FTC=emtricitabine; HIV-1= human immunodeficiency virus type 1; ISL=islatravir; N=total number of participants in the study; n=number of participants in the intervention group; OLE=open-label extension; RNA=ribonucleic acid; TAF=tenofovir alafenamide.

a Participants are expected to enroll as soon as possible after eligibility is confirmed. In cases of unexpected delays in receiving repeat screening laboratory results, a screening period of up to 45 days is allowed.

b Sentinel Cohort participation is limited to those with screening HIV-1 RNA ≤100,000 copies/mL. Enrollment of participants with screening HIV-1 RNA >100,000 copies/mL is contingent upon the Week 24 Sentinel Cohort futility assessment.

c Only Group 2 participants in the OLE (ie, switch to DOR/ISL) have an extra visit at Week 148.

1.3 Schedule of Activities

1.3.1 Schedule of Activities – Screening Through Week 144 (Base Study)

This SoA applies to all participants in the blinded treatment period (base study).

- The Early Discontinuation of Treatment visit applies to any participant who discontinues study intervention prior to Week 144 per Section 8.11.3.1.
- Manage participants with viremia per Sections 8.2.2 and 8.11.4 (SoA Section 1.3.2).
- Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 (SoA Section 1.3.3).
- Manage pregnant participants per Section 8.11.6.
- For the OLE, see Section 8.11.2.3 (SoA Section 1.3.5).

Study Period	**Screen**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**															**End of Treatment**		**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Administrative Procedures																			
Informed Consent	X																		

Study Period	**Screen**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**															**End of Treatment**		**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Informed Consent for FBR	X																		
Post-Base Study Disposition Planning														X	X	X			Proactively discuss prior to Week 144 visit. See Section 8.11.2.2.
Unblinding of Treatment Group Assignment																X			Complete after documenting all AEs (including causality).
Informed Consent for OLE																X			Obtain prior to dispensing study intervention at Week 144.
Informed Consent for Study Intervention During Pregnancy			< ----------X---------- >																Obtain upon confirmation of pregnancy. See Section 8.1.1.3.
Collect and Enter Data from Prenatal Care Provider			< ----------X---------- >																See Section 8.11.6 for prenatal safety monitoring.
Informed Consent for Infant Data Collection			< ----------X---------- >																Obtain after confirmation of continuing pregnancy. See Sections 8.1.1.4 and 8.11.6.4.

Study Period	**Screen**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**															**End of Treatment**		**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Administration of EQ-5D-5L and HIV-SI/SDM Patient Questionnaires		X	X		X			X				X					(X)		Administer in the order listed, before the participant is seen by the investigator, before discussing medical conditions or test results. (Do not administer after the Week 96 visit.)
Inclusion/ Exclusion Criteria	X	X																	Review <u>prior</u> to randomization on Day 1 to confirm eligibility.
Participant Identification Card	X	X																	Site personnel will add randomization number.
Medical History	X																		
Tobacco and Alcohol Assessments	X							X				X				X			
Prior and Concomitant Medications Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Register Study Visit in IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Study Period	**Screen**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**															**End of Treatment**		**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Intervention Randomization		X																	All pretreatment procedures should be completed <u>prior</u> to randomization on Day 1.
Dispense Study Intervention Using IRT		X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)			(Dispense at Week 144 for participants entering the optional OLE and if needed for those whose pregnancy and/or postpartum visit(s) extends beyond Week 144 per Section 1.3.4.)
Study Intervention Compliance Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			For participants whose pregnancy or postpartum visit(s) extends past Week 144 per Section 1.3.4.
Efficacy Procedures																			
Plasma HIV-1 RNA Quantification	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.2.1. See Section 8.11.6.1 for testing in participants who become pregnant.
TBNK Panel/CD4+ T-cell Count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Study Period	**Screen**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**															**End of Treatment**		**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Blood (Plasma) for HIV-1 Viral Drug Resistance Testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Screening performed at the central laboratory or a local laboratory with a validated assay; all other samples should be processed by the central laboratory. Analysis will be performed by Sponsor if indicated per Section 8.2.2.4.
Whole Blood for HIV-1 Viral Drug Resistance Testing		X																	
Safety Procedures																			
Full Physical Examination	X																X		
Height		X																	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period	**Screen**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**															**End of Treatment**		**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Local 12-Lead ECG		X																	Performed up to 7 days prior to dose on Day 1 and after <u>all</u> other eligibility criteria are confirmed.
Contraceptive Use Confirmation (POCBP Only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Contraception is required for 42 days after the last dose of study intervention (see Section 8.3.4).
Urine Pregnancy Test (hCG) (POCBP Only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Pregnancy must be excluded on Day 1 before randomization. Manage randomized participants who have a positive or indeterminant urine test per Section 8.11.6. For participants known to be pregnant, defer until 6 weeks postpartum.
Serum Pregnancy Test (hCG) (POCBP Only)	X																		A highly sensitive urine or serum pregnancy test can be performed at screening, See Section 5.1.
HIV-1 and HIV-2 Serology	X																		

Study Period	**Screen**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**															**End of Treatment**		**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Hepatitis B Serology with Reflex HBV DNA	X							X				X				X			Repeat serology with reflex HBV DNA at Weeks 48, 96, and 144 (annual surveillance). Encourage HBV vaccination to participants who are not immune to HBV.
Hepatitis B Serology with Reflex HBV DNA in Pregnant Participants (DOR/ISL Only)		< ----------(X)---------- >																	Collect once after pregnancy is confirmed or report local laboratory results. See Section 8.11.6.1.
Hepatitis C Serology	X																		See Section 8.3.7. Repeat screening if indicated per local standard of care.
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Fasting required at Day 1 and Weeks 24, 48, 72, 96, 120, and 144. See Section 8.3.9.3 and Appendix 2. Pregnant participants should not fast.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PT/INR	X																		
Urinalysis		X				X		X		X		X		X		X	X		
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period	**Screen**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**															**End of Treatment**		**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Blood (Plasma) for ISL PK		X	X	X	X	X		X											At Week 4, if daytime dosing, obtain pre- and postdose or, if evening dosing, collect only 1 sample irrespective of time of last dose. See Section 8.6.1 (Table 6). Do not collect if participant unblinded and assigned to BIC/FTC/TAF.
Blood (Plasma) for Investigational ISL PK							X		X	X	X	X					X		Do not collect during pregnancy or if participant unblinded and assigned to BIC/FTC/TAF. Analysis performed by Sponsor as needed. See Section 8.6.1.
Blood (Plasma) for DOR and ISL PK in Pregnant Participants (DOR/ISL Only)		< ----------X---------- >															X		Collect during the 1st, 2nd, and 3rd trimesters and postpartum. See Section 8.11.6.1 (Table 7).
Blood for Inflammatory Markers		X				X		X				X				X			Do not collect during pregnancy.
Blood and Urine for Renal Markers		X				X		X				X				X			Do not collect during pregnancy.

Study Period	**Screen**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**															**End of Treatment**		**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Blood for Energy and Metabolism Markers		X				X		X		X		X				X			Do not collect during pregnancy.
Waist and Hip Measurements		X						X				X				X			Not applicable to pregnant participants.
DEXA Scan (Only Where Permitted by Local Law)		X						X				X				X			Perform after <u>all</u> eligibility criteria are confirmed. Must be performed prior to 45 days after Day 1 and ±45 days of the Weeks 48, 96, and 144 visits. Perform only for participants with valid baseline images. Do not perform on pregnant participants. See Appendix 7 for Country-specific requirements.
Biomarkers																			
Blood for Genetic Analysis[c]		X																	Collect predose. See Section 8.8.

Study Period	**Screen**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**															**End of Treatment**		**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Whole Blood for FBR		X				X		X				X		X		X	X		Optional participation; requires FBR consent. Collect Day 1 predose; remaining samples may be collected at any time irrespective of last dose. See Section 8.9.

AE=adverse event; BIC=bictegravir; DEXA=dual-energy X-ray absorptiometry; DNA=deoxyribonucleic acid; DOR=doravirine; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5-dimensional descriptive system, 5-level version; FBR=future biomedical research; FTC=emtricitabine; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HIV-1=human immunodeficiency virus type 1; HIV-2= human immunodeficiency virus type 2; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/symptom distress module; INR=international normalized ratio; IRT=interactive response technology; ISL=islatravir; NA=not applicable; OLE=open-label extension; PK=pharmacokinetic(s); POCBP=participant/participants of childbearing potential; PT=prothrombin time; RNA=ribonucleic acid; SAE=serious adverse event; SoA=schedule of activities; TAF=tenofovir alafenamide; TBNK=T and B lymphocyte and natural killer cells.

[a] Participants are expected to enroll as soon as possible after eligibility is confirmed. In cases of unexpected delays in receiving repeat screening laboratory results, a screening period of up to 45 days is allowed. Screening laboratory tests (local or central) should be obtained within 45 days prior to randomization to verify study eligibility. Resistance testing results may be obtained from a local laboratory with a validated assay ≤90 days prior to Day 1.

[b] Participants who discontinue at a scheduled visit should complete the assessments for the scheduled visit as well as for the Early Discontinuation of Treatment visit. Collection of laboratory samples should not be duplicated.

[c] This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant (or their legally acceptable representative) provides documented informed consent for FBR. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

1.3.2 Schedule of Activities – Viremia Confirmation and End of Treatment For Participants With Viremia (Except Those With Specified Decreases in Total Lymphocyte Count and/or CD4+ T-cell Count)

This SoA only applies to participants requiring viremia confirmation in the base study and/or OLE.

- Clinically significant confirmed viremia requires discontinuation per Sections 8.2.2.2 and 8.11.4.
- Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 (SoA Section 1.3.3).

Study Period	**Viremia Confirmation**	**End of Treatment (Base Study)**		**End of Treatment (OLE)**		**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-Up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-Up (OLE)	
Visit Window	Within 4 weeks (±1 week) of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after end of treatment	NA	42 (+7) days after end of treatment	
Administrative Procedures						
Prior and Concomitant Medications Review	X	X	X	X		
Register Study Visit in IRT	X	X		X		
Study Intervention Compliance Review	X	X				

Study Period	Viremia Confirmation	End of Treatment (Base Study)		End of Treatment (OLE)		Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-Up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-Up (OLE)	
Visit Window	Within 4 weeks (±1 week) of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after end of treatment	NA	42 (+7) days after end of treatment	
Administration of EQ-5D-5L and HIV-SI/SDM Patient Questionnaires		(X)				Administer in the order listed, before the participant is seen by the investigator, before discussing medical conditions or test results. (Do not administer after the Week 96 visit).
Efficacy Procedures						
Plasma HIV-1 RNA Quantification	X	X	X	X	X	See Section 8.2.1.
TBNK Panel/CD4+ T-cell Count		X		X		
Plasma for HIV-1 Drug Resistance	X	X		X		Analysis performed by Sponsor if indicated per Section 8.2.2.4.
Safety Procedures						
Full Physical Examination		X				
Directed Physical Examination			X	X	X	
Weight		X	X			
Vital Signs		X	X			
Contraceptive Use Confirmation (POCBP Only)	X	X	X	X	X	Contraception required for 42 days after last dose of study intervention (Section 8.3.4).

Study Period	Viremia Confirmation	End of Treatment (Base Study)		End of Treatment (OLE)		Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-Up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-Up (OLE)	
Visit Window	Within 4 weeks (±1 week) of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after end of treatment	NA	42 (+7) days after end of treatment	
Urine Pregnancy Test (hCG) (POCBP Only)	X	X	X	X	X	Confirm positive or indeterminant test with serum. If positive, manage participant per Section 8.11.6. For participants known to be pregnant, defer until 6 weeks postpartum.
Chemistry		X				
Hematology		X		X		
Urinalysis		X				
AE/SAE Review	X	X	X	X	X	
Pharmacokinetics						
Blood (Plasma) for Investigational ISL (and DOR, as needed) PK	X	X				Do not collect during pregnancy or if participant unblinded and assigned to BIC/FTC/TAF. Analysis performed by Sponsor as needed. See Section 8.6.1.
Blood (Plasma) for DOR and ISL PK	X	X		X		Only for pregnant participants on DOR/ISL. Collect irrespective of time of last dose and record time of last dose of study intervention in appropriate source documentation.
Biomarkers						
Whole Blood for Future Biomedical Research	X	X				Optional participation; requires FBR consent. Collect irrespective of time of last dose. See Section 8.9.

Study Period	Viremia Confirmation	End of Treatment (Base Study)		End of Treatment (OLE)		Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-Up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-Up (OLE)	
Visit Window	Within 4 weeks (±1 week) of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after end of treatment	NA	42 (+7) days after end of treatment	

AE=adverse event; BIC=bictegravir; DOR=doravirine; FBR=future biomedical research; FTC=emtricitabine; hCG=human chorionic gonadotropin; HIV-1=human immunodeficiency virus type 1; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/symptom distress module; IRT=interactive response technology; ISL=islatravir; NA=not applicable; OLE=open-label extension; PK=pharmacokinetic(s); POCBP=participant/participants of childbearing potential; RNA=ribonucleic acid; SAE=serious adverse event; SoA=schedule of activities; TAF=tenofovir alafenamide; TBNK=T and B lymphocyte and natural killer cells.

[a] Participants who discontinue at a scheduled visit should complete the assessments for the scheduled visit as well as for the Early Discontinuation of Treatment visit. Collection of laboratory samples should not be duplicated.

1.3.3 Schedule of Activities for Participants Who Meet the Discontinuation Criteria for Specified Decreases in Total Lymphocyte Count and/or CD4+ T-cell Count

This SoA applies only to participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts in the base study or OLE per Section 8.11.5. See Appendix 7 for Country-specific requirements.

- Manage participants with viremia per Sections 8.2.2 and 8.11.4 (SoA Section 1.3.2).

Study Period	**Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation**	**End of Treatment (Base Study)**		**End of Treatment (OLE)**		**Total Lymphocyte Count and/or CD4+ T-Cell Count Monitoring (DOR/ISL Only)**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-up (OLE)	Total Lymphocyte Count and/or CD4+ T-Cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding confirmation interval, discontinuation, and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Administrative Procedures							
Prior and Concomitant Medications Review	X	X	X	X		X	
Register Study Visit in IRT	X	X		X		X	

Study Period	**Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation**	**End of Treatment (Base Study)**		**End of Treatment (OLE)**		**Total Lymphocyte Count and/or CD4+ T-Cell Count Monitoring (DOR/ISL Only)**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-up (OLE)	Total Lymphocyte Count and/or CD4+ T-Cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding confirmation interval, discontinuation, and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Study Intervention Compliance Review	X	X					
Administration of EQ-5D-5L and HIV-SI/SDM Patient Questionnaires		(X)					Administer in order listed, before participant is seen by investigator, before discussing medical conditions or test results. (Do not administer after the Week 96 visit.)
Efficacy Procedures							
Plasma HIV-1 RNA Quantification		X	X	X			See Section 8.2.1.
TBNK Panel/CD4+ T-cell Count	X	X	X	X	X	X	

Study Period	**Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation**	**End of Treatment (Base Study)**		**End of Treatment (OLE)**		**Total Lymphocyte Count and/or CD4+ T-Cell Count Monitoring (DOR/ISL Only)**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-up (OLE)	Total Lymphocyte Count and/or CD4+ T-Cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding confirmation interval, discontinuation, and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Plasma for HIV-1 Viral Drug Resistance Testing		X		X			Analysis performed by Sponsor if indicated per Section 8.2.2.4.
Safety Procedures							
Full Physical Examination		X					
Directed Physical Examination			X	X	X		
Weight		X	X				
Vital Signs		X	X				
Contraceptive Use Confirmation (POCBP Only)		X	X	X	X		Contraception is required for 42 days after discontinuation of study intervention (see Section 8.3.4).

Study Period	**Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation**	**End of Treatment (Base Study)**		**End of Treatment (OLE)**		**Total Lymphocyte Count and/or CD4+ T-Cell Count Monitoring (DOR/ISL Only)**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-up (OLE)	Total Lymphocyte Count and/or CD4+ T-Cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding confirmation interval, discontinuation, and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Urine Pregnancy Test (hCG) (POCBP Only)		X	X	X	X		Confirm positive or indeterminant urine test with serum. If positive, manage participant per Section 8.11.6. For participants known to be pregnant, defer until 6 weeks postpartum.
Chemistry		X					
Hematology	X	X	X	X	X	X	
Urinalysis		X					
AE/SAE Review	X	X	X	X	X	X	

Study Period	Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation	End of Treatment (Base Study)		End of Treatment (OLE)		Total Lymphocyte Count and/or CD4+ T-Cell Count Monitoring (DOR/ISL Only)	Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-up (OLE)	Total Lymphocyte Count and/or CD4+ T-Cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding confirmation interval, discontinuation, and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Pharmacokinetics							
Blood (Plasma) for Investigational ISL PK	X	X					Do not collect during pregnancy or if participant unblinded and assigned to BIC/FTC/TAF. Analysis performed by Sponsor as needed. See Section 8.6.1.
Biomarkers							
Whole Blood for Future Biomedical Research		X					Optional participation; requires FBR consent. Collect irrespective of time of last dose.

Study Period	**Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation**	**End of Treatment (Base Study)**		**End of Treatment (OLE)**		**Total Lymphocyte Count and/or CD4+ T-Cell Count Monitoring (DOR/ISL Only)**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-up (OLE)	Total Lymphocyte Count and/or CD4+ T-Cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding confirmation interval, discontinuation, and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	

AE=adverse event; BIC=bictegravir; DOR=doravirine; EQ-5D-5L=EuroQol 5-dimensional descriptive system, 5-level version; FBR=future biomedical research; FTC=emtricitabine; hCG=human chorionic gonadotropin; HIV-1=human immunodeficiency virus type 1; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/symptom distress module; IRT=Interactive Response Technology; ISL=islatravir; NA=not applicable; OLE=open-label extension; PK=pharmacokinetic(s); POCBP=participant/participants of childbearing potential; RNA=ribonucleic acid; SAE=serious adverse event; SoA=schedule of activities; TAF=tenofovir alafenamide; TBNK=T and B lymphocyte and natural killer cells.

[a] Participants who discontinue at a scheduled visit should complete the assessments for the scheduled visit as well as for the Early Discontinuation of Treatment visit. Collection of laboratory samples should not be duplicated.

1.3.4 Schedule of Activities for Participants Whose Pregnancy and/or Postpartum Visit(s) Extends Beyond Week 144

This SoA only applies to eligible participants who are pregnant at Week 144 or who become pregnant in the OLE and consent to continue study intervention during pregnancy. See Appendix 7 for Country-specific requirements.

- Participants will have visits every 12 weeks during the pregnancy and once postpartum. If delivery is premature or the 1st trimester visit is missed, the participant may have ≤3 visits before delivery plus the postpartum visit. See Section 8.11.6.
- Manage participants with viremia per Sections 8.2.2 and 8.11.4 (SoA Section 1.3.2).
- Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 (SoA Section 1.3.3).

Study Period	**Pregnancy**			**Postpartum**	**End of Treatment**	**Notes**
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	
Scheduled Week	Pregnancy 1	Pregnancy 2 (12 weeks from Pregnancy 1)	Pregnancy 3 (12 weeks from Pregnancy 2)	Pregnancy 4 (Postpartum ≤8 weeks after delivery)	End of Treatment Follow-Up[a]	
Visit Window	± 7 days				42 (+7) days after end of treatment	
Administrative Procedures						
Collect and Enter Data From Prenatal Care Provider	< ----------X---------- >					Obtain relevant prenatal clinical and laboratory data to monitor the safety of the mother and fetus per Section 8.11.6
Register Study Visit in IRT	X	X	X	X	X	
Dispense Study Intervention Using IRT	X	X	X	(X) (DOR/ISL Only)		(Postpartum participants on DOR/ISL may continue treatment through the optional OLE [Section 1.3.5] if DOR/ISL is not yet commercially accessible; those on BIC/FTC/TAF should transition to commercially accessible ART at postpartum visit [Section 8.6.11.1].)

Study Period	Pregnancy			Postpartum	End of Treatment	Notes
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	
Scheduled Week	Pregnancy 1	Pregnancy 2 (12 weeks from Pregnancy 1)	Pregnancy 3 (12 weeks from Pregnancy 2)	Pregnancy 4 (Postpartum ≤8 weeks after delivery)	End of Treatment Follow-Up[a]	
Visit Window	± 7 days				42 (+7) days after end of treatment	
Study Intervention Compliance Review	X	X	X	X		
Prior and Concomitant Medications Review	X	X	X	X	X	
Efficacy Procedures						
Plasma HIV-1 RNA Quantification	X	X	X	X		See Section 8.2.1.
TBNK Panel/CD4+ T-cell Count		X	X	X	X	
Plasma for HIV-1 Viral Drug Resistance Testing	X	X	X	X	X	Analysis performed by Sponsor if indicated in Section 8.2.2.4.
Safety Procedures						
Weight	X	X	X	X	X	
Directed Physical Examination	X	X	X	X	X	
Vital Signs	X	X	X	X	X	
Hepatitis B Serology with Reflex HBV DNA (DOR/ISL Only)	< ----------X---------- >					Collect once after pregnancy is confirmed or report local laboratory results. See Section 8.11.6.1.
Chemistry	X	X	X	X	X	
Hematology	X	X	X	X		

Study Period	**Pregnancy**			**Postpartum**	**End of Treatment**	**Notes**
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	
Scheduled Week	Pregnancy 1	Pregnancy 2 (12 weeks from Pregnancy 1)	Pregnancy 3 (12 weeks from Pregnancy 2)	Pregnancy 4 (Postpartum ≤8 weeks after delivery)	End of Treatment Follow-Up[a]	
Visit Window	± 7 days				42 (+7) days after end of treatment	
Urinalysis	X	X	X	X	X	
AE/SAE Review	X	X	X	X	X	
Pharmacokinetics						
Blood (Plasma) for DOR and ISL PK	X	X	X	X	X	Collect only for participants on DOR/ISL during the 1st, 2nd, and 3rd trimesters and postpartum. See Section 8.11.6.1.1 (Table 7).

AE=adverse event; ART=antiretroviral therapy; BIC=bictegravir; DNA=deoxyribonucleic acid; DOR=doravirine; FTC=emtricitabine; HBV=hepatitis B virus; HIV-1= human immunodeficiency virus type 1; IRT=Interactive Response Technology; ISL=islatravir; PK=pharmacokinetic(s); OLE=open-label extension; RNA=ribonucleic acid; SAE=serious adverse event; SoA=schedule of activities; TAF=tenofovir alafenamide; TBNK=T and B lymphocyte and natural killer cell.

[a] The procedures in this End of Treatment Follow-Up Visit should be followed for those participants not continuing in the OLE.

1.3.5 Schedule of Activities – Week 144 Through Week 240 (OLE)

This SoA only applies to participants who enter the optional OLE at Week 144.

- Duration of participation in the OLE is dependent on when DOR/ISL becomes commercially accessible, with a maximum treatment duration of 96 weeks (ie, total study intervention duration of up to 240 weeks).
- Manage participants with viremia per Sections 8.2.2 and 8.11.4 (SoA Section 1.3.2).
- Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 (SoA Section 1.3.3).
- Manage pregnant participants per Section 8.11.6 (SoA Section 1.3.4).

Study Period	**Optional OLE**					**End of Treatment**		**Notes**
Visit Number	17	18	19	20	21	Unscheduled		
Scheduled Day/Week	Week 148 (Group 2 Only)	Week 168	Week 192	Week 216	Week 240	Discontinuation of Treatment (OLE)[a]	End of Treatment Follow-Up (OLE)	
Visit Window	±14 days (Calculate each visit from date of Day 1)					NA	42 (+7) days after end of treatment	
Evaluate Local Accessibility of DOR/ISL	X	X	X	X	X			Once DOR/ISL is commercially accessible, participants should return for the Discontinuation of Treatment visit and transition to local supply.
Prior and Concomitant Medications Review	X	X	X	X	X	X	X	
Register Study Visit in IRT	X	X	X	X	X	X		
Dispense Study Intervention Using IRT	X	X	X	X	(X)			(Dispense at Week 240 if needed for pregnant participants. See Section 1.3.4.)

Study Period	Optional OLE					End of Treatment		Notes
Visit Number	17	18	19	20	21	Unscheduled		
Scheduled Day/Week	Week 148 (Group 2 Only)	Week 168	Week 192	Week 216	Week 240	Discontinuation of Treatment (OLE)[a]	End of Treatment Follow-Up (OLE)	
Visit Window	±14 days (Calculate each visit from date of Day 1)					NA	42 (+7) days after end of treatment	
Study Intervention Compliance Review	X	X	X	X	X	X		
Plasma HIV-1 RNA Quantification	X	X	X	X	X	X		See Section 8.2.1.
TBNK Panel/CD4+ T-cell Count	X	X	X	X	X	X		
Blood (Plasma) for HIV-1 Viral Drug Resistance Testing	X	X	X	X	X	X		Samples should be processed by the central laboratory. Analysis will be performed by Sponsor if indicated per Section 8.2.2.4.
Hepatitis B Serology with Reflex HBV DNA			X		X			Repeat serology with reflex HBV DNA at Weeks 192 and 240 (annual surveillance). Encourage HBV vaccination to participants who are not immune to HBV.
HBsAg and HBV DNA	(X)	(X)	(X)	(X)	(X)	(X)		(Only for Group 2 participants with positive anti-HBc. See Section 8.3.6.)
Hematology	X	X	X	X	X	X		
Directed Physical Examination	X	X	X	X	X	X	X	
AE/SAE Review	X	X	X	X	X	X	X	
Contraceptive Use Confirmation (POCBP Only)	X	X	X	X	X	X	X	Contraception is required for 42 days after the last dose of study intervention (see Section 8.3.4).

Study Period	**Optional OLE**					**End of Treatment**		**Notes**
Visit Number	17	18	19	20	21	Unscheduled		
Scheduled Day/Week	Week 148 (Group 2 Only)	Week 168	Week 192	Week 216	Week 240	Discontinuation of Treatment (OLE)[a]	End of Treatment Follow-Up (OLE)	
Visit Window	±14 days (Calculate each visit from date of Day 1)					NA	42 (+7) days after end of treatment	
Urine Pregnancy Test (hCG) (POCBP Only)	X	X	X	X	X	X	X	Manage participants who have a positive or indeterminant urine test per Sections 1.3.4 and 8.11.6. For participants known to be pregnant, defer until 6 weeks postpartum.
Informed Consent for Study Intervention During Pregnancy	< ----------X---------- >							Obtain upon confirmation of pregnancy. See Sections 1.3.4 and 8.1.1.3.

AE=adverse event; anti-HBc=hepatitis B core antibody; BIC=bictegravir; DNA=deoxyribonucleic acid; DOR=doravirine; FTC=emtricitabine; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HIV-1=human immunodeficiency virus type 1; IRT=interactive response technology; ISL=islatravir; NA=not applicable; OLE=open-label extension; POCBP=participant/participants of childbearing potential; RNA=ribonucleic acid; SAE=serious adverse event; SoA=schedule of activities; TAF=tenofovir alafenamide; TBNK=T and B lymphocyte and natural killer cells.

[a] If discontinuation occurs at a scheduled visit, perform Discontinuation of Treatment (OLE) visit assessments.

2 INTRODUCTION

DOR/ISL (also known as MK-8591A) is a novel 2-drug FDC of DOR (100 mg) (an approved NNRTI) and ISL (0.25 mg) (an investigational NRTTI). DOR/ISL is being developed for QD treatment of HIV-1 infection.

2.1 Study Rationale

As treatment regimens have improved, HIV-1 infection has become a chronic, manageable condition, and PLWH receiving effective ART regimens can expect to live near-normal lifespans [Trickey, A., et al 2017]. Anticipating that individuals can receive decades of treatment during their lifetime, long-term tolerability and safety of antiretrovirals have become increasingly important considerations.

The current standard of care for the treatment of HIV-1 is a combination of 2 NRTIs with a third agent (eg, InSTI, NNRTI, or PI) [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022] [European AIDS Clinical Society 2021] [World Health Organization 2021]. Although such regimens have become increasingly well tolerated and highly efficacious, the current paradigm of lifelong daily treatment is associated with a need for simpler and safer regimens, that reduce overall drug exposure [Llibre, J. M., et al 2018] [Cahn, P., et al 2019] [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022]. As this population ages, there is increasing concern about polypharmacy, long-term toxicity, and DDIs related to comorbidity and multimorbidity and risks associated with the emergence of HIV-1 variants resistant to InSTI, NRTI, and NNRTI treatments.

There is evidence that 2-drug regimens can achieve efficacy comparable to that of 3-drug regimens, offer better tolerability, and improve quality of life, all of which can support adherence and help to sustain virologic suppression [Llibre, J. M., et al 2018] [Cahn, P., et al 2019] [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022]. The effectiveness of 2 drug regimens depends on both components having distinct mechanisms of action with at least one of the components having a relatively high barrier to resistance.

DOR/ISL has the potential to be an effective and well tolerated 2-drug regimen for the treatment of HIV-1 infection in TN patients due to its potent antiretroviral activity (including activity against common NRTI- and NNRTI-resistant variants) multiple mechanisms of action, lack of food requirements, and favorable DDI profiles observed to date (see Section 2.2.3).

2.2 Background

Refer to the approved labeling for DOR and to the IB for ISL for detailed background information.

2.2.1 Islatravir

ISL is a novel and potent NRTTI that blocks HIV-1 reverse transcriptase by novel mechanisms of action. It is a nucleoside analogue that is converted to the pharmacologically active triphosphate (ISL-TP) form via endogenous intracellular kinases. It acts through

multiple mechanisms, including immediate chain termination by blocking translocation and delayed chain termination by preventing nucleotide excision [Michailidis E 2014].

ISL is differentiated from other HIV-1 antiretrovirals by its high potency, long half-life, and favorable drug resistance profile. At the proposed dose of 0.25 mg QD, ISL achieves higher steady-state IQs (the ratio of drug exposure to viral susceptibility [C_{trough}/IC_{50}]) against wild-type HIV-1 than any NRTI currently approved for treatment. It also exhibits potent activity against the most prevalent NRTI resistance mutations, including M184V.

2.2.2 Doravirine

DOR, a potent NNRTI with demonstrated efficacy and good tolerability, was first approved for the treatment of HIV-1 infection by the FDA and the EMA in 2018. It is differentiated from other NNRTIs by its distinct resistance profile, low likelihood of selection for viral resistance in vivo, and low potential for DDIs. DOR exhibits potent activity against both wild-type HIV-1 virus and frequently transmitted NNRTI-resistant variants (eg, K103N, Y181C, G190A, and E138K) in vitro. The efficacy and safety profiles of DOR have been well characterized in Phase 3 studies conducted in TN adult participants [Orkin, C., et al 2019] [Molina, J. M., et al 2018] and in virologically suppressed adult participants switching from a stable antiretroviral regimen [Johnson, M., et al 2019].

2.2.3 Doravirine/Islatravir

DOR/ISL is an FDC containing DOR (100 mg) and ISL (0.25 mg) administered as a single tablet QD. DOR and ISL represent 2 distinct antiretroviral agents that inhibit reverse transcription by different mechanisms. Based on the profiles of each and data available to date, the combination DOR/ISL is expected to be well tolerated and highly efficacious, with a high barrier to resistance. The combination has demonstrated additive antiretroviral activity, with complementary resistance profiles, and suppressed the emergence of resistance in vitro at clinically relevant concentrations.

DOR (100 mg)/ISL (0.75 mg) has demonstrated antiretroviral activity in Phase 3 studies in virologically suppressed (MK-8591A-017 and MK-8591A-018) and TN adults (MK-8591A-020) with HIV-1. Additional details are available in the IB.

In MK-8591-011 (Phase 2 dose-ranging study), ISL doses of 0.25, 0.75, and 2.25 mg were administered to TN adults initially in a 3-drug regimens (ISL+DOR+3TC) until virologic suppression (HIV-1 RNA <50 copies/mL) was achieved, at which point the regimen was simplified to a 2-drug regimen (ISL+DOR) for maintenance of suppression. The DOR+ISL regimens achieved efficacy (HIV-1 RNA <50 copies/mL) comparable with the FDC comparator (DOR/3TC/TDF) used in MK-8591-011. No participant met criteria for clinically significant confirmed viremia (HIV-1 RNA ≥200 copies/mL) through Week 144. The overall AE profile for ISL+DOR (±3TC) was similar for each dose of ISL and generally comparable with DOR/3TC/TDF through Week 144. Differences in changes from baseline in total lymphocyte and CD4+ T-cell counts were observed for different ISL dose groups (see Section 2.3).

In MK-8591A-020, DOR/ISL (100 mg/0.75 mg) was non-inferior to BIC/FTC/TAF, as assessed by the percentage of the participants achieving virologic suppression (HIV-1 RNA <50 copies/mL) at Week 48 using the FDA snapshot approach (88.9% vs 88.3%, respectively). Treatment-emergent resistance was observed for 2 participants (DOR/ISL group) which was considered in both cases to be due to nonadherence to treatment as the participants' ISL levels were BLOQ at the time of viremia. *Note that study enrollment was stopped early (597 of 680 planned participants had been randomized and treated [~88%]) due to CD4+ T-cell/total lymphocyte declines observed in the ISL program.*

2.2.4 Information on Other Study-related Therapy

BIC/FTC/TAF was first approved in 2018 for the treatment of HIV-1 infection in patients naïve to ART and will be administered at the approved marketed dose. Refer to approved labeling for detailed information for BIC/FTC/TAF.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

The totality of available nonclinical and clinical data support continued evaluation of DOR/ISL 100 mg/0.25 mg FDC in Phase 3 studies.

There remains significant unmet need for novel ART as an alternative option for HIV-1 treatment that is suitable across the population of PLWH, including the elderly and those with multiple comorbidities. High in vitro potency against wild-type HIV-1 virus and a high barrier to resistance make DOR and ISL suitable candidates for treatment of HIV-1 infection. Administration of ISL in doses of 0.25, 0.75, and 2.25 mg with DOR 100 mg and 3TC 300 mg in MK-8591-011 achieved virological suppression in >90% of TN participants by Week 24, which was maintained after switching from the 3-drug regimen (ISL+DOR+3TC) to the 2-drug regimen (ISL+DOR) through Week 144. The antiviral efficacy and overall AE profile through Week 72 (the dose-ranging part of MK-8591-011) were not distinguishable among the 3 ISL dose groups (0.25, 0.75, and 2.25 mg).

DOR/ISL (100 mg/0.75 mg QD) was highly efficacious in maintaining virologic suppression (>95% and >93% of participants had HIV-1 RNA <50 copies/mL at Week 48) in participants who switched from various baseline ARTs, including BIC/FTC/TAF, in 2 Phase 3 studies (MK-8591A-017 and -018, respectively). To date, viral resistance was observed for 2 participants receiving DOR/ISL across the Phase 2 (MK-8591-011) and the Phase 3 (MK-8591A-017, MK-8591A-018 and MK-8591A-020) programs in which 1693 treatment-naïve and suppressed participants with HIV-1 infection received DOR/ISL. These participants were enrolled in the MK-8591A-020 study. Across the ISL clinical development program involving approximately 2300 participants enrolled in Phase 2 and Phase 3 studies, there was a low incidence of drug-related AEs, SAEs, and deaths with ISL when administered alone or with DOR; decreases in lymphocyte counts were observed.

Comprehensive nonclinical safety evaluations of DOR and ISL as mono-entities have not revealed toxicities of concern. Nonclinical developmental and reproductive toxicity studies did not identify any clinically relevant concerns that would preclude continued dosing of DOR/ISL in participants who become pregnant during the study. Both DOR and ISL may be administered without regard to food and have a low potential for DDIs, a favorable attribute for those who have multiple chronic comorbidities.

Decreases in total lymphocyte and lymphocyte subsets (including CD4+ T-cell) counts have been observed in Phase 2 and Phase 3 studies with ISL given QM (60 and 120 mg), QW (20 mg in combination with MK-8507, an NNRTI), and QD (0.75 mg in combination with DOR 100 mg). As a result, dosing was stopped in DEC-2021 for ISL 60 mg QM for HIV-1 PrEP, ISL 20 mg QW (with MK-8507) for HIV-1 treatment, and DOR/ISL (100 mg/0.75 mg) QD for HIV-1 treatment in pediatric participants.

The Sponsor has conducted a comprehensive investigation into ISL-related decreases in lymphocyte counts to identify possible mechanism(s) of action and to assess the timing and extent of lymphocyte decreases while on treatment with ISL and the recovery of lymphocyte counts when off treatment with ISL.

Investigations of possible mechanisms for the lymphocyte decreases support the conclusion that the preferential accumulation of ISL-TP in lymphocytes can lead to inhibition of cell growth and apoptosis at high ISL-TP concentrations. Toxicity due to high TP levels is a common mechanism among HIV nucleoside analog drugs. Mitochondrial toxicity is not a contributing mechanism to the decrease in lymphocytes.

An overall summary of the comprehensive investigation into ISL-related decreases in lymphocyte counts is as follows:

- No changes in general hematology parameters (including hemoglobin, basophils, eosinophils, monocytes, leukocytes, neutrophils, platelets) were observed for participants receiving ISL alone or in combination with other ART in any study.
- ISL dose-dependent decreases from baseline were observed in mean total lymphocyte counts and lymphocyte subset (CD4+ T-cell, CD8+ T-cell, B-cell) counts, with greater decreases observed at the higher ISL doses administered QW (20 mg) and QM (60 mg) compared with QD (0.75 mg) administration.
  - In VS participants in MK-8591A-017 and MK-8591A-018 receiving DOR/ISL 100 mg/0.75 mg QD, mean percent changes from baseline were observed in total lymphocyte (-10.6% and -8.4%, respectively), CD4+ T-cell (-0.68% and +0.87%, respectively), CD8+ T-cell (-8.2% and -7.4%, respectively), and B-cell (-4.4% and 8.6%, respectively) counts at Week 48.
  - In VS participants in MK-8591-013 receiving ISL 20 mg + MK-8507 100 to 400 mg QW, mean percent changes from baseline were observed in total lymphocyte (-15.1% to -30.9%), CD4+ T-cell (-7.6% to -28.1%), CD8+ T-cell (18.1% to -32.8%), and B-cell (-36.8% to -46.3%) counts were observed at Week 24.

  - In participants with low risk of HIV-1 infection receiving ISL 60 or 120 mg QM for PrEP, the on-treatment mean decreases from baseline in total lymphocyte count were -21.3% and -35.6% at Week 24, respectively.

- Stabilization of the decreases from baseline in mean total lymphocyte count and lymphocyte subset counts observed for the DOR/ISL 100 mg/0.75 mg QD program occurred between Weeks 48 and 72, depending on the lymphocyte subset.
- Decreases from baseline in mean total lymphocyte count and lymphocyte subset counts were not associated with increased incidence of infection.
- A return toward baseline in lymphocyte and lymphocyte subset counts has been observed across the ISL clinical development program. However, a full recovery was not observed by 24 weeks after stopping ISL. The most robust data on recovery of lymphocyte counts available at this point was from the studies involving administration of ISL QW (20 mg) and QM (60-120 mg), as detailed below. Data on recovery to baseline following discontinuation of DOR/ISL 100 mg/0.75 mg QD in VS adults (MK-8591A-017 and -018) are not yet available.
- Approximately 6 months after discontinuation of ISL 20 mg QW in adult VS participants (MK-8591-013), among those with ≥30% decrease in total lymphocyte or CD4+ T-cell counts at their last on-treatment measurement and at least 1 follow-up result, 10/40 (25%) and 15/32 (47%) participants demonstrated an increase in total lymphocyte and CD4+ T-cell counts, respectively, to within 10% of baseline.
- Approximately 5 months after discontinuation of ISL 60 mg QM in adults at risk of HIV-1 infection, 43 (29.9%) of the 144 participants in MK-8591-022 and MK-8591 024 with a ≥30% decrease in total lymphocyte count at the last on-treatment visit demonstrated an increase in total lymphocyte counts to within 10% of baseline.

Overall, the evaluation of data from across the ISL clinical programs to date suggest that the decreases in mean total lymphocyte and lymphocyte subset counts are ISL dose-dependent with lower doses less likely to cause decreases. A new FDC of DOR/ISL containing a 0.25 mg dose of ISL will be evaluated in the current study. In the dose-ranging phase of MK-8591-011 (Part 1 and Part 2 through Week 72), participants who received ISL 0.25 mg QD had changes in total lymphocyte and CD4+ T-cell counts comparable to those observed for participants in the DOR/3TC/TDF comparator group. The results of modeling analyses of ISL exposure-effect predict no meaningful decreases in total lymphocyte or CD4+ T-cell counts with the 0.25 mg daily dose of (see Section 4.3). To mitigate any risk, close monitoring and discontinuation criteria (Sections 1.3.3, 7.1, and 8.11.5) for individuals who experience significant decreases in lymphocytes are included in the protocol.

BIC/FTC/TAF is currently an approved InSTI-based single-tablet regimen for the treatment of HIV-1 infection in patients naïve to ART or to replace the current ART regimen in those who are virologically suppressed. Refer to approved labeling for detailed benefit-risk information on BIC/FTC/TAF.

Additional details regarding DOR can be found in the local product label. Details regarding ISL and DOR/ISL can be found in the accompanying IB.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

The following objectives will be evaluated in participants ≥18 years of age who are infected with HIV-1 and naïve to antiretroviral therapy.

Primary Objective	**Primary Endpoint**
To evaluate the antiretroviral activity of DOR/ISL compared to BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48 **Hypothesis (H1):** DOR/ISL is non-inferior to BIC/FTC/TAF, as assessed by the percentage of participants with HIV 1 RNA <50 copies/mL at Week 48. A margin of 10 percentage points is used to define non-inferiority	HIV-1 RNA
To evaluate the safety and tolerability of DOR/ISL compared with BIC/FTC/TAF as assessed by review of the accumulated safety data through Week 48	Adverse events Adverse events leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
To evaluate the antiretroviral activity of DOR/ISL compared with BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA <50 copies/mL at Week 96 and Week 144	HIV-1 RNA
To evaluate the antiretroviral activity of DOR/ISL compared with BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA <200 copies/mL at Week 48, Week 96, and Week 144	HIV-1 RNA
To evaluate the immunologic effect of DOR/ISL compared with BIC/FTC/TAF, as assessed by the mean change from baseline in CD4+ T-cell count at Week 48, Week 96, and Week 144	CD4+ T-cell count
To evaluate the development of viral drug resistance in participants who receive DOR/ISL and in those who receive BIC/FTC/TAF	Viral resistance-associated substitutions

To evaluate the effect of DOR/ISL compared with BIC/FTC/TAF on weight, as assessed by the mean change from baseline to Week 48, Week 96, and Week 144 Hypothesis (H2): DOR/ISL is superior to BIC/FTC/TAF as assessed by lower mean increase from baseline in weight at Week 48 Hypothesis (H3): DOR/ISL is superior to BIC/FTC/TAF as assessed by lower mean increase from baseline in weight at Week 96	Weight
To evaluate the safety and tolerability of DOR/ISL compared with BIC/FTC/TAF as assessed by review of the accumulated safety data through Week 144	Adverse events Adverse events leading to discontinuation of study intervention
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate the effects on body composition, fasting lipid and metabolic profiles, renal function, and inflammation of DOR/ISL compared with BIC/FTC/TAF, as assessed by the mean change from baseline to Week 48, Week 96, and Week 144 in these parameters	Body composition, BMD, radiological markers, and laboratory markers
To evaluate the effect of DOR/ISL compared with BIC/FTC/TAF on total lymphocyte count at Week 48, Week 96, and Week 144	Total lymphocyte count
To describe PROs (assessing HRQoL and HIV symptoms) for participants who receive DOR/ISL compared with BIC/FTC/TAF at Week 48 and Week 96	EQ-5D-5L and HIV-SI/SDM
To evaluate the pharmacokinetics of ISL when administered as a component of DOR/ISL	Pharmacokinetic values, e.g. AUC, Cmax, and C24

To evaluate the long-term antiretroviral activity of DOR/ISL in participants initially randomized to Group 1 and the antiretroviral activity of a switch to DOR/ISL in participants initially randomized to Group 2, as assessed by the percentage of participants with: - HIV-1 RNA ≥50 copies/mL - HIV-1 RNA <50 copies/mL - HIV-1 RNA <200 copies/mL in those enrolled in the open-label extension	HIV-1 RNA
To evaluate the long-term immunologic effect of DOR/ISL, as assessed by mean changes in CD4+ T-cell count over time in participants enrolled in the open-label extension	CD4+ T-cell count
To evaluate the long-term effect of DOR/ISL on total lymphocyte count in participants enrolled in the open-label extension	Total lymphocyte count
To evaluate the development of viral drug resistance to DOR/ISL in the open-label extension	Viral resistance-associated substitutions
To evaluate the long-term safety and tolerability of DOR/ISL, as assessed by review of the safety data accumulated in participants enrolled in the open-label extension	Adverse events Adverse events leading to discontinuation of study intervention
To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanism of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study	Germline genetic variation and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, active-controlled, multisite, double-blind study to evaluate the antiretroviral activity, safety, and tolerability of DOR/ISL QD in TN participants with HIV-1. The active control selected for this study is the 3-drug combination of BIC/FTC/TAF QD with demonstrated antiretroviral activity against HIV-1 in TN patients.

The study consists of a screening period of up to 45 days and blinded treatment period (base study) of 144 weeks with participants receiving either DOR/ISL or BIC/FTC/TAF, followed by an optional open-label study extension (OLE) of up to 96 weeks with participants continuing on or switching to DOR/ISL (Figure 1).

Base Study

A total of approximately 500 participants will be randomized, stratified by screening HIV-1 RNA level (≤100,000 copies/mL, >100,000 copies/mL) and screening CD4+ T-cell count (<200 cells/mm^3, ≥200 cells/mm^3), in a 1:1 ratio into 1 of 2 treatment groups (Figure 1).

- Group 1 (n = approximately 250): DOR/ISL (taken with matching placebo to BIC/FTC/TAF) on Day 1 through Week 144.

- Group 2 (n = approximately 250): BIC/FTC/TAF (taken with matching placebo to DOR/ISL) on Day 1 through Week 144.

Initial enrollment will be limited to those with screening HIV-1 RNA levels ≤100,000 copies/mL until the Sentinel Cohort Week 24 futility assessment is completed; see details below.

All participants will receive 144 weeks of assigned blinded therapy in the base study. Participants who complete the last visit in the base study (Week 144) will be given an option to receive open-label DOR/ISL until it is commercially available (Section 6.7). Study intervention will be extended open-label for participants who become pregnant on treatment and consent to continue study intervention (DOR/ISL or BIC/FTC/TAF in the base study or open-label DOR/ISL in the OLE) as specified in Sections 1.3.4 and 8.11.6.

Clinical site personnel and participants will remain blinded through Week 144 while Sponsor personnel will remain blinded through Week 48. Efficacy and safety laboratory test results, including HIV-1 RNA, will remain unmasked throughout the study. Viral resistance data will remain masked to the Sponsor through Week 48 and to site personnel and participants through Week 144. At Week 144, all participants and site personnel will be unblinded.

Any participants with clinically significant confirmed viremia (Section 4.2.1.1.2), will be assessed for development of viral drug resistance and discontinued from study intervention per the SoA (Section 1.3.2) and Section 7.1.

Participant safety and efficacy data will be monitored by an independent eDMC throughout the study per timing and milestones specified in the eDMC charter (Section 10.1.4) and summarized here:

- Periodic Safety and Efficacy Reviews:

  The eDMC will review accumulating efficacy and safety data at regular intervals throughout the study duration. Decisions regarding study continuation will be made based on the eDMC review and in consultation with the Sponsor.

- Sentinel Cohort Week 24 Futility Assessment:

  A minimum of the first 30 participants enrolled in each treatment group who reach Week 24 and have available HIV-1 RNA data, inclusive of participants who discontinue study treatment prior to Week 24 due to clinically significant confirmed viremia will be identified as the Sentinel Cohort. An external unblinded statistician will monitor participant status. An efficacy futility assessment (which will hereafter be referred to as the "Sentinel Cohort Week 24 futility assessment") will be conducted by an external unblinded statistician. All available efficacy data for all the eligible participants enrolled by that time will be reviewed. Decisions regarding study continuation will be made based on the eDMC review of the Sentinel Cohort Week 24 futility assessment and in consultation with the Sponsor.

- Other Ad Hoc Safety and Efficacy Reviews:

  In addition to the periodic safety and efficacy reviews and the Sentinel Cohort Week 24 futility assessment, the eDMC will also review accumulating efficacy and safety data at an ad hoc meeting if either of the following occur (as monitored and assessed by the external unblinded statistician):

  - In the Sentinel Cohort (prior to completion of the Sentinel Cohort Week 24 futility assessment):
    >3 participants in the DOR/ISL treatment group meet the definition for confirmed virologic rebound or incomplete virologic response
    (Section 4.2.1.1.2).
  - Following enrollment of the Sentinel Cohort:
    >10% of participants in the DOR/ISL treatment group meet the definition for confirmed virologic rebound or incomplete virologic response
    (Section 4.2.1.1.2).

Sponsor will not be aware if an ad hoc meeting is called unless the eDMC recommends changes to the study.

Enrollment will be capped up to a maximum of 180 participants prior to the availability of the Sentinel Cohort Week 24 futility assessment. All participants enrolled prior to the availability of these results must have a screening HIV-1 RNA level ≤100,000 copies/mL. Following the Sentinel Cohort Week 24 futility assessment and communication of study

continuation by the eDMC to the Sponsor, participants with a screening HIV-1 RNA level >100,000 copies/mL may be enrolled.

Open-Label Study Extension (OLE)

At Week 144, participants who meet criteria in Section 8.11.2.3 and consent to enter the OLE will continue (Group 1) or switch to (Group 2) open-label DOR/ISL up to Week 240, or until it is commercially accessible (whichever comes first). Procedures to be followed upon exiting the OLE are outlined in Section 6.7.

Consistent with global HIV-1 treatment guidelines [Food and Drug Administration (CDER) 2015] [European AIDS Clinical Society 2021] the OLE consists of in-clinic visits every 6 months to assess maintenance of virologic suppression, CD4+ T-cell count, and tolerability. Group 2 (BIC/FTC/TAF) participants who switch to DOR/ISL at Week 144 will have a follow-up visit at Week 148 to assess for continued viral suppression and tolerability 4 weeks after the switch, in accordance with HIV-1 treatment guidelines. Where local treatment guidelines require visits more frequently than every 6 months, these are permitted and should be conducted by the primary investigator and/or the treating physician.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

Base Study

The randomized, active-controlled, non-inferiority study design is consistent with the FDA CDER 2015 Guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment [Food and Drug Administration (CDER) 2015] and is considered appropriate for a study population with HIV-1 who are naïve to ART. Small differences in virologic efficacy, emergence of resistance, and loss of tolerability or safety may be detected in TN patients prior to 48 weeks of treatment, particularly for therapies with largely comparable characteristics. Therefore, an efficacy and safety outcome through 48 weeks is aligned with current regulatory guidance [Food and Drug Administration (CDER) 2015], and the primary efficacy and safety analyses will occur after 48 weeks of treatment with DOR/ISL or BIC/FTC/TAF. The blinded treatment (base study) duration is 144 weeks to allow for collection of long-term comparative efficacy and safety data for DOR/ISL vs BIC/FTC/TAF. Participants and investigators remain blinded for the duration of comparative data collection to minimize potential bias.

Open-Label Extension (OLE)

The primary rationale for the OLE is to provide access to DOR/ISL until it is commercially accessible. Participation in the OLE is optional and allows eligible participants who are deriving benefit from treatment in the DOR/ISL group to continue DOR/ISL and avoid interruption of treatment. The OLE also allows participants assigned to the comparator to have the option to switch to DOR/ISL at the completion of the base study in accordance with

standard practice in HIV trials. The OLE will also allow for long-term efficacy and safety data collection for DOR/ISL.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 HIV-1 RNA Measurements

Plasma HIV-1 RNA <50 copies/mL is a well-established, clinically meaningful endpoint and is the primary efficacy endpoint in this study. Clinical studies of antiretroviral agents in multiple drug classes have demonstrated that virologic suppression of HIV-1 RNA to <50 copies/mL reflects a clinically relevant standard used across development programs for antiretroviral therapies and in clinical practice [Vandenhende, M. A., et al 2015]. Suppressing HIV-1 RNA to <50 copies/mL preserves the immune system and minimizes the risk of opportunistic infections and disease progression.

The secondary efficacy endpoint of plasma HIV-1 RNA <200 copies/mL corresponds to a clinically relevant threshold, with values ≥200 copies/mL indicating an increased risk of development of resistance.

4.2.1.1.2 Definition of Clinically Significant Confirmed Viremia

For the purpose of managing participants in this study, clinically significant confirmed viremia is defined as:

- **Virologic Rebound**: Two consecutive (4 weeks [±1 week] apart) occurrences of HIV-1 RNA ≥200 copies/mL after achieving HIV-1 RNA <50 copies/mL at any time during the study,

  or as

- **Incomplete Virologic Response**: Two consecutive (4 weeks [±1 week] apart) occurrences of HIV-1 RNA ≥200 copies/mL at or after Week 24 in the absence of previous suppression of HIV-1 RNA to <200 copies/mL*

  *Except for participants who exhibit consistent clinically appropriate decline in HIV-1 RNA, but remain ≥200 copies/mL. These participants derive benefit from continued treatment and may continue in the study upon Sponsor consultation with additional monitoring. If HIV-1 RNA is >200 copies/mL at Week 48 and confirmed 4 weeks (±1 week) later, the participant must be discontinued from study intervention.

There is currently no global standard for the definition of low-level viremia, and the predictive implication of such low-level viremia is uncertain [Vandenhende, M. A., et al 2015] [Charpentier, C., et al 2014]. The US Department of Health and Human Services guidelines currently define virologic failure as confirmed HIV RNA ≥200 copies/mL and do not recommend that low-level viremia (detectable HIV RNA <200 copies/mL) automatically result in treatment modification or more frequent virologic monitoring [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022]. PLWH with HIV-1 RNA ≥50

and <200 copies/mL have a lower risk of developing resistance compared with those with HIV-1 RNA ≥200 copies/mL. Therefore, study participants with HIV-1 RNA ≥50 and <200 copies/mL should continue on their current regimen, with HIV-1 RNA levels monitored as outlined in Section 8.2.2.3.

An HIV-1 RNA value of ≥50 copies/mL following suppression of HIV-1 RNA to <50 copies/mL at any time during the study or an HIV-1 RNA >200 copies/mL at or after Week 24 in the absence of previous suppression to <200 copies/mL must be confirmed and requires further management, as described in Section 8.2.2.2.

If a participant has an HIV-1 RNA value ≥50 copies/mL, a reflex HIV-1 RNA test will be conducted by the central laboratory on the same plasma sample obtained at that visit, if available. For management of participants see Section 8.2.2.

4.2.1.2 Safety Endpoints

Safety evaluations will include physical examinations (including vital signs) and laboratory tests (eg, hematology, TBNK, chemistry, and urinalysis) performed per the SoA in Section 1.3. AEs will be evaluated at each visit and assessed according to the guidelines in Section 8.4 and Appendix 3. Participants may be asked to return for unscheduled visits to perform additional safety monitoring.

Due to decreases in total lymphocyte counts observed in clinical studies with DOR/ISL (100 mg/0.75 mg), these parameters will be evaluated as exploratory endpoints at Weeks 48, 96, and 144 and the OLE.

4.2.1.3 Weight, Body Composition, and Radiological and Laboratory Markers

The study will evaluate changes from baseline at Week 48, Week 96, and Week 144 in weight, body composition, and radiological and laboratory markers in the treatment groups to evaluate the impact of DOR/ISL on the following parameters per the SoA (Section 1.3):

Weight

Compared with other antiretroviral classes, use of integrase inhibitors in patients with HIV-1 has been associated with greater increases in body weight [Hill, A., et al 2019]. The mean change in weight will be compared between participants taking DOR/ISL and those taking BIC/FTC/TAF (Section 8.3.9.4).

Body Composition

Decreases in BMD and lipodystrophy (peripheral and central fat redistribution) have been reported in patients with HIV-1 receiving ART [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022] [McComsey, G. A., et al 2018], particularly with the use of certain NRTIs. Key indicators of body composition (including waist-to-hip ratio and DEXA assessments) will be measured (Sections 8.3.9.4 and 8.3.9.5, respectively).

Inflammation

Causes of persistent inflammation and thrombotic activity in patients with HIV-1 remain topics of debate and ongoing research [Baker, J. V., et al 2011] [Knudsen, T. B., et al 2016] [Wang, H., et al 2016]; thus, key indicators of inflammation will be measured (Section 8.3.9.1).

Renal Function

Decreases in renal function have been noted with the use of certain NRTIs [U.S. Prescribing Information 2019]; thus, key indicators of renal function will be measured (Section 8.3.9.2).

Fasting Lipid and Metabolic Profiles

Some antiretrovirals have been associated with lipid abnormalities [U.S. Prescribing Information 2017]; thus, key indicators of fasting lipid profiles will be measured (Section 8.3.9.3).

Insulin resistance has been reported with certain antiretroviral therapies [Carr, A., et al 1998]. It is associated with metabolic complications including diabetes, cardiovascular disease, fatty liver, and weight gain [Vazquez-Carrera, M. 2016]. Fasting insulin and glucose will be measured to calculate HOMA-IR (Section 8.3.9.3). HbA1C will be measured to evaluate glycemic control over time.

Leptin and adiponectin will be measured as exploratory measurements of metabolic function [Taylor, E. B. 2021]. These are established markers for lipid metabolism and energy metabolism utilization to be explored against BIC/FTC/TAF, particularly as more data emerge about the metabolic effects of InSTIs.

4.2.1.4 Pharmacokinetic Endpoints

PK samples collected from all participants as described in the SoAs (Section 1.3) and Section 8.6 will be used to evaluate PK concentrations of ISL, and as appropriate, PK-efficacy, PK-pharmacodynamic, and PK-AE relationships of ISL. PK values including AUC, C_{max}, and C_{24} will be explored.

4.2.1.5 Patient-Reported Outcomes

PROs can provide unique information on the impact of HIV infection and its treatment from the patient's perspective as some domains are difficult to observe or are subjective and best collected through patient report. HIV infection and its treatment can impair HRQoL. Symptom burden associated with HIV treatment has decreased with improvements in ART regimens, but persists despite viral suppression and immunologic recovery. In conjunction with efficacy and safety, PRO data may help clinicians and patients with informed decision-making on appropriate ART regimens. HTA authorities in many countries recommend patient perspective data and HRQoL measurement as part of their drug benefit evaluations. HRQoL data are used to estimate health utility scores, which inform cost-effectiveness model analysis.

The study will include 2 self-administered PRO questionnaires. The EQ-5D-5L, a generic HRQoL questionnaire, will provide a simple descriptive profile and index value for health status used to compute health utilities for health economic analyses. The HIV-SI/SDM is a 20-item HIV disease-specific questionnaire designed to assess the prevalence and burden of adverse effects associated with ART regimens. The PRO questionnaires will be completed up to Week 96 at the time points specified in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3).

4.2.1.6 Planned Exploratory Biomarker Research

4.2.1.6.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug ADME; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to understand study disease or related conditions.

See Section 8.8.1.

4.2.1.7 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

The 3-drug regimen of BIC/FTC/TAF will be the comparator in this study. BIC/FTC/TAF has been approved by the EMA and the FDA for use in TN patients and is a recommended initial regimen for most people infected with HIV-1 [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022].

Matching placebo will be used to provide a robust evaluation of the safety and tolerability profile of DOR/ISL by maintaining double-blind, double-dummy therapy through Week 144.

4.2.3 Rationale for the Selected Participant Population

The rationale for the participant population selected for this study is as follows:

- **Antiretroviral TN Participants**: The current paradigm of lifelong treatment for HIV creates the desire for safe, simple regimens. While the standard of care has been a 3-drug regimen for the treatment of HIV, there is growing interest in 2-drug regimens for a TN population. This study is designed to evaluate the antiretroviral efficacy and safety of DOR/ISL QD compared to the 3-drug regimen of BIC/FTC/TAF QD in TN participants using a randomized, double-blind, active-controlled non-inferiority design. The combination of ISL+DOR is being studied in a randomized Phase 2 multicenter study of HIV-1 infected antiretroviral TN adult participants (MK-8591-011). At Week 24, all ISL+DOR treatment groups demonstrated potent antiretroviral activity comparable to DOR/3TC/TDF as demonstrated by the primary efficacy endpoint, the proportion of participants with HIV-1 RNA <50 copies/mL. Efficacy was observed to be comparable for the 0.25 mg and 0.75 mg doses of ISL at Week 48 and Week 72 time points.

4.2.4 Rationale for Collecting Race and Ethnicity Data

The differential effect on the safety and efficacy based on any demographic parameter, including race or ethnicity, cannot be predicted when evaluating a new investigational drug. Therefore, it is important to collect race and ethnicity data to ensure that there is not a differential effect based on these parameters and to gain assurance the results observed in the clinical study will be representative of the drug's use in a broader population. As an example, non-Caucasian females and males were found to have higher plasma concentrations of EFV (an NNRTI) than their Caucasian counterparts, indicating an increased risk of EFV-induced toxicity in non-Caucasian persons [Burger, D., et al 2005]. As another example, among PLWH in the US, those of African heritage have been found to be less likely to maintain virologic suppression compared to other groups, and the factors contributing to this remain to be elucidated [Weintrob, A. C., et al 2009] [Ribaudo, H. J., et al 2013]. Thus, subgroup analyses on race and ethnicity will be performed to better understand how these parameters may influence clinical outcome and toxicity.

4.2.5 Rationale for Collecting Gender Identity Data

Transgender people, defined as those whose gender identities and/or expressions differ from the sex assigned to them at birth, have a high prevalence and incidence of HIV infection

globally [Poteat, T., et al 2016]. When considering HIV treatment, the WHO considers transgender people to be a separate key population because of their specific health needs and high vulnerability [Department of HIV/AIDS 2015]. Data will be collected in this study to assess clinical outcomes in the transgender population.

4.2.6 Rationale for Infant Safety Data Collection

Follow-up through 1 year of age for infants born to participants who become pregnant while receiving study intervention provides the ability to monitor growth and development as well as potential adverse effects that may be associated with prenatal drug exposure. Growth parameters (ie, length, weight, and head circumference) within normal range at approximately 1 year of age are key noninvasive indicators that a serious congenital malformation caused by in utero drug exposure is unlikely.

4.2.7 Rationale for Continuing Study Intervention During Pregnancy

The US Department of Health and Human Services guidelines currently advise that persons who become pregnant while receiving ART for HIV should continue their regimen provided it is safe, well tolerated, and effective at virologic suppression since altering the regimen could cause an increase in viral load [Panel on Treatment of Pregnant Women with HIV Infection and Prev 2018]. Nonclinical developmental and reproductive toxicology studies did not identify any teratogenicity or other clinically relevant concerns that would preclude continued dosing of DOR/ISL in eligible participants who become pregnant and who consent to continue study intervention (where allowed by local regulations, health authorities, and ethics committees and as appropriate based on available data/local standard of care guidelines) (Sections 8.1.1.3 and 8.11.6).

There are no clinical data currently available to support breastfeeding by participants who are receiving DOR/ISL or BIC/FTC/TAF.

See Appendix 7 for Country-specific requirements.

4.2.8 Rationale for Collecting Alcohol and Tobacco Use

Both alcohol use and tobacco use are associated with poor health outcomes. A significant number of PLWH die of cardiovascular disease, non-AIDS malignancies, and liver disease, which are associated with alcohol and tobacco use [Farahani, M., et al 2017]. New or worsening existing clinical signs/symptoms, including abnormal laboratory test results, can be influenced by alcohol and/or tobacco use. The prospective collection of these data, occurring once prior to randomization and annually thereafter, is intended to assist in the medical management of study participants to help better understand comorbid disease outcomes as well as the primary investigators' determination of the likelihood that the study intervention may have caused a potential AE (ie, causality assessment). With smoking and alcohol use as known risk factors for cardiovascular disease and liver disease, collection of data to monitor these risks among participants is essential to comprehensive safety monitoring and better understanding the safety profile of the IMP(s) against the background of comorbid conditions.

4.3 Justification for Dose

IQ (C_{trough}/IC_{50}) is the ratio of drug exposure to viral susceptibility. In a Phase 1b proof of concept study (MK-8591-003), single doses as low as 0.5 mg ISL showed robust antiretroviral activity at 7 days postdose; this low single dose provided an IQ threshold of 5 for wild-type HIV-1 virus. Simulations suggest the ISL-TP trough concentrations achieved 24 hours after a single dose of 0.25 mg ISL provide IQs of ~11 for wild-type virus and ~2 for M184V virus. After 3 daily doses of 0.25 mg ISL, IQs increase to ~29 for wild-type virus and ~6 for M184V/I virus. Steady-state concentrations at later time points will produce even higher IQs, as ISL-TP reaches steady-state at ~28 days. These simulations support the selection of 0.25 mg ISL in combination with 100 mg DOR in TN participants with HIV-1.

In the Phase 2 clinical study (MK-8591-011), 3 daily doses of ISL (0.25, 0.75, and 2.25 mg) were evaluated in combination with DOR (100 mg) + 3TC for 24 weeks and subsequently with DOR alone through Week 48. All 3 doses of ISL with DOR ± 3TC demonstrated potent antiretroviral activity comparable with the comparator (DOR/3TC/TDF) at Week 24 (as a 3-drug regimen, ISL+DOR+3TC) and at Week 48 (as a 2-drug regimen, ISL+DOR). Overall, no ISL dose response for efficacy was observed. Graphical analysis of steady-state ISL-TP trough concentrations and response at Week 48 from MK-8591-011 showed no trends in exposure-response. The totality of these efficacy data supports the conclusion that the dose range studied (0.25 to 2.25 mg daily) is on the plateau of the dose-response curve. MK-8591-011 also demonstrated that all doses of ISL studied, when administered with DOR + 3TC or DOR alone, had a favorable AE and tolerability profile through Week 144, comparable with that of DOR/3TC/TDF. In the dose-ranging phase of MK-8591-011 (Part 1 and Part 2 through Week 72), participants who received ISL 0.25 mg QD had similar changes in total lymphocyte counts and comparable increases in CD4+ T-cell counts to those in the DOR/3TC/TDF group. See Section 2.2.3 for additional DOR/ISL background information.

DOR will be administered at the approved dose of 100 mg. This dose has been studied in Phase 1 to Phase 3 studies in TN and virologically suppressed participants with HIV-1 and was selected based upon favorable efficacy, safety, tolerability, and metabolic profiles as confirmed in the Phase 3 studies [Orkin, C., et al 2019] [Molina, J. M., et al 2018] [Johnson, M., et al 2019]. Of note, in MK-1439A-024 and MK-1439A-030 [Johnson, M., et al 2019] [Wong, A., et al 2019], among 32 participants infected with HIV-1 harboring the NNRTI resistance mutations K103N, Y181C, and/or G190A at study entry, all achieved virologic suppression following 48 weeks of treatment with DOR/3TC/TDF (24 of 32 participants had been virologically suppressed on PI or InSTI regimens and 8 had been TN). Across the Phase 2 and Phase 3 DOR/ISL program, viral resistance was observed for 2 TN participants who had received DOR/ISL in study MK-8591A-020.

In summary, a 0.25 mg dose of ISL in combination with 100 mg DOR is predicted to have an acceptable safety profile and provide concentrations that will demonstrate potent antiretroviral activity against both wild-type virus and most common NRTI- and NNRTI-resistant variants.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

Early study termination may also be considered if the Sentinel Cohort meets the futility criteria as assessed at the Sentinel Cohort Week 24 futility assessment or after review of accumulating efficacy and safety data by the eDMC (Section 9.7).

5 STUDY POPULATION

Participants with HIV-1 ≥18 years of age who are naïve to ART will be enrolled in this study.

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Note: Screening laboratory tests (local or central) should be obtained within 45 days prior to randomization to verify study eligibility. Resistance testing will be performed by the central laboratory as part of the screening assessments unless resistance testing results are obtained from a local laboratory with a validated assay ≤90 days prior to Day 1.

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Is HIV-1 positive with plasma HIV-1 RNA ≥500 copies/mL at screening.

Note: A single repeat of the plasma HIV-1 RNA screening test will be allowed, provided results are available within the 45-day screening window.

Note: Participants enrolled prior to the availability of the Sentinel Cohort Week 24 futility assessment results must have HIV-1 RNA ≤100,000 copies/mL at screening.

2. Is naïve to ART defined as having received no prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection.

Note: The use of any PrEP or PEP prior to diagnosis of HIV-1 infection is permissible up to 1 month prior to screening. The use of cabotegravir, lenacapavir, or any other long-acting HIV prevention regimen at any time is prohibited.

Demographics

3. Is an individual of any sex/gender, at least 18 years of age, at the time of providing documented informed consent.

Participants Assigned Female Sex at Birth

4. A participant assigned female sex at birth is eligible to participate if not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a POCBP
  OR

- Is a POCBP and:
  - Uses an acceptable contraceptive method, or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 6 weeks after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
  - Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.4 and Appendix 2.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

5. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the study without participating in FBR.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Has HIV-2 infection.
2. Has hypersensitivity or other contraindication to any of the components of the study interventions as determined by the investigator.

3. Has a diagnosis of an active AIDS-defining opportunistic infection within 30 days prior to screening.
4. Has active HBV infection (defined as HBsAg-positive or HBV DNA-positive).

   Note: Past HBV infection or previous HBV vaccination (defined as HBsAg-negative and Anti-HBs-positive) is not an exclusion criterion.
5. Has chronic HCV infection (detectable HCV RNA) with laboratory values consistent with cirrhosis (serum albumin <2.8 g/dL or INR >1.7 or platelets <100 x 10^9 cells/L).

   Note: Treatment with direct-acting antiviral therapies is not exclusionary.
6. Has a history of malignancy ≤5 years prior to providing documented informed consent except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or cutaneous Kaposi's sarcoma.
7. Has a history or current evidence of any condition (including active tuberculosis infection), therapy, laboratory abnormality, or other circumstance (including drug or alcohol use or dependence) that might, in the opinion of the investigator, confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate.

Prior/Concomitant Therapy

8. Has been treated for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1, including, but not limited to, the following: adefovir, TDF, TAF, FTC, or 3TC.
9. Is taking or is anticipated to require systemic immunosuppressive therapy, immune modulators, or strong and moderate CYP3A inducers (or any other prohibited therapies outlined in Section 6.5) from 45 days prior to Day 1 through the study treatment period.

   Note: Time-limited courses of corticosteroids (eg, for asthma exacerbation) are allowed.

Prior/Concurrent Clinical Study Experience

10. Is currently participating in or has participated in a clinical study and received (or is receiving) an investigational compound or device from 45 days prior to Day 1 through the study treatment period.

    Note: Participants who have had prior exposure to ISL (any duration any time prior to Day 1) are excluded.

    Note: BIC/FTC/TAF is not considered investigational in countries where it has received health authority approvals, regardless of commercial availability.

    Note: Concurrent participation in observational or noninterventional studies may be permitted and must be discussed with the Sponsor prior to enrollment and through the study duration.

Diagnostic Assessments

11. Has a documented or known virologic resistance to any approved HIV-1 reverse transcriptase inhibitor, or any study intervention, as demonstrated by any of the following resistance substitutions (according to the 2017 IAS-USA drug resistance mutations list) [Wensing, A. M., et al 2017]:
    - FTC: K65R/E/N or M184I/V.
    - TAF: K65R/E/N or K70E.
    - NRTI resistance substitutions: T69insert, Q151M, or 3 or more of thymidine analogue-associated mutations (M41L, D67N, K70R, L210W, T215F/Y, K219E/Q).
    - DOR resistance substitutions: V106A/M, V108I, Y188L, H221Y, P225H, F227C/L/V, M230I/L, L234I, P236L, or Y318F.

    Note: This exclusionary list is for the purpose of this study and includes major (or primary) DOR resistance substitutions, but not substitutions that are minor and found as naturally occurring polymorphisms.

    Note: Resistance testing will be performed by the central laboratory as part of the screening assessments unless resistance testing results are obtained from a local laboratory with a validated assay ≤90 days prior to Day 1.

12. Has exclusionary laboratory values within 45 days prior to Day 1 as listed in Table 1:

    Note: A single repeat of a laboratory screening test will be allowed for test results that are unexpected based on documented prior laboratory results, but the repeat test results must be available within the 45-day screening window.

Table 1 Laboratory Exclusion Criteria

Laboratory Assessment	**Exclusionary Values**
ALP	>3 × ULN
AST	>5 × ULN
ALT	>5 × ULN
Calculated CrCL	≤30 mL/min based on the Cockcroft-Gault equation (Appendix 8)
Hemoglobin	<9.0 g/dL (female) or <10.0 g/dL (male)
ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCL=creatinine clearance; ULN=upper limit of normal.	

Other Exclusions

See Appendix 7 for Country-specific requirements.

5.3 Lifestyle Considerations

There are no lifestyle restrictions.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (study interventions provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2.

Country-specific requirements are noted in Appendix 7.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Group 1	Experimental	doravirine/ islatravir	Drug	Tablet	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Day1 to Week 144	Test Product	IMP	Provided centrally by Sponsor
Group 1	Experimental	Placebo to bictegravir/ emtricitabine/ tenofovir alafenamide	Drug	Tablet	0 mg	0 mg QD	Oral	Day 1 to Week 144	Placebo	IMP	Provided centrally by Sponsor
Group 1	Experimental	doravirine/ islatravir	Drug	Tablet	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Week 144 up to Week 240	Test Product	IMP	Provided centrally by Sponsor
Group 2	Active Comparator	bictegravir/ emtricitabine/ tenofovir alafenamide	Drug	Tablet	50 mg/ 200 mg/ 25 mg	50 mg/ 200 mg/ 25 mg QD	Oral	Day 1 to Week 144	Comparator	IMP	Provided centrally by Sponsor
Group 2	Active Comparator	Placebo to doravirine/ islatravir	Drug	Tablet	0 mg	0 mg QD	Oral	Day 1 to Week 144	Placebo	IMP	Provided centrally by Sponsor
Group 2	Experimental	doravirine/ islatravir	Drug	Tablet	100 mg/ 0.25 mg	100 mg/ 0.25 mg	Oral	Week 144 up to Week 240	Test Product	IMP	Provided centrally by Sponsor

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; QD=once-daily.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Study intervention will be extended open-label for participants who become pregnant on treatment and consent to continue study intervention (DOR/ISL or BIC/FTC/TAF) as specified in Sections 1.3.4 and 8.11.6.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

All placebos were created by the Sponsor to match the active product.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to Group 1 (DOR/ISL and placebo to BIC/FTC/TAF) or Group 2 (BIC/FTC/TAF and placebo to DOR/ISL), respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

- Screening HIV-1 RNA level (≤100,000 copies/mL, >100,000 copies/mL)
- Screening CD4+ T-cell count (<200 cells/mm^3, ≥200 cells/mm^3)

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. DOR/ISL and BIC/FTC/TAF will be packaged identically relative to their matching placebos so that the blind is maintained.

As described in Section 4.1, clinical site personnel and participants will remain blinded through Week 144, while Sponsor personnel will remain blinded through Week 48. Sponsor personnel involved in performing and reviewing results of the Week 48 analysis will be unblinded at the time of the Week 48 database lock.

Participants and all field and study-site personnel will remain blinded throughout the study.

Restricted Sponsor personnel involved in performing and reviewing PK data may be unblinded before the Week 48 database lock to allow timely completion of population PK modeling. No personnel directly associated with study conduct will be unblinded before the Week 48 database lock. Before granting select study personnel access to unblinded PK data, an official memo detailing unblinding procedures will be generated per Sponsor SOP. This memo will list the names of the personnel who will have access to unblinded PK data before the Week 48 database lock.

6.4 Study Intervention Compliance

Participants should be instructed to bring the study intervention bottles to their visits. At each visit, the number of tablets remaining in the study packaging will be counted, reviewed, and recorded. The results will be used to assess participant compliance. If a discrepancy is noted, the investigator/study coordinator must discuss the discrepancy with the participant and the

explanation must be documented. All participants should be reminded of the importance of taking their study intervention as instructed for the entire duration of the study.

Decisions to temporarily withhold study intervention because of an AE or other reason(s) will be reviewed on a case-by-case basis by the investigator.

Interruptions from the protocol-specified treatment plan that are expected to be ≥7 consecutive days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

- When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets/capsules, etc, during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.
- A record of the number of DOR/ISL/placebo and BIC/FTC/TAF/placebo tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded in the CRF.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication or vaccination. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

The Sponsor Clinical Director should be contacted if there are any questions regarding prior or concomitant therapy.

Prior and concomitant therapies listed in Table 3 are not permitted from 45 days prior to Day 1 through the study intervention period. Table 3 is not comprehensive, and the investigator should use medical judgment when assessing a participant's prior and concomitant therapy(ies). The Sponsor Clinical Director or designee should be contacted if

there are any questions about a therapy not on the list below or regarding potential DDI interactions with a specific treatment that the participant may plan to receive.

In instances where the local product circular for DOR or BIC/FTC/TAF is more restrictive with regard to prohibited (ie, contraindicated or not recommended) therapies, the local product circular supersedes this section. In addition, the recommendations below for coadministration with BIC/FTC/TAF should be followed for all participants receiving blinded study intervention:

- For participants taking metformin, close monitoring is recommended (BIC/FTC/TAF may increase metformin levels). Sucralfate and inhibitors of P-gp and/or BCRP should be used with caution. Refer to the local product circular for BIC/FTC/TAF for additional information.

For participants taking medications or oral supplements containing polyvalent cations (eg, Mg, Al, Ca, Fe) during the base study, study intervention should be taken either 2 hours before or 6 hours after taking any polyvalent cation-containing medicine.

Concomitant medications (ie, dofetilide) prohibited due to interaction with BIC/FTC/TAF in the base study are allowed during the OLE.

Table 3 Prohibited Therapies

Strong and moderate CYP3A inducers	Including, but not limited to: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin Enzalutamide Rifabutin Rifampin Rifapentine Mitotane St. John's Wort Herbal remedies *(only those that are strong or moderate CYP3A inducers)* Modafinil Bosentan Nafcillin Lumacaftor Metamizole

Nonstudy ART	All nonstudy antiretrovirals including treatments for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1 *The use of any long-acting HIV prevention regimen (eg, cabotegravir, lenacapavir) is not permitted at any time.* *Time-limited course of ritonavir as a PK enhancer is permissible (eg, nirmatrelvir/ritonavir for the treatment of COVID-19)*
Immunosuppressive therapies	Immune therapy agents, immune modulators, or other systemic immunosuppressive therapy, including interferon-based treatment for hepatitis *Time-limited courses of corticosteroids (eg, for asthma exacerbation) are permitted.*
Investigational agents	All nonstudy investigational agents including devices Any agents (eg, vaccine or therapy for COVID-19) approved locally for Emergency Authorized Use, or equivalent, that do not have a known or anticipated DDI with study intervention, are permitted.
Antiarrhythmics	Dofetilide
Additional prohibited therapies based on ISL	Pentostatin
ART=antiretroviral therapy; COVID-19=coronavirus disease caused by severe acute respiratory syndrome coronavirus 2; CYP3A=cytochrome P450 3A; DDI=drug-drug interaction; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus type 1; ISL=islatravir.	

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

No dose modification of DOR/ISL or BIC/FTC/TAF is allowed during the base study (see Section 4.3 for dose justification).

6.7 Intervention After the End of the Study

If DOR/ISL is commercially accessible, participants in both groups who complete the Week 144 visit should follow end of treatment procedures in Section 1.3.1 and transition to commercially accessible DOR/ISL or local standard of care, as clinically appropriate.

If DOR/ISL is not commercially accessible, participants in both groups who complete the Week 144 visit will be provided the option to receive DOR/ISL in an OLE until Week 240 or until DOR/ISL becomes commercially accessible (whichever comes first). Participants who do not enter the OLE should follow Section 1.3.1 and transition to local standard of care, as clinically appropriate.

The OLE ends at Week 240. Provided DOR/ISL development continues, there will be a future mechanism (eg, prelicense patient access program) beyond the end of the study for

participants to continue receiving DOR/ISL until it becomes commercially accessible. The details of this mechanism will vary per local regulations.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Clinical site personnel and participants will remain blinded through Week 144, while Sponsor personnel will remain blinded through Week 48.

6.9 Standard Policies

At the close of the study after unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the comparator's product to provide the following advice:

"You have participated in a study conducted by the Sponsor. This letter is to advise you that you were among those who received a look-alike tablet created by the Sponsor to resemble the drug/vaccine BIKTARVY 50/200/25 mg (BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) as much as possible. You did not receive the active drug/vaccine BIKTARVY 50/200/25 mg (BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) as manufactured by Gilead Sciences, Inc."

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

Discontinuation of study intervention does not represent withdrawal from the study.

Participants who discontinue study intervention before completion of the protocol-specified treatment period may continue to be monitored in the study as specified in Section 8.11.3, unless the participant has withdrawn from the study (see Section 7.2).

A participant must be discontinued from study intervention for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- After prolonged study intervention interruption that prohibits restarting study intervention (per Section 6.4).
- The participant has a medical condition or personal circumstance, which in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.
- The participant is continuing their pregnancy (see Section 8.11.6) and any of the following criteria apply:
  - The participant does not provide consent to continue study intervention during pregnancy or to allow communication with and record review by their obstetric provider.
  - Continuation of study intervention during pregnancy is not allowed per local regulations (see Appendix 7 for country-specific requirements).
  - Viral load has not been adequately suppressed (HIV-1 RNA <50 copies/mL) for the past 3 months.
  - CD4+ T-cell count is <200 cells/mm^3.

- The participant chooses to breastfeed.
  Note: Study intervention can continue until breastfeeding is initiated.
- The participant has clinically significant confirmed viremia as defined in Section 4.2.1.1.2. Do not discontinue prior to consultation with the Sponsor when feasible.

- The participant has an SAE or Grade 4 laboratory AE assessed by the investigator to be related to study intervention AND is life-threatening or results in prolonged hospitalization.
- After Week 24, a participant must be discontinued from study intervention and managed per Section 8.11.5 if any of the criteria in Table 4 are confirmed, unless the investigator has reason to believe there is an alternative explanation for the result (eg, COVID-19). In this instance, consultation between the investigator and Sponsor is required when evaluating the participant for discontinuation. See Appendix 7 for Country-specific requirements.

Table 4 CCI

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7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent or assent, when applicable, may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent or assent, when applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The amount of blood collected from each participant over the duration of the study is provided in Appendix 2.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.1.3 Consent for Continuation of Study Intervention During Pregnancy

Upon confirming that a participant is pregnant (Section 8.3.4) and eligible to continue study intervention (Section 8.11.6) (see Appendix 7 for Country-specific requirements), the investigator or medically qualified designee and the participant will discuss the potential benefits and risks of continuing (or discontinuing) study intervention (Section 8.11.6). A separate consent is required to continue study intervention (regardless of treatment group or whether participant has been unblinded to treatment assignment) in participants who become pregnant (Section 8.11.6.1). Open-label study intervention (DOR/ISL or BIC/FTC/TAF, depending on study intervention assignment at the time of the confirmatory pregnancy test) will be provided to participants in either treatment group who consent to continue study intervention during pregnancy. Note, participants who become pregnant are not allowed to switch study intervention at any time during the pregnancy. The investigator or medically qualified designee will explain the consent to the participant, or the participant's legally acceptable representative, answer all questions, and obtain documented informed consent

before continuing study intervention. A copy of the informed consent will be given to the participant.

8.1.1.4 Consent for Postnatal Infant Safety Data Collection Through One Year of Age

Once a pregnancy is confirmed to be continuing, the investigator or medically qualified designee will explain the infant safety data collection consent to the participant, or the participant's legally acceptable representative, answer all questions, and obtain documented informed consent to collect any data related to infant safety. A copy of the informed consent will be given to the participant.

8.1.1.5 Consent for Open-Label Extension

The investigator or medically qualified designee will explain the consent for the OLE to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to OLE. A copy of the informed consent will be given to the participant. The participant must be informed that, once DOR/ISL becomes commercially accessible, they will discontinue from the study.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history should include information pertaining to the diagnosis of HIV-1 and AIDS (if applicable) and year diagnosed. If the participant has been previously diagnosed with any AIDS-defining conditions or CD4+ T-cell count <200 cells/mm^3, the condition as well as a corresponding medical history of AIDS must be recorded. In addition, participants' history of smoking and alcohol consumption should be obtained and recorded on the appropriate eCRF.

For participants assigned female sex at birth, childbearing potential should be assessed. Menstrual history, contraceptive use, and recent sexual activity should be reviewed for POCBP to exclude potential or early, undiagnosed pregnancy prior to and on Day 1.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant within 45 days before the first dose of study intervention. All prior HIV medication use, regardless of timing, including PrEP, must be recorded.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication(s), if any, taken by the participant during the study.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any individual who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.7 Assignment of Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after treatment randomization. Once a randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 randomization number.

8.1.8 Study Intervention Administration

Study intervention will be provided per Table 2 and dispensed through the IRT system at visits indicated in the SoA (Sections 1.3.1, 1.3.4, and 1.3.5).

Study intervention should begin within 24 hours of randomization (ie, on the day of randomization after all pretreatment assessments, as specified in the SoA, are performed or as soon as possible after randomization).

8.1.8.1 Timing of Dose Administration

The first dose of study intervention will be administered at the study site on Day 1. Following Day 1, all study interventions will be taken together QD by the participant at approximately the same time each day without regard to food.

From Day 1 to Week 144, participants will take 2 tablets of blinded study intervention (1 tablet from each of 2 containers):

[1] Bottle A: DOR/ISL or placebo to DOR/ISL; and

[2] Bottle B: BIC/FTC/TAF or placebo to BIC/FTC/TAF). If more than 1 Bottle A is dispensed at a time, the participant is instructed to use all of the study intervention in 1 Bottle A before opening another Bottle A.

From Week 144 up to Week 240, participants will take 1 tablet of open-label study intervention (DOR/ISL) QD at approximately the same time each day.

If a participant misses a dose of any of the study interventions, the following guidance should be followed:

- If ≤12 hours from the missed dose, the missed dose should be taken, and the normal dosing schedule resumed.
- If >12 hours from the missed dose, the missed dose should be skipped, and the normal dosing schedule resumed. The participant should not double the next dose to compensate for what has been missed.

For participants who become pregnant and consent to continue their assigned study intervention, see Section 8.11.6.1.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the base study should have an Early Discontinuation of Treatment visit performed per the SoA (Section 1.3.1) and should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.1.

Participants who end study intervention while in the OLE (after Week 144 and prior to Week 240) should have a Discontinuation of Study Treatment visit performed per the SoA (Section 1.3.5) and should be followed as outlined in the SoA and Section 8.11.3.2.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the Early Discontinuation of Treatment visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

Participants who discontinue study intervention due to specified decreases in total lymphocyte counts or CD4+ T-cell counts should be managed per Section 8.11.5 and Table 4 until their counts recover. Participants who become pregnant and discontinue study intervention should be managed per Section 8.11.6.2.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 HIV-1 RNA

Plasma HIV-1 RNA quantification will be performed at the central laboratory using a PCR assay with a lower limit of detection of <50 copies/mL (Appendix 2).

8.2.2 Management of Participants With Viremia

When viremia (HIV-1 RNA ≥50 copies/mL) is detected (Section 4.2.1.1.2) following suppression of HIV-1 RNA to <50 copies/mL at any time during the study or at or after Week 24 in the absence of previous suppression to <200 copies/mL, the investigator should query the participant regarding adherence to study intervention, intercurrent illness, or recent immunization. All cases of viremia must be confirmed, and **the participant should continue to take the full assigned dosage of study intervention while awaiting confirmation.**

If a participant has an on-treatment HIV-1 RNA value ≥50 copies/mL following suppression of HIV-1 RNA to <50 copies/mL at any time during the study or has a value of ≥50 copies/mL at or after Week 24, a reflex HIV-1 RNA test will be conducted by the central laboratory on the same plasma sample obtained at that visit, if available. Management of participants should be based on reflex HIV-1 RNA results if available.

- If the reflex HIV-1 RNA result is <50 copies/mL, no further action is required.

- If the reflex HIV-1 RNA result is ≥50 copies/mL, or there is insufficient sample available for reflex testing, the participant will be asked to return to the clinic in 4 (± 1) weeks for Viremia Confirmation (see Section 8.2.2.1 and the SoA Section 1.3.2).

Allow approximately 4 weeks after resolution of illness, treatment nonadherence, or other treatment interruption before drawing these confirmation samples.

Immunization: Redraw at least 4 weeks following any immunization, during which time the participant should continue to receive the assigned dosage of study intervention(s) without interruption.

8.2.2.1 Viremia Confirmation

At the Viremia Confirmation visit:

- If the HIV-1 RNA value is ≥50 copies/mL, a reflex HIV-1 RNA test will be conducted by the central laboratory on the same plasma sample obtained at that visit, if available.
- If the reflex HIV-1 RNA result is <50 copies/mL, no further action is required.
- If the HIV-1 RNA is ≥200 copies/mL (on both primary and reflex results, if available) on consecutive visits 4 (±1) weeks apart, then clinically significant viremia is confirmed, and the participants will be assessed for potential discontinuation from study intervention (Sections 7.1 and 8.2.2.2).

For participants with confirmed low-level viremia, see Section 8.2.2.3.

8.2.2.2 Participants With Clinically Significant Viremia (≥200 Copies/mL)

Participants with confirmed HIV-1 RNA of ≥200 copies/mL (Section 4.2.1.1.2) (following suppression to <50 copies/mL or at or after Week 24 in the absence of previous suppression to <200 copies/mL) will be assessed for development of viral drug resistance (Section 8.2.2.4) and discontinuation from study intervention (Section 7.1). Consult with Sponsor prior to discontinuation or unblinding. If it is determined that study intervention discontinuation is appropriate, "Early Discontinuation of Treatment" and "End of Treatment Follow-Up" visit procedures should be completed (Sections 1.3.2 and 8.11.3) and the participant managed by the investigator per local standard of care.

8.2.2.3 Participants With Low-Level Viremia (≥50 and<200 Copies/mL)

Study participants with confirmed HIV-1 RNA of ≥50 copies/mL and <200 copies/mL should continue study intervention and all regularly scheduled study visits during which HIV-1 RNA levels will be monitored per the SoA (approximately every 3 months). Additional visits may be conducted to monitor HIV-1 RNA levels more frequently than every 3 months, if appropriate, after discussion with the Sponsor.

Investigators should use their clinical judgment regarding the most appropriate clinical management of participants, if more stringent local guidelines apply, and may contact the

Sponsor's Clinical Director to discuss questions on clinical management of individual participants.

8.2.2.4 HIV-1 Viral Drug Resistance Testing

Participants with confirmed virologic rebound or incomplete virologic response (Section 4.2.1.1.2), or who discontinue study intervention for another reason and have HIV-1 RNA ≥200 copies/mL at the time of discontinuation, will be assessed for development of viral drug resistance.

Samples will be collected for genotypic and phenotypic HIV-1 viral drug resistance testing per the SoA (Section 1.3) and used to assess resistance-associated substitutions and viral susceptibility as applicable during the study.

If clinically significant viremia is confirmed, the plasma sample from the Viremia Confirmation visit will be the primary sample used for HIV-1 genotypic and phenotypic testing.

8.2.3 T and B Lymphocyte and Natural Killer Cell (TBNK) Profile

A TBNK panel, including CD4+ T-cell count, will be performed as specified in Appendix 2. Refer to Section 8.11.5 for guidance on management of participants with decreased total lymphocyte counts or decreased CD4+ T-cell counts. TBNK panel assessments that are considered exploratory do not need to be evaluated by the investigator.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in Appendix 2.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at the visits specified in the SoA (Section 1.3). The full physical examination will include examination of body systems including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system.

Height will also be measured and recorded as specified in the SoA (Section 1.3). Height measurements should be taken using a stadiometer (recommended, but not required). Participants should remove their shoes and stand as tall and straight as possible.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. This

examination will be sign- and symptom-directed and based on the participant's condition and circumstances. The investigator should note any changes in the participant's condition (body systems) since the last examination, not precluding examination of any body system(s) as clinically indicated.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.1 Weight

Weight will be measured and recorded at the visits specified in the SoA (Section 1.3). Participants should remove their shoes and wear a single layer of clothing at each measurement.

8.3.2 Vital Signs

Vital signs will be measured after approximately 5 to 10 minutes of rest and will include temperature, pulse, RR, and systolic and diastolic BP.

Note: Oral temperatures are preferred, but not required.

8.3.3 Electrocardiograms

A local 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3.1). Results must be available prior to randomization. Sites are to use an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Clinically significant findings must be documented in the source documents and captured in the appropriate eCRF.

If an ECG is performed for any medical reason while the participant is on study intervention or during the follow-up period, any clinically significant changes compared with the baseline ECG must be appropriately reported as per requirements of safety reporting.

8.3.4 Confirmation of Contraception and Pregnancy Testing

POCBP are required to confirm heterosexual abstinence or use of contraception to prevent pregnancy during the base study, optional OLE, and for 42 days after the last dose of study intervention administration (in the base study or OLE). POCBP will be tested for pregnancy at each visit as outlined in Section 1.3, Section 5.1, and Appendix 5.

Participants should be asked at study visits per the SoA to verbally confirm heterosexual abstinence or use of contraception since the prior visit, according to the Contraceptive Guidance in Appendix 5. Confirmation should be noted in the source documents for each visit.

Urine pregnancy test kits will be provided by the central laboratory to perform locally at each visit. In the event of a positive urine or indeterminate pregnancy test result, serum pregnancy testing for confirmation of the pregnancy must be performed by the central laboratory. A

duplicate serum pregnancy test may be sent to a local laboratory to expedite results per investigator discretion. Positive urine pregnancy test results (except those from the screening visit), that have been confirmed by serum testing must be reported to the Sponsor using the appropriate eCRF within 24 hours of learning of the event. If a participant becomes pregnant, refer to Section 8.11.6.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during participation in the study.

8.3.5 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Table 19 in Appendix 2, must be conducted in accordance with the operations/laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 42 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.
- If laboratory values indicate specified decreases in total lymphocyte count or CD4+ T-cell count (Table 4), participants must be managed per Section 8.11.5. TBNK panel assessments that are considered exploratory do not need to be evaluated by the investigator (Section 8.2.3 and Table 18).

8.3.6 HBV Assessments

All eligible participants must be HBsAg-negative at screening. Individuals who are anti-HBc-positive and HBV DNA-positive at screening are excluded. Individuals who are anti-HBc-positive but HBV DNA-negative at screening are eligible to enroll. All participants will have hepatitis B serology with reflex HBV DNA testing at screening and at Weeks 48, 96, 144 during the base study (per the SoA Section 1.3.1) and Weeks 192 and 240 during the OLE (per the SoA Section 1.3.5).

Investigators should pay close attention to changes from baseline in ALT, AST, bilirubin, and ALP. Participants who are confirmed to be HBsAg-positive or have confirmed quantifiable HBV DNA after randomization may be unblinded and managed by the investigator per local standard of care and/or referred for management of their HBV infection. Participants may be allowed to continue study intervention if deemed medically appropriate upon consultation with the Sponsor.

In the OLE, Group 2 participants with anti-HBc-positive results should be monitored for possible HBV reactivation; samples will be taken to monitor for HBsAg and HBV DNA (per the SoA Section 1.3.5). In the OLE, participants who are confirmed to be HBsAg-positive or have confirmed quantifiable HBV DNA will be managed by the investigator per local standard of care and/or referred for management of their HBV infection.

8.3.7 HCV Assessment

HCV serology will be performed at screening and if the individual is HCV antibody positive, reflex testing will be performed for HCV RNA to assess study eligibility. Repeat screening if indicated per local standard of care.

8.3.8 Tobacco and Alcohol Assessments

Information on tobacco/vaping and alcohol use by participants will be collected and recorded as specified in the SoA (Section 1.3.1).

8.3.9 Exploratory Clinical Marker Assessments

The following samples will be collected as specified in the SoA (Section 1.3.1) and Appendix 2 (Table 18) for exploratory evaluation of markers of inflammation, renal function, body composition, and energy and metabolism:

- Blood for inflammatory markers (Section 8.3.9.1)
- Blood for renal function markers (Section 8.3.9.2)
- Urine for renal function markers (Section 8.3.9.2)
- Blood for fasting lipid and metabolic profiles (sample collected as part of Chemistry panel [Section 8.3.5]) (Section 8.3.9.3)
- Blood for energy and metabolism markers (Section 8.3.9.3)

8.3.9.1 Inflammation

Blood samples will be collected to evaluate the inflammatory and thrombotic response as measured by the following laboratory markers, as indicated in the SoA (Section 1.3.1) and Appendix 2 (Table 18):

- IL-6
- D-dimer
- sCD-163
- hs-CRP

8.3.9.2 Renal Function

Urine and blood samples will be collected to evaluate renal function as measured by key indicators, such as the following potential analyte and calculations, as indicated in the SoA (Section 1.3.1) and Appendix 2 (Table 18):

- Urine: albumin, protein, beta-2-microglobulin/creatinine ratio, and retinol binding protein/creatinine ratio
- Serum: cystatin-C and creatinine clearance

Equations for CrCl calculation (Cockcroft-Gault) and eGFR calculation are in Appendix 8.

8.3.9.3 Fasting Lipid and Metabolic Profiles

Participants will be asked to fast for at least 8 hours prior to visits where blood will be taken to measure insulin, glucose, HDL-C, LDL-C, TGs, TC, and non-HDL-C, as indicated in the SoA (Section 1.3). HOMA-IR will be calculated (SoA Section 1.3 and Appendix 2).

Note: Participants with type 1 diabetes mellitus and participants who are pregnant should not fast and should not have insulin levels or lipids tested. Participants with type 2 diabetes mellitus taking medications that may result in hypoglycemia should delay their diabetic medication while fasting and take it as soon as possible after testing.

HbA1c should be collected for all nonpregnant participants irrespective of fasting or nonfasting status; HbA1c should not be collected in pregnant participants.

Blood to evaluate energy and metabolism, as measured by adipokines, leptin and adiponectin, will be collected as indicated in the SoA (Section 1.3.1).

8.3.9.4 Waist and Hip Measurements

Participants should be asked to stand erect, relaxed and should not hold in their stomach during measurements. Waist circumference will be measured midway between the iliac crest and the lower rib margin. Hip circumference will be measured at the intertrochanteric level. Measurements should be taken with a stretch-resistant measuring tape held parallel to the floor. Waist-to-hip ratios will be calculated as waist (cm)/hip (cm) circumferences.

BMI will be calculated by the Sponsor using weight and height measurements taken as specified in the SoA (Section 1.3).

Waist and hip measurements should not be performed for pregnant participants.

8.3.9.5 DEXA Assessments

DEXA images to monitor fat distribution and BMD should be collected from all participants/sites willing and able to have the test performed and according to country law (Appendix 7, Section 1.3). These participants will undergo total body DEXA scans for BMD of the spine and hip as well as peripheral and trunk fat. Participants will not be excluded from participation in the study if unwilling/unable to have DEXA images performed.

Only those participants who are confirmed eligible to be randomized will undergo DEXA images for BMD of the spine and hip as well as peripheral and trunk fat. For Day 1 (baseline), DEXA images should be performed after eligibility is confirmed and may be performed up to 45 days after randomization. The DEXA images at subsequent visits should be performed ±45 days of the scheduled visit. Only participants with valid baseline DEXA images should have DEXA images performed at subsequent visits as indicated in the SoA (Section 1.3). If scans cannot be performed within the protocol-specified time window or at a site approved by the central imaging reader, consultation is required between the investigator and the Sponsor to confirm the clinical appropriateness of performing further testing.

DEXA images will be evaluated by a central imaging reader. For clinical management of the participant, the DEXA images should be concurrently reviewed and interpreted locally by a qualified individual. Clinically significant findings noted in the local interpretation of the baseline DEXA images should be recorded in the participant's medical history. Clinically significant findings noted in the local interpretation of the DEXA images during the treatment period should be recorded appropriately. Refer to the Site Imaging Manual for additional details regarding DEXA procedures including participant preparation instructions to be considered prior to DEXA imaging.

DEXA scans should not be performed on pregnant participants.

8.3.10 Administration of Patient Questionnaires

Participants will complete 2 PRO questionnaires as specified in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3). Participants are to complete the questionnaires on their own at the site on paper during the appropriate study visit (per the SoA) prior to being seen by the investigator, discussing any medical conditions with the study personnel, or receiving any medical results.

The questionnaires should not be administered to participants who are unable to complete questionnaires unassisted, or for whom native language translations of the questionnaires are unavailable. The questionnaires are to be administered in the following order: EQ-5D-5L and HIV-SI/SDM.

The participant responses to questionnaires will be entered into the appropriate eCRF by site staff according to data entry guidelines.

PROs questionnaires are not administered after Week 96.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment; if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention randomization through study duration, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside the period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

For infants born to participants who become pregnant and consent to infant safety data collection, SAEs (including perinatal HIV-1 infection) occurring through 1 year of age must be reported by the investigator to the Sponsor within 24 hours of learning of the event.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 5 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified AE Collection Period**	**Reporting Period: After the Protocol-specified AE Collection Period**	**Time Frame to Report Events and Follow-up Information to Sponsor**
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified AE Collection Period	**Reporting Period:** After the Protocol-specified AE Collection Period	Time Frame to Report Events and Follow-up Information to Sponsor
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
Potential or confirmed DILI events (requires regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI/confirmed DILI – to be reported as an ECI and SAE with OME criteria in the absence of other serious criteria	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report if: - requiring regulatory reporting	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event (unless an SAE)
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless an SAE)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event (unless an SAE)

Potential DILI/DILI=drug-induced liver injury; ECI= event of clinical interest; NSAE=nonserious adverse event; OME=Other Important Medical Event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. SAEs and other reportable safety events, including potential or confirmed DILI events, pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). The investigator will also make every attempt to follow nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding (spontaneously reported to the investigator or their designee), that occurs in a participant during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing that the fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

This section is not applicable to the study.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

ECIs for this study include:

All potential or confirmed DILI events will be reported to the Sponsor as both an ECI and SAE, with OME criteria in the absence of other SAE criteria, within 24 hours of learning of the event. Potential or confirmed DILI events are defined as:

- an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN, **and**
- an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN, **and**
- at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
  *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

Additional ECIs for this study that require reporting to the Sponsor within 24 hours of learning of the event include:

1. During the first 48 weeks of study intervention, an elevated AST or ALT laboratory value that is greater than 10× the ULN

2. During the first 48 weeks of study intervention, an elevated AST or ALT laboratory value that is greater than 3× the ULN with an elevated total bilirubin laboratory value that is greater than 2× the ULN

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than twice the prescribed dose of study intervention (3 or more tablets of a single study intervention) in a day.

No specific information is available on the treatment of overdose.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

8.6.1 Blood Collection for Plasma ISL

Venous blood samples will be collected for measurement of ISL. The Sponsor may assess these samples for DOR PK as needed. Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

Investigational PK samples will be collected from all participants (except during pregnancy or when the participant has been unblinded and is known to be taking BIC/FTC/TAF) as outlined in the SoA (Section 1.3). Investigational ISL PK samples will be collected irrespective of time of last dose. The time of last dose of study intervention taken prior to the sample collection will be verbally reported to study staff by the participant and recorded in the appropriate source documentation. Analysis of these samples will be performed by the Sponsor as needed.

Population PK samples will be collected from all participants as outlined in Table 6. The time of the doses of study interventions taken prior to the sample collection will be verbally reported to study staff by the participant and recorded in the appropriate source documentation.

At the Week 4 visit participants that routinely take their study intervention during the day, will have a predose and postdose sample collected per Table 6. Participants that routinely take their study intervention in the evening should continue to do so, and will have only 1 sample collected at the Week 4 visit irrespective of the time of the last dose.

For participants receiving DOR/ISL (base study or OLE) who become pregnant and consent to continue DOR/ISL, PK samples will be collected to evaluate DOR and ISL concentration levels per Table 7 in Section 8.11.6.1.1.

Table 6 Collection of Population PK Samples

Study Visit	Sample Time Relative to Dose of Study Intervention[a]
Day 1	Predose
Week 4	Daytime dosing: Predose AND within 0.5 to 2 hours postdose OR Evening dosing: Only 1 sample irrespective of time of last dose
Week 8	Irrespective of time of last dose
Week 16	Irrespective of time of last dose
Week 24	Irrespective of time of last dose
Week 48	Irrespective of time of last dose

PK=pharmacokinetic(s).
[a] Time of last dose and time of PK sample collection must be documented for all samples.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3):

- Blood for Genetic Analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Sample collection, storage and shipment instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.9 Future Biomedical Research Sample Collection

If the participant has provided documented informed consent for FBR, FBR-specific specimen collections, including leftover specimens, will be obtained. The following specimens will be included for FBR:

- Whole blood for FBR
- Leftover extracted DNA for future research
- Leftover main study plasma from HIV-1 RNA quantification
- Leftover main study plasma from HIV-1 viral drug resistance samples

8.10 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Screening/Rescreening

8.11.1.1 Screening

Prior to randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Participants are expected to enroll as soon as possible after eligibility is confirmed. In cases of unexpected delays in receiving repeat screening laboratory results, a screening period of up to 45 days is allowed.

8.11.1.2 Rescreening

If the screening window has been exceeded, participants are allowed to rescreen following approval from the Sponsor. Once a participant has started the rescreening process, a new screening period (ie, an additional ≤45-day window) will begin, during which time screening procedures may be repeated.

The following assessments must be repeated for participants who are rescreened:

- Vital signs, weight, and directed physical examination
- Review medical history and prior/concomitant medications for new information
- All laboratory assessments (includes serum and/or urine hCG pregnancy testing for POCBP), with the exception of resistance testing; resistance (central or local) sample collected ≤90 days prior to Day 1 is acceptable
- Review of AEs

If the informed consent form has been updated, participants should be reconsented before rescreening. If no updates have been made, documented informed consent obtained during the original screening period should be reviewed with the participant and a verbal reconsent to continue in the study should be documented.

If a participant had a Day 1 ECG during the original screening period, it should be repeated (at the Day 1 visit or within 7 days prior).

If a participant had a baseline Day 1 DEXA scan during the original screening period and >45 days have elapsed, the Day 1 DEXA should be repeated. If ≤45 days have elapsed since the DEXA, it is not necessary to repeat the Day 1 DEXA scan during rescreening.

8.11.2 Treatment Period

All procedures and their timing should be completed as per the SoA (Section 1.3).

8.11.2.1 Fasting

Visits at Day 1 and Weeks 24, 48, 72, 96, 120, and 144 require that participants fast (ie, do not consume any food or beverages except water) for at least 8 hours prior to the visit. The investigator/study coordinator must remind participants to fast prior to these visits and must confirm with participants their fasting status and record in the appropriate source documentation and laboratory requisition(s).

Note: Participants with type 1 diabetes mellitus and participants who are pregnant should not fast and should not have insulin levels or lipids tested. Participants with type 2 diabetes mellitus taking medications that may result in hypoglycemia should delay their morning dose of diabetic medication while fasting and take it after the blood draw for testing.

8.11.2.2 End of Base Study Week 144 Visit

Procedures for the blinded treatment period (base study) are to be conducted per the SoA (Section 1.3.1). Week 144 represents the end of the base study and the end of blinded treatment administration. Prior to the end of the base study/Week 144 visit, site staff should proactively discuss the potential plan for treatment to facilitate either a transition to locally available ART or DOR/ISL in the optional OLE. For participants entering the OLE, the Week 144 visit serves as the first visit of the OLE. Open-label DOR/ISL will be dispensed and participants will follow procedures as outlined in the SoA (Section 1.3.5).

Participants who are pregnant at Week 144 will be managed per Section 8.11.6 (SoA 1.3.4).

Participants who have laboratory values at the Week 144 visit that meet any of the discontinuation criteria for specified decreases in total lymphocyte counts or CD4+ T-cell counts (Section 7.1 and Table 4) must be managed per Section 8.11.5.

8.11.2.3 Optional OLE (Week 144 up to Week 240)

If DOR/ISL is not commercially accessible by Week 144, participants in both treatment groups will be provided the option to enroll in an OLE to receive DOR/ISL up to Week 240 or until DOR/ISL becomes commercially accessible (whichever comes first) per the SoA (Section 1.3.5).

A participant entering the OLE must meet all of the following criteria:

- Is considered, in the opinion of the investigator, to benefit from continued study participation.
- Understands the procedures in study extension and provides documented informed consent to enter the study extension.
- Does not meet any of the discontinuation criteria (see Section 7.1).

Once DOR/ISL becomes commercially accessible, participants should be contacted and informed that they will complete the Discontinuation of Treatment (OLE) visit and transition to DOR/ISL or other commercially accessible ART per local standard of care at their next study visit (or sooner at the PI's discretion). In rare circumstances and with permission of the Sponsor, study participation may be extended for a limited amount of time to ensure all participants are able to secure continued treatment access in the commercial market before exiting the study.

The Week 240 visit represents the end of the OLE and the end of the study.

Manage participants with viremia per Section 8.11.4 (SoA 1.3.2). Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 (SoA Section 1.3.3). Participants who are pregnant will be managed per Section 8.11.6 (SoA Section 1.3.4).

8.11.3 Participants Who Discontinue Study Intervention

A participant must be discontinued from study intervention for any of the reasons listed in Section 7.1.

When it is determined that discontinuation from study intervention is appropriate, the participant should have both an Early Discontinuation of Treatment visit (Section 8.11.3.1) and an End of Treatment Follow-Up visit (Section 8.11.3.2) conducted. After the visit procedures are completed, the participant will be withdrawn from the study and managed for treatment of their HIV-1 infection per local standard of care.

Guidance for management of participants who discontinue study intervention due to confirmed decreased CD4+ T-cell count (Section 7.1 and Table 4) or decreased total lymphocyte counts is provided in Section 8.11.5.

Participants who discontinue study intervention due to other reasons but have laboratory values at the Early Discontinuation of Treatment visit that meet any of the discontinuation criteria for specified decreases in total lymphocyte count or CD4+T-cell count (Section 7.1 and Table 4) must be managed per Section 8.11.5. Country-specific requirements are noted in Appendix 7.

8.11.3.1 Discontinuation of Treatment

Participants who discontinue study intervention due to specified decreases in total lymphocyte counts or CD4+ T-cell counts (per Section 7.1) will be managed per Section 8.11.5.

Early Discontinuation (Base Study)

Participants who discontinue study intervention early (prior to Week 144) in the base study for any reason(s) should have an Early Discontinuation of Treatment visit as outlined in the SoA (Section 1.3.1, 1.3.2, or 1.3.3). If discontinuation occurs during the time frame of a scheduled study visit, the assessments for the scheduled visit as well as the Early Discontinuation of Treatment visit should be conducted, however, collection of laboratory samples should not be duplicated.

Discontinuation (OLE)

Participants in the OLE who discontinue study intervention (after Week 144) for any reason(s) or who complete study intervention in the OLE (up to Week 240 or until transition to commercially accessible DOR/ISL) should have a Discontinuation of Treatment (OLE) visit as outlined in the SoA (Section 1.3.5).

8.11.3.2 End of Treatment Follow-Up

Participants who discontinue study intervention for any reason(s) will have an End of Treatment Follow-Up visit 42 days (+7 days) after the last dose of study intervention. Assessments for this visit are outlined in Section 1.3.1, 1.3.2, 1.3.3, and 1.3.5, as applicable.

8.11.4 Viremia Confirmation

If a participant has a viral load of ≥50 copies/mL (confirmed as described in Sections 4.2.1.1.2 and 8.2.2.1) following suppression of HIV-1 RNA to <50 copies/mL at any time during the study or at or after Week 24 in the absence of previous suppression to <200 copies/mL, a Viremia Confirmation visit must be conducted within 4 weeks (±1 week) after the initial HIV-1 viremia, as specified in the SoA (Section 1.3.2). If a scheduled visit is to occur within the timeframe that a participant would return for a Viremia Confirmation visit, the assessments for the scheduled visit should be conducted, and the HIV-1 viral drug resistance sample must be collected. PK will be assessed for both DOR and ISL (from the same sample) at the time of viremia confirmation.

8.11.5 Management of Participants With Specified Decreases in Total Lymphocyte Counts or CD4+ T-cell Counts

To meet the protocol-defined discontinuation criteria in the base study or OLE, participants must have a confirmed total lymphocyte count or CD4+ T-cell count that indicates a specified decrease on 2 consecutive measurements 10 to 14 weeks apart. A minimum interval of 10 weeks between consecutive tests is required to meet discontinuation criteria (unless otherwise specified in Table 4). The confirmation visit must occur within 10 to 14 weeks after the initial decrease, as specified in the SoA (Section 1.3.3) and Table 4. See Appendix 7 for Country-specific requirements.

Repeat testing may be performed sooner at the discretion of the investigator (Appendix 2).

If repeat testing occurs sooner than 10 weeks and shows resolution, results may be used to confirm the resolution, and testing should be resumed per the routine SoA. If repeat occurs sooner than 10 weeks and does not show resolution, discontinuation is not required.

Management of Participants Who Discontinue Study Intervention Due to Specified Decreases in Total Lymphocyte Count or CD4+ T-Cell Count

Participants discontinued from study intervention due to specified decreases in total lymphocyte count or CD4+ T-cell count (Section 7.1 and Table 4; see Appendix 7 for Country-specific requirements) should undergo assessments for the Early Discontinuation of Treatment visit and the End of Treatment Follow-up visit (regardless of treatment assignment) as specified in the SoA (Section 1.3.3). After discontinuation from study intervention, participants will be managed for treatment of their HIV-1 infection per local standard of care. Consult with Sponsor prior to discontinuation or unblinding if the investigator believes there is an alternative explanation for the result (eg, COVID-19). No subsequent monitoring is required for participants in the BIC/FTC/TAF group who meet discontinuation criteria in Table 4.

Monitoring for Participants Receiving DOR/ISL

After completion of the Discontinuation of Treatment visit and the End of Treatment Follow-Up visit (in the base study or OLE), participants who discontinued for confirmed decreases in total lymphocyte count or CD4+ T-cell count (per Table 4), should have monitoring visits every 10 to 14 weeks (Section 1.3.3; see Appendix 7 for Country-specific requirements). Participants should be monitored until the total lymphocyte count or CD4+T-cell count no longer meet the criteria in Table 4 at 2 consecutive visits. If conditions that affect lymphocytes arise during the follow-up monitoring period and are expected to persist, monitoring may be stopped.

Management of Participants Receiving DOR/ISL Who Discontinue Study Intervention Due to Reasons Other Than Decreases in Total Lymphocyte Count or CD4+ T-Cell Count

Participants noted to have their first decreases in total lymphocyte count or CD4+ T-cell count that meet the criteria in Table 4 at the Discontinuation of Treatment visit (base study or

OLE) or at the Week 144 visit only require monitoring as described above if the count declines are confirmed by the End of Treatment Follow-Up visit.

8.11.6 Clinical Management of Participants Who Become Pregnant

If a participant becomes pregnant (confirmed by a positive serum pregnancy test result), the investigator should refer the participant to a local provider for care per local standard of care. The provider should be informed of the participant's study participation by site personnel. See Appendix 7 for Country-specific requirements.

All pregnancies must be followed to completion or termination of the pregnancy by the investigator per Section 8.4.5. Severity assessment of AEs that are pregnancy-related complications should follow guidance provided as part of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017, version 2.1 (Appendix 3) "Addendum 1: Female Genital Grading Table for Use in Microbicide Studies," particularly the section "Complications of Pregnancy."

Participants with a confirmed pregnancy prior to Week 144 should be unblinded by the investigator (Section 8.1.10). Upon Sponsor consultation and approval, unblinding is not required in participants who will not have a continuing pregnancy (ie, pregnancy termination or nonviable pregnancy).

Participants who become pregnant during the study must meet the following criteria to continue study medication:

- CD4+ T-cell count of ≥200 cells/mm^3
- Achieved sustained virologic suppression (HIV-1 RNA <50 copies/mL) for the past 3 months

Participants who become pregnant and do not meet the above criteria must be discontinued from study intervention and transitioned to local standard of care (Section 8.11.6.2).

Upon confirmation of pregnancy by serum testing, the investigator or appropriate designee should discuss the following with the participant:

- The appropriateness of continuing study intervention based on available data and local standard of care guidelines (where allowed by local regulations, health authorities, and ethics committees). For participants receiving BIC/FTC/TAF, the investigator should refer to the local product circular and local guidelines to determine if treatment may be continued. **Documented informed consent must be obtained to continue study intervention regardless of treatment assignment** (Section 8.1.1.3).
- Joining a pregnancy registry (the Antiretroviral Pregnancy Registry), which collects information about the outcome of the pregnancy, if applicable.

Upon confirmation that the pregnancy is continuing, the site will discuss with the participant (per timing at the discretion of the Principal Investigator):

- Intentions for breastfeeding (Section 8.11.6.3)
- Consenting to infant safety data collection per Sections 8.1.1.4 and 8.11.6.4

8.11.6.1 Continuing Study Intervention in Pregnancy

Participants who become pregnant and are eligible to continue study medication during pregnancy and consent to continue their assigned study intervention (Sections 8.1.1.3 and 8.11.6) will be transitioned to open-label study intervention (DOR/ISL or BIC/FTC/TAF) and should complete all remaining protocol-specified visits and procedures per the regular schedule in the applicable SoA (Section 1.3), with the following exceptions:

- Only participants receiving DOR/ISL will have PK samples collected (per the timing in Table 7). Participants in the BIC/FTC/TAF group will not have PK collection.
- DEXA scans will not be performed for either group.
- Participants on DOR/ISL who are pregnant at Week 144 will have the opportunity to continue into the OLE.
- Participants on BIC/FTC/TAF who are pregnant at Week 144 will continue on BIC/FTC/TAF through the postpartum visit and will then complete the study.

Pregnancy visits are to occur at least every 12 weeks (~1 during each trimester and 1 postpartum ≤8 weeks after delivery) in both the base study and the OLE (Sections 1.3.1 and 1.3.4, as applicable). This applies to participants whose pregnancy extends beyond Week 240 (Section 1.3.4). More frequent HIV-1 RNA testing should be performed per local guidelines or as determined by the investigator. If HIV-1 RNA testing is performed in a local laboratory with an approved assay (Section 10.10), the results must be promptly recorded in the appropriate CRF.

For participants receiving study intervention and continuing their pregnancy, prenatal care should be coordinated between the investigator and the local obstetric care provider. The investigator (or designee) is responsible for reviewing records for prenatal care at each study visit and obtaining relevant clinical and laboratory data from the obstetric care provider to monitor the safety and well-being of the mother and fetus. Relevant data obtained by the site should be entered into the appropriate CRF and source documentation.

The participant's medical records will be collected and reviewed by the study site for:

- Clinical safety laboratory assessments
- Pregnancy screening laboratory assessments (for participants on DOR/ISL only) for hepatitis B serology and reflex HBV DNA, if indicated; if local laboratory test results are unavailable, collect central laboratory sample

- Plasma HIV-1 RNA levels
- Results of 2nd trimester ultrasound(s) providing gestational age and anatomic survey
- Any complications associated with the pregnancy
- Outcome of pregnancy
- Information that could indicate congenital abnormalities

For participants who are pregnant at the last regularly scheduled study visit and are eligible to continue study medication during pregnancy (Week 144 in the base study or up to Week 240 in the OLE), their visit schedule will be extended through the duration of the pregnancy to allow assessments through each trimester and postpartum and, as applicable, a 42-day follow-up period with an End of Treatment Follow-Up visit (Section 1.3.4). After completion of the pregnancy the participant will have completed the study after either completing the Postpartum visit (if the participant chooses to breastfeed) or completing the End of Treatment Follow-Up visit (if the participant does not choose to breastfeed and completes the 42-day follow-up period). Participants on DOR/ISL at the completion of their pregnancy will have continued access to DOR/ISL through the OLE, until DOR/ISL becomes commercially accessible per Section 6.7. Participants on BIC/FTC/TAF at the completion of their pregnancy will have their last dispensing of study intervention at their 3rd trimester (Pregnancy 3) visit per the SoA (Section 1.3.4).

8.11.6.1.1 Collection of Population PK Samples During Pregnancy and Postpartum (Participants Continuing DOR/ISL Only)

For participants who continue DOR/ISL, PK samples will be collected at their scheduled visit/pregnancy visit during the 1st, 2nd, and 3rd trimesters and postpartum to evaluate DOR and ISL concentration levels per Table 7. These samples will be used to characterize the PK profile of DOR/ISL during pregnancy. Participants who do not learn of their pregnancy until the 2nd trimester may not have had a PK sample collection during the 1st trimester.

Participants who routinely take their DOR/ISL during the day will have a predose and 2 postdose samples collected per Table 7. Participants who routinely take their DOR/ISL in the evening should continue to do so and will have only 1 sample collected at the 2nd Trimester, 3rd Trimester, and Postpartum visits irrespective of the time of the last dose. Time of last dose and time of PK sample collection must be documented for all samples. The time of last dose of study intervention taken prior to the sample collection will be verbally reported to study staff by the participant and recorded in the appropriate source documentation.

Table 7 Collection of Population PK Samples During Pregnancy and Postpartum

Study Visit	Sample Time Relative to Dose of DOR/ISL[a]
1st Trimester[b]	Daytime dosing: Predose OR Evening dosing: Irrespective of time of last dose
2nd Trimester	Daytime dosing: Predose AND within 0.5 to 2 hours AND within 4 to 6 hours postdose OR Evening dosing: Only 1 sample irrespective of time of last dose
3rd Trimester	Daytime dosing: Predose AND within 0.5 to 2 hours AND within 4 to 6 hours postdose OR Evening dosing: Only 1 sample irrespective of time of last dose
Postpartum[c]	Daytime dosing: Predose AND within 0.5 to 2 hours AND within 4 to 6 hours postdose OR Evening dosing: Only 1 sample irrespective of time of last dose

DOR=doravirine; ISL=islatravir; PK=pharmacokinetic(s).

[a] Time of last dose and time of PK sample collection must be documented for all samples.

[b] Collect at the scheduled 1st Trimester visit after a participant reports gravid status. (May not be collected if participant does not learn of their pregnancy until after the first trimester).

[c] Postpartum visit ≤8 weeks after delivery.

8.11.6.2 Discontinuing Study Intervention for Pregnancy

Participants who become pregnant and discontinue their assigned study intervention should have a Discontinuation of Treatment (base study or OLE) visit per the SoA (Section 1.3.1 or 1.3.5, as applicable). If the decision to discontinue study intervention occurs during the time frame of a scheduled study visit, the assessments for the scheduled visit as well as for the Discontinuation of Treatment visit should be completed. Collection of laboratory samples should not be duplicated. In addition, these participants will have an End of Treatment Follow-Up visit 42 days (+7 days) after the last dose of study intervention.

The investigator (or local HIV care provider, if not the study site) should develop a new treatment plan per local standard of care before discontinuing study intervention to minimize the risk of a gap in combination ART.

8.11.6.3 Participants Who Choose to Breastfeed

A participant who chooses to breastfeed must discontinue study intervention before initiating breastfeeding (Section 7.1) and be followed in the study per Section 8.11.6.2. The investigator (or local HIV care provider, if not the study site) should make every effort to

develop a new treatment plan (per local standard of care) within sufficient time prior to delivery to minimize the likelihood of a gap in ART.

8.11.6.4 Infant Safety Data Collection

For participants who become pregnant while receiving study intervention, or within 42 days after the last dose of study intervention, the data in Section 8.11.6.4.1 should be obtained by the site and entered into the appropriate CRF and source documentation.

Infant SAEs, including perinatal HIV-1 infection, will be collected as per Section 8.4.1 and should be reviewed at the participant's scheduled study visits that occur during this time. Infant safety data collection will be captured if exposure to study intervention occurs during pregnancy.

8.11.6.4.1 Schedule of Activities: Infant Safety Data Collection

Time Point	At Birth[a]	1-Year After Birth[a,b]
Visit Name	NA	Infant Follow-Up-1
Administrative and Safety Procedures		
Infant informed consent		X[c]
Gestational age at birth	X	
Apgar score	X	
Length	X	X
Weight	X	X
Head Circumference	X	X
Directed pediatric examination	X	
Concomitant medications review[d]	X	X
Review Infant SAEs[e]	----------X----------	

HIV=human immunodeficiency virus; NA=not applicable; SAE=serious adverse event.

[a] Data to be collected and entered at the site within 12 weeks of each time point.

[b] If a participant withdraws from the study, data from 1 year after birth should be collected at the time of withdrawal.

[c] Consent for infant safety data collection can be obtained from the mother at any time following confirmation of pregnancy.

[d] Concomitant medications taken by the infant (for SAEs or HIV postpartum prophylaxis).

[e] Collect SAEs, including any congenital anomalies and HIV infection in the infant, per Section 8.4.1 and review at participant's regularly scheduled study visits.

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (eg, those specific to the analyses of PK data, PROs, and FBR) will be documented in separate analysis plans, and safety data collected from the OLE (for those participants who consent to enter the OLE) will be summarized separately using only descriptive statistics.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Phase 3, Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate the Antiretroviral Activity, Safety, and Tolerability of Doravirine/Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in HIV-1 Infected Treatment-Naïve Participants
Treatment Assignment	Approximately 500 participants will be randomly assigned in a 1:1 ratio to either DOR/ISL (Group 1) or BIC/FTC/TAF (Group 2). Randomization will be stratified by screening HIV-1 RNA level (≤100,000 copies/mL, >100,000 copies/mL) and screening CD4+ T-cell count (<200 cells/mm^3, ≥200 cells/mm^3). Clinical site personnel and participants will remain blinded to study intervention assignments through Week 96, while Sponsor personnel will remain blinded through Week 48.
Analysis Populations	Efficacy: FAS, FAS-E, PP, ITT, and Resistance Analysis Subset Safety: APaT, APaT-E
Primary Endpoints	1. Percentage of participants with HIV-1 RNA <50 copies/mL at Week 48 2. Percentage of participants who experience AEs and percentage of participants who discontinue study intervention due to AEs through Week 48
Secondary Endpoints	1. Percentage of participants with HIV-1 RNA <50 copies/mL at Week 96 and Week 144 2. Percentage of participants with HIV-1 RNA <200 copies/mL at Week 48, Week 96, and Week 144 3. Mean change from baseline in CD4+ T-cell count at Week 48, Week 96, and Week 144 4. Viral resistance-associated substitutions 5. Mean change from baseline in weight at Week 48, Week 96, and Week 144 6. General safety and tolerability through Week 144

Statistical Methods for Key Efficacy Analyses	For the primary hypothesis (H1), DOR/ISL will be considered non-inferior to BIC/FTC/TAF if the lower bound of the 2-sided multiplicity-adjusted 95% CI for the between-treatment difference in the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48 (DOR/ISL minus BIC/FTC/TAF) is greater than -10 percentage points (non-inferiority margin). The CI will be based on the stratified Miettinen and Nurminen method with CMH weights (stratified by screening HIV-1 RNA level [≤100,000 copies/mL, >100,000 copies/mL] and screening CD4+ T-cell count [<200 cells/mm^3, ≥200 cells/mm^3]) [Miettinen, O. and Nurminen, M. 1985]. The FDA snapshot algorithm will be used to handle missing data for the analysis of the primary efficacy hypothesis.
Statistical Methods for Key Safety Analyses	For overall safety endpoints, specific AEs, and safety topics of special interest that meet predefined threshold rules, point estimates and 2-sided nominal 95% CIs for the differences between treatment groups (DOR/ISL minus BIC/FTC/TAF) in the percentages of participants with events will be provided using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. Inferential analyses with 2-sided multiplicity-adjusted CIs and p-values obtained using ANCOVA models will be provided for the differences between groups (DOR/ISL minus BIC/FTC/TAF) in the mean change from baseline in weight at Week 48 and Week 96 in accordance with the multiple testing strategy.
Interim Analyses	IAs will be performed in this study. Results will be reviewed by an eDMC. These IAs are summarized below. • Sentinel Cohort Week 24 futility assessment Once at least 30 participants in each treatment group have completed the Week 24 visit and have available HIV-1 RNA results (the Sentinel Cohort, defined in Section 9.5.1), an efficacy futility assessment (referred to as the "Sentinel Cohort Week 24 futility assessment") will be conducted by the external unblinded statistician and reviewed by the eDMC. If the lower bound of the 2-sided 95% CI for the treatment difference (Group 1 minus Group 2) in the percentage of participants in the Sentinel Cohort with Week 24 HIV-1 RNA <200 copies/mL is less than -30 percentage points, consideration may be given to stop the study. • Periodic safety and efficacy reviews In addition to the Sentinel Cohort Week 24 futility assessment described above, the eDMC will review accumulating safety and efficacy data at regular intervals throughout the study duration, or at modified intervals based on the recommendation of the eDMC, or on an ad hoc basis as described in Section 4.1. • Week 48 analysis The Week 48 analysis will be conducted to test the primary non-inferiority efficacy hypothesis once all participants have completed the Week 48 visit assessments. The analysis of the data will be performed by the unblinded team of the Sponsor. All available efficacy and safety data will be reviewed at this interim time point. Additional details are provided in Section 9.7.

Multiplicity	A formal futility analysis at Week 24 is planned as described in Section 9.7, a small amount of alpha (a=0.00001) will be allocated for this IA, purely for statistical rigor. The gatekeeping method will be implemented in this study to control the overall 1-sided 2.499% alpha level for H1, H2 and H3 hypotheses testing. Primary efficacy hypothesis (H1) will be tested at a 1-sided 2.499% Type I error rate. The secondary safety hypotheses (H2 and H3) will be tested only if the null hypothesis of H1 is rejected and in accordance with the method by Maurer et al [Maurer, W., et al 2011]. Full details for testing these hypotheses (H1, H2, and H3) at a strongly controlled 1-sided 2.499% Type I error rate is described in Section 9.8.
Sample Size and Power	The planned sample size is 500 participants (250 per treatment group). For the primary efficacy endpoint of the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48, the study has approximately 95.4% power to demonstrate that DOR/ISL is non-inferior to BIC/FTC/TAF at a 1-sided 2.5% alpha level if the true rate of participants with of HIV-1 RNA <50 copies/mL at Week 48 is 90.0% in both treatment groups. This power calculation does not account for the futility assessment at Week 24.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

Day 1 through Week 48 will be conducted as a double-blind study under in-house blinding procedures. The official, final database for Day 1 through Week 48 will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. The clinical database and Sponsor personnel directly involved in the Week 48 analysis and reporting will become unblinded at the time of the Week 48 database lock, although study participants and site personnel will remain blinded until Week 144. The results of the interim analysis will not be shared with the investigators before completion of the base study.

PK data may be unblinded early for the purpose of preparing a population PK model. A separate team from the protocol team will be unblinded for the purpose of preparing the PK model. Efficacy and safety data will not be unblinded for the purpose of preparing the PK model. Interim data or results will not be shared with the protocol team before unblinding of the Sponsor at the Week 48 database lock.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study intervention assignment. Randomization will be implemented via an IRT.

Blinding issues related to the planned IAs are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

Success of this study is predicated only on establishing non-inferiority of DOR/ISL to BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48 (ie, establishing statistical significance of H1).

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

9.4.1 Efficacy/Pharmacokinetics Endpoints

9.4.1.1 Efficacy Endpoints

An initial description of efficacy measures is provided in Section 4.

Percentage of Participants With HIV-1 RNA <50 copies/mL and Percentage of Participants With HIV-1 RNA <200 copies/mL

A PCR assay with a lower level of detection of <50 copies/mL will be used to measure the HIV-1 RNA level in blood samples obtained at each visit. The primary objective will be assessed based on the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48. Secondary objectives will assess the percentage of participants with HIV-1 RNA <50 copies/mL at Weeks 96 and 144, and the percentage of participants with HIV-1 RNA <200 copies/mL at Weeks 48, 96, and 144.

In the OLE, the percentage of participants with HIV-1 RNA <50, ≥50, and <200 copies/mL will be summarized over time using the DAO approach for participants who consent to the OLE.

Change From Baseline in CD4+ T-cell Count

The mean change from baseline in CD4+ T-cell count will be calculated at each time point at which CD4+ T-cell count is collected. A secondary objective will compare the mean change from baseline in CD4+ T-cell count between treatment groups at Weeks 48, 96, and 144.

For analyses of the mean change from baseline in CD4+ T-cell count, baseline measurements are defined as the Day 1 value for each participant. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline, when available.

The change from baseline in CD4+ T-cell count in the OLE will be analyzed over time for participants who consent to OLE. The baseline for Group 2 will be the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement prior to the switch to DOR/ISL).

Clinically Significant Confirmed Viremia

Participants with confirmed virologic rebound or incomplete virologic response as defined in Section 4.2.1.1.2 will be identified.

Viral Resistance-associated Substitutions

Participants who meet the definition of confirmed virologic rebound or incomplete virologic response (Section 4.2.1.1.2), or who discontinue study intervention for another reason and have HIV-1 RNA ≥200 copies/mL at the time of discontinuation, will be assessed for development of viral drug resistance. Among such participants, those with HIV-1 RNA ≥400 copies/mL will be included in the resistance analyses. In addition, anyone for whom available genotypic or phenotypic data show evidence of resistance, irrespective of viral load, will also be included in the resistance analyses. The resistance analyses will count the number of participants in each treatment group who have evidence of resistance-associated substitutions. The data will be summarized with primary interest at Weeks 48, 96, 144, and during the OLE.

9.4.1.2 Pharmacokinetic Endpoints

PK samples collected from all participants as described in the SoA (Sections 1.3.1, 1.3.2, 1.3.3, and/or 1.3.4) and Section 8.6 will be used to evaluate PK concentrations of ISL and, as appropriate, PK-efficacy, PK-pharmacodynamics, and PK-AE relationships of ISL.

9.4.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values, and vital signs.

Adverse Events

The following clinical and laboratory AEs will be summarized: 1) participants with at least 1 AE; 2) participants with at least 1 drug-related AE; 3) participants with at least 1 SAE; 4) participants with at least 1 Grade 3 or 4 AE; 5) participants with at least 1 serious and drug-related AE; 6) participants with at least 1 AE, which is both Grade 3 or 4 and drug-related; 7) participants who discontinued study intervention due to an AE; 8) participants who discontinued study intervention due to a drug-related AE; and 9) participants with an AE leading to death.

Predefined Limits of Change in Laboratory Parameters

For the summaries of laboratory test results, participants must have both a baseline and post-randomization on-treatment measurement to be included. Participants' laboratory values (based on their most abnormal laboratory test values in the direction of interest while on study intervention) will be classified as to whether they fall outside of the PDLC and are worse in grade (ie, more abnormal in the direction of interest) than at baseline. The criteria

are adapted from the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017, version 2.1 (Appendix 3) [National Institute of Allergy and Infectious Diseases 2017].

Weight, Laboratory Markers, and Radiological Markers

The mean change from baseline to Weeks 48, 96, and 144 in select weight, laboratory markers, and radiological markers of fasting lipid and metabolic profiles, renal function, inflammation, and body composition will be summarized.

The mean change from baseline in weight will be summarized at each time point at which weight is collected. A secondary objective will assess the mean change from baseline in weight at Week 48 and Week 96.

Total Lymphocyte Count

The mean change from baseline in total lymphocyte count will be calculated at each time point at which lymphocytes are collected. The mean change from baseline in total lymphocyte counts between treatment groups will be assessed at Weeks 48, 96, and 144.

For analyses of the mean change from baseline in lymphocyte, baseline measurements are defined as the Day 1 value for each participant. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline, when available.

The change from baseline in total lymphocyte count during the OLE will be analyzed over time for participants who consent to enter the OLE. The baseline for Group 2 will be the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement before the switch to DOR/ISL).

Definition of Baseline Measurements for Safety Analyses

For analyses of changes from baseline in safety parameters (eg, weight, vital signs, laboratory, and radiological parameters), baseline measurements are defined as the Day 1 value for each participant. In the rare event that data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline, when available.

For analyses of DEXA parameters (ie, bone density and body composition), if no Day 1 or screening values are available, the earliest measurement within 45 days after the start of study intervention will be used as baseline, when available.

The change from baseline in safety parameters during the OLE will be analyzed over time for participants who consent to the OLE. The baseline for Group 2 will be the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement prior to the switch to DOR/ISL).

9.4.3 Patient-reported Outcome Endpoints

An initial description of patient-reported outcome measures is provided in Section 4.2.1.5.

PROs from each questionnaire at Day 1 and Weeks 4, 16, 48, and 96 will be summarized for each treatment group.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

Sentinel Cohort

A minimum of the first 30 participants enrolled and evaluable in each treatment group who reach Week 24 and have available HIV-1 RNA data, inclusive of participants who discontinue study treatment prior to Week 24 due to clinically significant confirmed viremia will be identified as the Sentinel Cohort.

Specifically, to be considered "enrolled and evaluable" at Week 24 for inclusion in the Sentinel Cohort, participants must be randomized in the study and 1) have at least one on-treatment HIV-1 RNA measurement in the Week 24 analysis window or 2) discontinue study intervention prior to or within the Week 24 analysis window due to clinically significant confirmed viremia. Participants who do not meet these criteria will not be eligible for inclusion in the Sentinel Cohort population. An external unblinded statistician will monitor participant status throughout the trial to identify the first 30 participants in each treatment group (by date of study intervention discontinuation due to lack of efficacy or the date of clinically significant confirmed viremia/date of the Week 24 HIV-1 RNA measurement) who meet the requirements for inclusion in the Sentinel Cohort. Due to additional data becoming available between identification of first 30 participants in each group and the data cutoff, the Sentinel Cohort will likely include slightly more than 30 participants in each group; any additional participants beyond the first 30 who otherwise meet the criteria above will be included in the Sentinel Cohort.

FAS Population

The FAS population will serve as the primary population for the analysis of efficacy data in the base study. The FAS population consists of all randomized participants who meet the following criteria:

- Receive at least 1 dose of study intervention
- Have baseline data for those analyses that require baseline data

Note that the number of participants included in the FAS population may vary across endpoints due to the applicability of exclusion criteria to each endpoint (eg, the need for baseline data only applies to those endpoints that are derived relative to baseline). Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data FAS population.

PP Population

The secondary analysis set for the efficacy analyses in the base study is defined as the PP population, which will exclude participants in the FAS population who have any important deviations from the protocol that may substantially affect the results of the efficacy endpoints. Potential deviations that may result in the exclusion of a participant from the PP population include:

- Receipt of any ongoing prohibited therapies listed in Table 3
- Nonadherence to study intervention: <95% drug compliance rate (see Section 9.11)
- Pregnancy
- Unblinding for any reason (eg, due to HBV acute infection/reactivation, accidental unblinding, etc.)

The PP analysis will be performed for the percentages of participants with HIV-1 RNA <50 copies/mL and HIV-1 RNA <200 copies/mL at Weeks 48, and 96, and 144 (see Table 9).

The final determination of important protocol deviations, and thereby the composition of the PP population, will be made prior to unblinding of the Sponsor at the Week 48 database lock and will be documented. A participant who deviates from the protocol at randomization (eg, violation of certain inclusion or exclusion criteria, such as the use of a prohibited prior treatment) will be excluded from the PP population. For participants who have important deviations from the protocol during the study (eg, taking a prohibited concomitant medication), data obtained after the deviation will be excluded from analysis. As such, the composition of the PP population may vary by the analysis time point, based on the number of participants who satisfy the PP criteria at that time point. Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using the PP population.

ITT Population

Another analysis set for the efficacy analyses in the base study is defined as the ITT analysis set, which includes all randomized participants, regardless of their receipt of study intervention or availability of post-baseline measurements.

The ITT analysis may be performed for the percentage of participants with HIV-1 RNA <50 copies/mL at Weeks 48, 96 and 144 and the percentage of participants with HIV-1 RNA <200 copies/mL at Weeks 48, 96 and 144 (see Table 9).

FAS-E Population for the OLE

The FAS-E population will be used to analyze efficacy data in the OLE. It consists of all FAS participants in the base study who entered the OLE and received at least 1 dose of the OLE study intervention.

Resistance Analysis Subset

The resistance analysis subset will include all treated participants with HIV-1 RNA ≥400 copies/mL and any participants for whom available genotypic or phenotypic data show evidence of resistance, irrespective of viral load.

9.5.2 Safety Analysis Populations

APaT Population

The APaT population will be used for the analysis of safety data in the base study. The APaT population consists of all randomized participants who receive at least 1 dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the treatment group corresponding to the study intervention actually received.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study intervention is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required. The composition of the APaT population may vary based on the availability of baseline measurements for the relevant safety parameters of interest.

APaT-E Population for the OLE

The APaT-E population will be used to analyze safety data in the OLE period. It consists of all APaT participants in the base study who transitioned and received at least 1 dose of the OLE study intervention.

9.6 Statistical Methods

The statistical methods used to evaluate the primary and secondary objectives are described below. Methods related to evaluation of exploratory objectives will be described in the sSAP.

Definition of On-treatment Measurements for Efficacy Analyses

For participants who have either discontinued or completed study intervention, all measurements within 1 day following the last dose of study intervention will be considered to be on-treatment measurements. For participants who are on study intervention (ie, have not discontinued or completed study intervention), all measurements will be considered to be on-treatment measurements.

Definition of On-treatment Measurements for Safety Analyses

For participants who have either discontinued or completed study intervention, all measurements within 42 days following the last dose of study intervention will be considered to be on-treatment measurements; the 42-day window was selected to account for the

half-life of ISL. For participants who are on study intervention (ie, have not discontinued or completed study intervention), all measurements will be considered to be on-treatment measurements.

9.6.1 Statistical Methods for Efficacy Analyses

Time Windows

Definitions of time windows (day-ranges) and target days for the scheduled study visits, which will be used for all statistical analyses by time point, as shown in Table 8. The last available on-treatment measurement within a window will be used for analyses at a specific time point, unless otherwise specified. Results from additional time points beyond Week 96 may be summarized, and day-range rules for determining the analysis time windows will follow the same pattern where the ranges start and end at the midpoints between target days.

Table 8 Definitions of Study Time Points

Treatment Phase	Treatment Period	Visit	Day-Range[a]	Target Day[a]
Pretreatment	Baseline	Day 1	≤1	1
Treatment	Blinded Intervention: DOR/ISL or BIC/FTC/TAF	Week 4	≥2 and ≤42	29
		Week 8	≥43 and ≤84	57
		Week 16	≥85 and ≤140	113
		Week 24	≥141 and ≤210	169
		Week 36	≥211 and ≤294	253
		Week 48	≥295 and ≤378	337
		Week 60	≥379 and ≤462	421
		Week 72	≥463 and ≤546	505
		Week 84	≥547 and ≤630	589
		Week 96	≥631 and ≤714	673
		Week 108	≥715 and ≤798	757
		Week 120	≥799 and ≤882	841
		Week 132	≥883 and ≤966	925
		Week 144	≥967 and ≤the last day of blinded intervention	1009

Treatment Phase	Treatment Period	Visit	Day-Range[a]	Target Day[a]
Treatment Extension[b]	Open-Label Intervention: DOR/ISL	Week 148[c]	Group 1: NA Group 2: ≥first day of open-label intervention and ≤1106	Group 1: NA Group 2: 1037
		Week 168	Group 1: ≥first day of open-label intervention and ≤1260 Group 2: ≥1107 and ≤1260	Group 1 and Group 2: 1177
		Week 192	1261≥ and ≤1428	1345
		Week 216	1429≥ and ≤1596	1513
		Week 240	1597≥ and ≤1764	1681

[a] Day-ranges and target days are computed relative to the first day of study intervention.
[b] The treatment extension phase visits apply only to participants who consent to the OLE.
[c] The Week 148 visit applies only to participants in Group 2 who consent to the OLE.

Missing Data Approaches

Three approaches will be used to handle missing HIV-1 RNA values. The primary approach for analysis of the percentage of participants with HIV-1 RNA <50 copies/mL is the FDA "snapshot" algorithm [Food and Drug Administration (CDER) 2015]. Using this approach, for data collected in a given analysis window (see Table 8), the last available measurement while the participant is on treatment is used to define the virologic outcome. Virologic outcome is defined according to the following categories:

HIV-1 RNA <50 copies/mL: Participants who have the last available on-treatment HIV-1 RNA measurement <50 copies/mL within the time point of interest analysis window specified in Table 8.

HIV-1 RNA ≥50 copies/mL: This includes participants

Who have the last available on-treatment HIV-1 RNA measurement ≥50 copies/mL within the time point of interest analysis window specified in Table 8.

Who do not have on-treatment HIV-1 RNA data in the time point of interest analysis window and

- Who discontinue study intervention prior to or in the time point of interest analysis window due to lack of efficacy, or

- Who discontinue study intervention prior to or in the time point of interest analysis window due to reasons other than lack of efficacy and AE/death and have the last available on-treatment HIV-1 RNA measurement ≥50 copies/mL.

No Virologic Data in Specified Analysis Time Window: This includes participants who do not have on-treatment HIV-1 RNA data in the time point of interest analysis window specified in Table 8 because of the following:

Discontinued study intervention due to AE or Death: This includes participants who discontinued study intervention because of an AE or death at any time point from Day 1 through the analysis window if this resulted in no on-treatment HIV-1 RNA measurements during the specified window.

Discontinued study intervention for Other Reasons: This includes participants who discontinued study intervention prior to or in the time point of interest analysis window due to reasons other than lack of efficacy and AE/death (ie, lost to follow-up, noncompliance with study intervention, physician decision, protocol deviation, withdrawal by participant, etc.) and have the last available on-treatment HIV-1 RNA measurement <50 copies/mL. In addition, this category will include participants who discontinued study intervention due to reasons other than lack of efficacy and AE/death and had no on-treatment HIV-1 RNA measurements during the entirety of the study.

On study intervention, but missing data in window: Only data in the predefined analysis window can be used for the statistical analysis at a given time point for participants remaining on study intervention. Participants with HIV-1 RNA results outside this window will be classified as "on study intervention, but missing data in window" regardless of the out of window HIV-1 RNA results.

For the primary evaluation of non-inferiority as assessed by the percentage of participants with HIV-1 RNA <50 copies/mL, the parameter for evaluation is the number of participants classified as "HIV-1 RNA <50 copies/mL" according to the FDA snapshot algorithm defined above, divided by the number of participants in the FAS. Similar logic will also be used to define the percentage of participants with HIV-1 RNA <200 copies/mL in accordance with the relevant secondary endpoint.

A second approach, the treatment failure (M=F) approach, will be performed as a sensitivity analysis for the percentage of participants with HIV-1 RNA <50 copies/mL. Under this approach, participants who 1) have the last available on-treatment measurement within the time point of interest analysis window specified in Table 8 <50 copies/mL, OR 2) are on study intervention and have no HIV-1 RNA measurements within the time point of interest analysis window specified in Table 8 and have both the immediately preceding and immediately subsequent on-treatment HIV-1 RNA values <50 copies/mL, will be classified as a virologic success (ie, HIV-1 RNA <50 copies/mL) at the time point of interest. Participants with other reasons for missing data will be classified as a virologic failure (ie, HIV-1 RNA ≥50 copies/mL) at the time point of interest.

A third approach, the OF approach, will also be performed as a sensitivity analysis for the percentage of participants with HIV-1 RNA <50 copies/mL. Under this approach, participants with non-intermittent missing data who discontinue study intervention early due to lack of efficacy or who discontinue study intervention for other reasons and are failures (HIV-1 RNA ≥50 copies/mL) at the time of study intervention discontinuation are considered to be failures at time points thereafter. Participants who discontinue study intervention for reasons other than lack of efficacy and who are not failures at the time of study intervention discontinuation will be excluded from the analyses at subsequent time points. Participants with intermittent missing data will be considered to be successes (HIV-1 RNA <50 copies/mL) if both the immediately preceding and immediately subsequent on-treatment HIV-1 RNA values are <50 copies/mL; all other intermittent missing results will be imputed as failures.

The same supportive approaches as described above will similarly be used for the analysis of the percentage of participants with HIV-1 RNA <200 copies/mL.

Percentage of Participants With HIV-1 RNA <50 copies/mL at Scheduled Visits (Base Period)

The snapshot approach will be used as the primary approach to analysis with respect to the percentage of participants with HIV-1 RNA <50 copies/mL.

Non-inferiority of DOR/ISL (Group 1) to BIC/FTC/TAF (Group 2) with respect to the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48 will be evaluated using the stratified Miettinen and Nurminen method with CMH weights (stratified by screening HIV-1 RNA level [≤100,000 copies/mL, >100,000 copies/mL] and screening CD4+ T-cell count [<200 cells/mm^3, ≥200 cells/mm^3]) [Miettinen, O. and Nurminen, M. 1985]. For the evaluation of the primary hypothesis at Week 48, a margin of 10 percentage points is used to define the non-inferiority of DOR/ISL to BIC/FTC/TAF; non-inferiority will be concluded if the lower bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA <50 copies/mL (Group 1 minus Group 2) is greater than -10 percentage points. A non-inferiority margin of 10 percentage points is clinically reasonable because it preserves a large portion of the treatment effect, which is expected to be >80%. Supportive analyses using the M=F and OF approaches (as defined above) will also be presented.

To address the secondary efficacy hypothesis and to summarize virologic response over time, the difference in percentages between treatment groups at each time point through Week 144 will be estimated and the associated 2-sided 95% CI will be derived in a similar fashion to that described for the primary efficacy analysis.

In addition, for participants who become pregnant and consent to continue study intervention, a listing of HIV-1 RNA values over time at the scheduled visits will be provided.

Percentage of Participants With HIV-1 RNA <200 copies/mL at Scheduled Visits (Base Period)

The snapshot approach will be used as the primary approach to analysis with respect to the percentage of participants with HIV-1 RNA <200 copies/mL. This endpoint will be summarized by treatment group at each time point, with primary interest at Weeks 48, 96, and 144 by comparing Group 1 and Group 2. For these time points of interest, the difference in percentages between treatment groups (Group 1 minus Group 2) and the associated 2-sided 95% CI will be calculated using the stratified Miettinen and Nurminen method with CMH weights (stratified by screening HIV-1 RNA level [≤100,000 copies/mL, >100,000 copies/mL] and screening CD4+ T-cell count [<200 cells/mm^3, ≥200 cells/mm^3]) [Miettinen, O. and Nurminen, M. 1985]. Supportive analyses using the M=F and OF approaches (as defined above) will also be presented.

Additional HIV-1 RNA Summaries

The percentages of participants with HIV-1 RNA <20 copies/mL (the LLOQ of the assay), 20 to <50, 50 to <100, 100 to <200, 200 to <400, and ≥400 copies/mL will be summarized by intervention groups at all scheduled study visit time points.

In the OLE, the percentage of participants with HIV-1 RNA <50 copies/mL, ≥50 copies/mL, and <200 copies/mL will be summarized at the scheduled visits using the DAO approach. This analysis will summarize based on number of participants who have reached to the timepoint of interest based on their visit scheduled.

Change From Baseline in CD4+ T-cell Count

The mean change from baseline in CD4+ T-cell count will be summarized by treatment group at each time point at which CD4+ T-cell count is scheduled to be collected in the base study. To estimate the treatment difference (Group 1 minus Group 2), and corresponding 2-sided 95% CI, in mean changes from baseline in CD4+ T-cell count at each time point, with primary interest at Weeks 48, 96, and 144, a cLDA method proposed by Liang and Zeger [Liang, K-Y and Zeger, S. L. 2000] will be used. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of the baseline value and the values observed at each post-baseline time point. The analysis model will adjust for treatment group, time, stratum, the interaction of time-by-treatment group, and the interaction of time-by-stratum. This model will allow for different baseline means for each stratum, but restrict the baseline mean within each stratum to be the same for both treatment groups. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood to make proper statistical inference [Kenward, M. G. and Roger, J. H. 1997].

Although the baseline measurement is included in the response vector, it is independent of treatment, and hence, the baseline means are constrained to be the same for different

treatment groups. Of note, if there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal ANCOVA model, which uses the baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and CIs for individual treatment effects. Moreover, this model allows the inclusion of participants who are missing either the baseline or post-baseline measurements, thereby increasing efficiency. Details of the model specification, assumptions, and SAS implementation codes will be provided in the sSAP.

The cLDA method assumes that data are MAR. In this study, it is expected that MAR/MCAR mechanisms will underlie most of the missingness, and the proportion of data MNAR, driven solely by unobserved values of the study endpoints, will be small. Reasons for discontinuation from the study may include lack of efficacy, death, withdrawal of consent, protocol deviations, lost to follow-up (eg, relocation), etc. Missing data caused by a participant's relocation are likely to be MCAR. Missing data caused by discontinuations due to lack of efficacy may belong to MAR because this type of discontinuation may depend on the observed efficacy outcomes. The MAR or MNAR mechanisms might each underlie the other reasons to some extent. If the assigned study intervention in large part determines the loss of data for these other reasons, the mechanism may be close to MAR since the intervention assignment is an observed variable and included in the analysis model.

The estimates of the between-group differences in the mean change from baseline in CD4+ T-cell count will not be subject to an absolute criterion for similarity as the clinical interpretation of treatment difference is dependent upon the absolute values at baseline and the magnitude and direction of the CD4+ T-cell count changes observed in each treatment arm.

In addition to CD4+ T-cell count, the observed mean CD4+ T-cell percent will also be summarized by study intervention groups at each time point at which the TBNK panel/CD4+ T-cell count is scheduled to be collected.

During the OLE, the change from baseline in CD4+ T-cell count will be summarized separately using descriptive statistics based on the DAO approach. For assessments of change from baseline in Group 2 during the OLE, the baseline measurement will be taken as the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement prior to the switch to DOR/ISL).

Clinically Significant Confirmed Viremia

The number of participants with confirmed virologic rebound or incomplete virologic response, as defined in Section 4.2.1.1.2, will be summarized for each treatment group.

Viral Resistance-associated Substitutions

The number of participants in the resistance analysis subset with genotypic and/or phenotypic resistance to each study intervention will be summarized for each treatment group with primary interest at Weeks 48, 96, and 144.

Unblinding of Participants During the Study

Given the objective nature of the HIV-1 RNA efficacy endpoint, if a participant becomes unblinded during the base study for any reason (eg, due to a safety event, acute infection/reactivation of HBV or pregnancy that requires unblinding, or accidental unblinding), such participants will not be treated as treatment failures in the primary efficacy analyses on the FAS population due to the unblinding alone.

HBV Acute Infection/Reactivation

If the clinical management of HBV acute infection/reactivation requires the addition of a concomitant therapy that is also active against HIV-1, efficacy assessments in these participants from that point forward will be handled in a similar manner as the FDA snapshot algorithm classification rules for participants with missing data due to discontinuation of study intervention in the base study. During the OLE, efficacy assessments from that point forward in these participants will be reported separately.

Participants Who Discontinue Due to Pregnancy or Breastfeeding

For participants who become pregnant and choose to discontinue study intervention or participants who choose to breastfeed and must discontinue study intervention in the base study, efficacy assessments from that point forward will be handled in a similar manner as the FDA snapshot algorithm classification rules for participants with missing data due to discontinuation of study intervention. Results for participants who become pregnant during the study will be reported separately.

Table 9 summarizes the key efficacy analyses of the base study.

Table 9 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary Versus Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypotheses H1				
Percentage of participants with HIV-1 RNA <50 copies/mL at Week 48	P	M&N with CMH weights[b]	FAS	Snapshot
	S	M&N with CMH weights[b]	FAS	M=F
	S	M&N with CMH weights[b]	PP	OF
	S	M&N with CMH weights[b]	ITT	M=F[d]

Endpoint/Variable (Description, Time Point)	Primary Versus Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Secondary Endpoints				
Percentage of participants with HIV-1 RNA <50 copies/mL at Weeks 96 and 144	P	M&N with CMH weights[b]	FAS	Snapshot
	S	M&N with CMH weights[b]	FAS	M=F
	S	M&N with CMH weights[b]	PP	OF
	S	M&N with CMH weights[b]	ITT	M=F[d]
Percentage of participants with HIV-1 RNA <200 copies/mL at Weeks 48, 96 and 144	P	M&N with CMH weights[b]	FAS	Snapshot
	S	M&N with CMH weights[b]	FAS	M=F
	S	M&N with CMH weights[b]	PP	OF
	S	M&N with CMH weights[b]	ITT	M=F[d]
Mean change from baseline in CD4+ T-cell count at Weeks 48, 96 and 144	P	cLDA[c]	FAS	Model-based

cLDA=constrained longitudinal data analysis; CMH=Cochran-Mantel-Haenszel; FAS=Full Analysis Set; HIV-1=human immunodeficiency virus type 1; M=F=missing equal to failure; M&N=Miettinen and Nurminen; OF=Observed Failure; PP=Per-Protocol; RNA=ribonucleic acid.

[a] P=primary approach; S=supportive approach.

[b] The M&N method with CMH weights will be stratified by screening HIV-1 RNA level (≤100,000 copies/mL, >100,000 copies/mL) and screening CD4+ T-cell count (<200 cells/mm^3, ≥200 cells/mm^3) [Miettinen, O. and Nurminen, M. 1985].

[c] The cLDA model will include terms for treatment group, time, stratum, the interaction of time-by-treatment group, and the interaction of time-by-stratum.

[d] The supportive analysis based on the ITT population will be performed if there are at least 1% of the total randomized population (ie, 5 based on the planned sample size) who were excluded from the FAS population.

The strategy to address multiplicity issues with regard to multiple treatment comparisons, multiple endpoints, multiple time points, and/or IAs is described in Sections 9.7 and 9.8.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory test results and vital signs. For analyses of safety by time point, the same analysis windows as specified in Table 8 will be used, unless otherwise specified. Analysis windows for DEXA measurements are provided in Table 10.

Table 10 Definition of Study Time Points for DEXA Analyses

Treatment Phase	Treatment Period	Visit	Day-Range[a]	Target Day[a]
Pretreatment	Baseline	Day 1	≤45	1
Treatment	Blinded Intervention: DOR/ISL or BIC/FTC/TAF	Week 48	≥253 and ≤420	337
		Week 96	≥589 and ≤756	673
		Week 144	≥925 and ≤1092	1009

BIC=bictegravir; DEXA=dual X-ray absorptiometry; DOR=doravirine; FTC=emtricitabine; ISL=islatravir; TAF=tenofovir alafenamide.

[a] Day-ranges and target days are computed relative to the first day of study intervention.

9.6.2.1 Overall Safety Assessment

The overall safety evaluation in the base study will include a summary by treatment group of the number and percentage of participants with any AE, with a drug-related AE, with an SAE, with a Grade 3 or 4 AE, with an AE that is both serious and drug-related, with an AE that is both Grade 3 or 4 and drug-related, who discontinued study intervention due to an AE, who discontinued study intervention due to a drug-related AE, and with an AE resulting in death. Point estimates and 2-sided 95% CIs for the differences between treatment groups (Group 1 minus Group 2) in the percentages of participants with the event will be provided. The CIs for the between-group differences will be provided using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

The number and percentage of participants with specific AEs will also be provided. Point estimates and 2-sided 95% CIs for the differences between treatment groups (Group 1 minus Group 2) in the percentages of participants with specific AEs will be provided for AEs that occur in at least 4 participants in any treatment group. This threshold for the number of participants with AEs was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when fewer participants per group have events and thus would add little to the interpretation of potentially meaningful differences. The CIs for the between-group differences will be provided using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

CIs that are not adjusted for multiplicity should only be regarded as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing statistical significance of between-group differences. Point estimates and 2-sided 95% CIs for the differences between treatment groups (Group 1 minus Group 2) in the percentages of

participants with safety parameters that meet predefined limits of change will be provided based on the same criteria used above for specific AEs.

For continuous safety measures, such as change from baseline in laboratory and vital signs parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group. For participants who become pregnant during the study, measurements collected after the estimated date of conception will be excluded from the analyses. Missing data will not be imputed.

For the mean change from baseline to Weeks 48, 96, and 144 in total lymphocyte count, the treatment difference (Group 1 minus Group 2) and corresponding 2-sided 95% CI will be estimated using ANCOVA models adjusted by baseline value and treatment group.

For lipid profile analyses, participants who receive lipid-lowering therapy at baseline will be excluded from all analyses. For participants who initiate lipid-lowering therapy during the study, the last lipid measurement before initiating the lipid-lowering therapy will be carried forward. For participants who become pregnant, lipid data collected after the estimated date of conception will be excluded. Missing lipid data will not be imputed; as such, any participant with a missing value will be excluded from the analyses. The percentages of participants who initiate or modify lipid-lowering therapy prior to Weeks 48, 96, and 144 will be summarized by treatment group. Additional details will be provided in the sSAP.

Safety data for participants who consent to the OLE (from Week 144 to Week 240) will be summarized separately. Additional details are provided in the sSAP.

9.6.2.2 Assessment of Safety Topics of Special Interest

The following are considered safety topics of special interest in the base study: opportunistic infections and the mean change from baseline in weight at Weeks 48, 96, and 144.

The number and percentage of participants with any opportunistic infection will be summarized by treatment group. The point estimate and 2-sided 95% CI for the difference between treatment groups (Group 1 minus Group 2) in the percentage of participants with any opportunistic infection will be provided. The number and percentage of participants with specific opportunistic infections will also be summarized by treatment group. Point estimates and 2-sided 95% CIs for the differences between treatment groups (Group 1 minus Group 2) in the percentages of participants with these events will be provided based on the criteria described above for specific AEs. CIs for between-treatment group differences will be provided using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. Opportunistic infections will be identified through SMQs using the MedDRA dictionary. SMQs on both broad and narrow PTs will be performed and will be summarized separately.

To evaluate the secondary objectives regarding the effect on weight of DOR/ISL compared to BIC/FTC/TAF at Weeks 48, 96, and 144, the treatment difference in the mean change from baseline and corresponding CI will be estimated using the cLDA method of Liang and Zeger [Liang, K-Y and Zeger, S. L. 2000], with similar model specifications as described above for the analyses of the mean change from baseline in CD4+ T-cell count (see Section

9.6.1). For the analyses of the mean change from baseline in weight, the cLDA model will adjust for treatment group, time, stratum, sex at birth, race, the interaction of time-by-treatment group, the interaction of time-by-stratum, the interaction of time-by-sex at birth, and the interaction of time-by-race. Superiority of DOR/ISL to BIC/FTC/TAF as assessed by having a lower mean increase from baseline in weight at Week 48/96 will be concluded if the upper bound of the 2-sided CI for the estimate of the between-group difference (Group 1 minus Group 2) is less than 0 (see Section 9.8 for the alpha levels used for the CIs in accordance with the multiplicity strategy for testing these hypotheses). P-values for the between-group comparisons at Weeks 48 and 96 will also be provided. For participants who become pregnant during the study, weight measurements after the estimated date of conception will be assigned as missing data and handled accordingly by the cLDA model.

9.6.2.3 Handling of Missing Data and Pregnancies in Safety Analyses

Missing safety parameters, unless otherwise specified, will not be imputed; as such, any participant with a missing value will be excluded from the analysis. Change from baseline summaries require a baseline value. Baseline measurements are defined as the Day 1 value for each participant. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline, when available. If no baseline result is available for a given analysis, that participant will not be included in the analysis. Safety data for participants who consent to enter the OLE at Week 144 will be summarized from Week 144 to Week 240. For the assessment of change from baseline in Group 2 in OLE, baseline will be the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement before the switch to DOR/ISL).

For participants who become pregnant during the study, all safety data collected on or after the estimated date of conception will be summarized separately from the primary and secondary safety analyses. Data collected for participants whose pregnancy or postpartum visit(s) extend beyond Week 144 will be reported separately. Infant safety data will also be reported separately.

Table 11 summarizes the analysis strategy for safety endpoints in the base study.

Table 11 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Between-group CI	Inferential Analysis
Overall Safety Assessment	Any AE	X	X	
	Any drug-related AE	X	X	
	Any SAE	X	X	
	Any Grade 3 or 4 AE	X	X	
	Any serious drug-related AE	X	X	
	Any Grade 3 or 4 drug-related AE	X	X	
	Discontinued study intervention due to an AE	X	X	
	Discontinued study intervention due to a drug-related AE	X	X	
	AE resulting in death	X	X	
	Specific AEs	X	X[a]	
	SOCs, PDLCs	X	X[a]	
	Mean Change from Baseline (Laboratory, Vital Signs, Body Composition, and Lymphocyte Parameters)	X	X	
Assessment of Safety Topics of Special Interest	Any Opportunistic Infection	X	X	
	Specific Opportunistic Infections and Corresponding SOCs	X	X[a]	
	Mean Change from Baseline in Weight	X	X	X[b]

AE=adverse event; CI=confidence interval; PDLC=predefined limit of change; SAE=serious adverse event; SOC=system organ class.

[a] The between-group 95% CI will only be provided for events that occur in at least 4 participants in any treatment group.

[b] P-values will be provided for the mean change from baseline at Week 48 and Week 96 in weight to support the evaluation of the corresponding secondary hypotheses.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, race, region, etc.), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

Participant safety and efficacy data will be monitored by an independent eDMC throughout the study per timing and milestones specified in the eDMC charter. Periodic efficacy and safety reviews, a formal futility assessment at Week 24 on the Sentinel Cohort, and possible ad hoc efficacy and safety reviews will be conducted.

The results of IAs will not be shared with the investigators prior to completion of Week 144. Participant-level unblinding will be restricted to an external unblinded statistician and scientific programmer performing the IAs, who will have no other responsibilities associated with the study. An eDMC will serve as the primary reviewer of the IAs and may make recommendations for discontinuation of the study or for protocol modifications to an executive committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim efficacy and safety reviews will be documented. Additional logistical details will be provided in the eDMC charter.

Once at least 30 participants in each treatment group in the Sentinel Cohort (defined in Section 9.5.1) have completed the Week 24 visit, an efficacy futility assessment (referred to as the "Sentinel Cohort Week 24 futility assessment") will be conducted by the external unblinded statistician and reviewed by the eDMC. If the lower bound of the 2-sided 95% CI for the treatment difference (Group 1 minus Group 2) in the percentage of participants in the Sentinel Cohort with Week 24 HIV-1 RNA <200 copies/mL is less than -30 percentage points, the eDMC may recommend the study be stopped.

The endpoint of <200 copies/mL for the futility assessment was selected in recognition that the time profile for viral suppression to <50 copies/mL may differ between the treatment groups and that participants with high viral loads at baseline (eg, >50,000 copies/mL) may be enrolled in the study. Such participants may not be able to achieve suppression to <50 copies/mL (the primary efficacy endpoint) by the Week 24 time point, but achieving an HIV-1 RNA level <200 copies/mL by Week 24 is clinically meaningful as it indicates that participants have declining viral loads.

A possibility exists that unblinded data from the Sentinel Cohort Week 24 futility assessment may ultimately be submitted to regulatory authorities prior to the Week 48 database lock when the Sponsor becomes unblinded to all participants' study intervention assignments. In that event, an unblinded team at the Sponsor will be identified and those working with these unblinded data, working on the submission, and responding to regulatory questions would be firewalled from those blinded Sponsor personnel working on the study. A separate data integrity/management plan will be developed to further define the roles and access for those on the unblinded team at the Sponsor should this occur.

The eDMC will also be convened for an ad hoc meeting in the event that the listed efficacy criteria for either the Sentinel Cohort prior to completion of the Sentinel Cohort Week 24 futility assessment or for the complete study population after enrollment of the Sentinel

Cohort are met, as assessed by the external unblinded statistician (see Section 4.1 for the listed efficacy criteria). The external unblinded statistician will monitor whether the ad hoc eDMC criteria have been met. Sponsor will not be aware if an ad hoc meeting is called unless the eDMC recommends changes to the study.

In addition to the Sentinel Cohort Week 24 futility assessment described above, the eDMC will review accumulating safety and efficacy data at regular intervals throughout the study duration, or at modified intervals based on the recommendation of the eDMC, or on an ad hoc basis as described in Section 4.1. The eDMC will recommend steps to ensure the safety of study participants and the integrity of the trial as needed.

The Week 48 analysis will be conducted to test the primary non-inferiority efficacy hypothesis once all participants have completed the Week 48 visit assessments. This will be the formal evaluation of the primary non-inferiority efficacy hypothesis, and the Sponsor will become unblinded at that time. The analysis of the data will be performed by the unblinded team of the Sponsor. All available efficacy and safety data will be reviewed at this interim time point. Treatment-level results from this analysis will be provided to the eDMC.

While the study remains blinded to the Sponsor (ie, until the Week 48 database lock), treatment-level results from all IAs will be provided to the eDMC by the external unblinded statistician. Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the IAs.

Participants and all field and study-site personnel will remain blinded throughout the study.

If the study is stopped early, the CSR will include all available data up to and including the close-out visits. This approach to include all available information is in line with the ICH-E9 guideline.

9.8 Multiplicity

As noted in Section 9.7, an eDMC will convene at routine intervals to monitor efficacy and safety. There is no intention of stopping the study due to positive efficacy at any of these reviews. A formal futility analysis at Week 24 is planned as described in Section 9.7, a small amount of alpha (α=0.00001) will be allocated for this IA, for statistical rigor.

The efficacy and safety hypotheses testing will be controlled at an overall 1-sided 2.499% alpha level. The gatekeeping method will be implemented in this study.

Primary efficacy hypothesis (H1) will be tested at the 1-sided 2.499% Type I error rate.

The secondary safety hypotheses (H2) testing superiority of Group 1 to Group 2 as assessed by having a lower mean increase from baseline in weight at Week 48 and (H3) testing superiority of Group 1 to Group 2 as assessed by having a lower mean increase from baseline in weight at Week 96 will be tested only if the null hypothesis of the primary efficacy hypothesis (H1) is rejected. These hypotheses will be tested using the following rules if H1 is rejected:

(1) (H2) will be tested at a 1-sided 1% Type I error rate denoted by α_1.

(2a) If (H2) is retained (ie, the null hypothesis is not rejected) at Week 48, (H3) will be tested at Week 96 at a 1-sided 1.499% Type I error rate denoted by α_2.

(2b) If (H2) is rejected at Week 48, (H3) will be tested at Week 96 at a 1-sided Type I error rate of $\alpha_1 + \alpha_2$.

(3) If (H2) is retained at Week 48 and (H3) is rejected at Week 96, (H2) will be retested at Week 96 at a 1-sided Type I error rate of α_2.

This approach strongly controls the overall 1-sided Type I error rate for the efficacy hypothesis (H1) and safety hypotheses (H2 and H3) at the 2.499% level [Maurer, W., et al 2011].

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

9.9.1.1 Evaluation of Non-Inferiority and Superiority Hypotheses

This section presents power calculations for the efficacy hypotheses of demonstrating non-inferiority of DOR/ISL to BIC/FTC/TAF and demonstrating superiority of DOR/ISL to BIC/FTC/TAF. The power calculations provided in this section do not account for the futility assessment at the Sentinel Cohort Week 24 futility assessment.

For efficacy analyses using the FDA snapshot algorithm, missing data (eg, due to study intervention discontinuation) are classified as either HIV-1 RNA ≥50 copies/mL or as No Virologic Data in Specified Analysis Time Window; in both cases, the data will contribute only to the denominator in the calculation of the percentage of participants with HIV-1 RNA <50 copies/mL. Therefore, the impact of missing data on study power is subsumed within the rates of HIV-1 RNA <50 copies/mL assumed in the power calculations throughout Section 9.9.1.

Non-inferiority will be concluded if the lower bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48 (Group 1 minus Group 2) is greater than -10 percentage points. The choice of non-inferiority margin is based on the portion of the treatment effect preserved that is clinically acceptable; with an anticipated effect >80%, a stringent margin of 10 percentage points is clinically acceptable.

Table 12 summarizes the power to declare DOR/ISL non-inferior to BIC/FTC/TAF under various assumptions for the response rate (ie, the percentage of participants with HIV-1 RNA <50 copies/mL) in Group 2 and the underlying between-group difference in response rates. For example, if the true rate of participants with HIV-1 RNA <50 copies/mL at Week 48 is 90% in both groups, this study has approximately 95.4% power to demonstrate non-inferiority. If the true rates are 85% in both groups, this study has approximately 87.3% power to demonstrate non-inferiority.

Table 12 Power (%) to Establish Non-inferiority at Week 48 Under Various Response Rate Assumptions

True Response Rate in Group 2	True Difference in Response Rates (Group 1 Minus Group 2)						
	-2.0 Percentage Points	-1.0 Percentage Point	-0.5 Percentage Points	0.0 Percentage Points	0.5 Percentage Points	1.0 Percentage Point	2.0 Percentage Points
85%	67.7	78.6	83.3	87.3	90.6	93.3	96.9
86%	69.8	80.7	85.2	89.0	92.1	94.5	97.7
87%	72.1	82.8	87.1	90.7	93.5	95.7	98.3
88%	74.6	85.0	89.1	92.4	94.9	96.7	98.8
89%	77.2	87.3	91.0	93.9	96.1	97.6	99.3
90%	80.0	89.5	92.9	95.4	97.2	98.4	99.6
91%	82.9	91.7	94.7	96.8	98.2	99.0	99.8
92%	85.9	93.8	96.3	97.9	98.9	99.5	99.9
93%	88.9	95.7	97.6	98.8	99.4	99.8	~100
94%	91.7	97.3	98.6	99.4	99.8	99.9	~100
95%	94.3	98.5	99.3	99.8	99.9	~100	~100

CI=confidence interval; HIV-1=human immunodeficiency virus type 1; RNA=ribonucleic acid.

250 Participants per group

The response rate is the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48

The non-inferiority margin is 10 percentage points. To establish non-inferiority, the lower bound of the 2-sided 95% CI for the difference between groups (Group 1 minus Group 2) in the percentage of participants with HIV-1 RNA <50 copies/mL must be >-10 percentage points.

The 95% CI is based on the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The 1-sided Type I error is 0.02499. Calculations were performed using PASS 16.

9.9.1.2 Evaluation of the Futility Criterion and Non-Inferiority at Week 48

The Week 24 Sentinel Cohort is defined as the first 30 participants in each treatment group who complete the Week 24 visit assessments (or who have discontinued prior to Week 24 due to lack of efficacy). The futility assessment will be conducted on the Week 24 Sentinel Cohort; the study may be stopped if the lower bound of the 2-sided 95% CI for the difference in the percentage of participants in the Sentinel Cohort with HIV-1 RNA <200 copies/mL at Week 24 (Group 1 minus Group 2) is less than -30 percentage points. At the time of the analysis, slightly more than 30 participants in each group could be included in the analysis. The power calculations provided here assume a minimum of 30 per group to be conservative.

Table 13 summarizes the probability of not meeting the futility criterion at Week 24 under various assumptions for the response rate (ie, the percentage of participants with HIV-1 RNA

<200 copies/mL) in Group 2 and the underlying between-group difference in response rates. For example, if the true rate of HIV-1 RNA <200 copies/mL at Week 24 is 85% in both groups, then the probability of not meeting the futility criterion is 87.3%. If the true rates are 90% in both groups, then the probability of not meeting the futility criterion is 94.0%. If the true rate in Group 1 is 85.5% and the true rate in Group 2 is 87.5%, then the probability of not meeting the futility criterion is 84.7%.

Table 13 Probability of Not Meeting the Futility Criterion at the Week 24 Interim Analysis (30 Participants Per Group)

True Response Rate in Group 2	True Difference in Response Rates (Group 1 Minus Group 2)						
	-2.0 Percentage Points	-1.0 Percentage Point	-0.5 Percentage Points	0.0 Percentage Points	0.5 Percentage Points	1.0 Percentage Point	2.0 Percentage Points
80%	74.7	78.0	79.7	81.2	82.8	84.2	86.9
82.5%	77.3	80.8	82.4	84.0	85.5	86.9	89.5
85%	80.8	84.2	85.8	87.3	88.7	90.0	92.4
87.5%	84.7	87.9	89.3	90.7	91.9	93.1	95.1
90%	88.7	91.6	92.8	94.0	95.0	95.9	97.4
92.5%	92.7	95.0	96.0	96.9	97.6	98.2	99.1
95%	96.5	98.0	98.6	99.0	99.4	99.6	99.9

CI=confidence interval; HIV-1=human immunodeficiency virus type 1; RNA=ribonucleic acid.

The response rate is the percentage of participants with HIV-1 RNA <200 copies/mL at Week 24.

Futility Criterion: Lower bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA <200 copies/mL at Week 24 (Group 1 minus Group 2) is less than -30 percentage points.

The 95% CI is based on the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The 1-sided Type I error is 0.025. Calculations were performed using PASS 16.

The probability of not meeting the futility criteria based on the Week 24 Sentinel Cohort data and the conditional and unconditional study power to demonstrate non-inferiority at Week 48 under a variety of assumptions is presented in Table 14.

The power calculations shown in Table 14 incorporate the futility assessment stopping rule. Of interest is the likelihood that the study would not meet the futility criterion at Week 24 for a variety of assumed Week 24 response rates and also whether the non-inferiority criterion at Week 48 would be subsequently met (ie, the conditional power of declaring DOR/ISL non-inferior to BIC/FTC/TAF at Week 48).

For example, if the true rate of HIV-1 RNA <200 copies/mL at Week 24 is 95% in both groups, the rate of HIV-1 RNA <50 copies/mL at Week 48 among participants who had HIV-1 RNA <200 copies/mL at Week 24 is 95% in both groups, and the rate of HIV-1 RNA <50 copies/mL at Week 48 among participants who had HIV-1 RNA ≥200 copies/mL at Week 24 is 10% in both groups, then the probability of not meeting the futility criterion at the Week 24 IA is 99.1% and the subsequent power to declare non-inferiority of DOR/ISL to BIC/FTC/TAF at Week 48 is 96.5%.

Table 14 Probability of Not Meeting the Futility Criterion at the Week 24 Interim Analysis and the Conditional Power to Declare Non-Inferiority at Week 48 for Various Underlying True Response Rates

Parameter	Base Case		Low Efficacy for DOR/ISL; Low Efficacy for BIC/FTC/TAF		Low Efficacy for DOR/ISL; High Efficacy for BIC/FTC/TAF		High Efficacy for DOR/ISL; Low Efficacy for BIC/FTC/TAF		High Efficacy for DOR/ISL; High Efficacy for BIC/FTC/TAF		Lowest Efficacy for DOR/ISL; High Efficacy for BIC/FTC/TAF	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Assumptions[a]												
% with Week 24 HIV-1 RNA <200 Copies/mL	95%	95%	92%	92%	92%	98%	98%	92%	98%	98%	88%	98%
% with Week 48 HIV-1 RNA <50 copies/mL if Week 24 HIV-1 RNA <200 copies/mL	95%	95%	95%	95%	95%	97%	97%	95%	97%	97%	95%	97%
% with Week 48 HIV-1 RNA <50 copies/mL if Week 24 HIV-1 RNA ≥200 copies/mL	10%	10%	3%	3%	3%	10%	10%	3%	10%	10%	3%	10%
% with Week 48 HIV-1 RNA <50 copies/mL	90.8%	90.8%	87.6%	87.6%	87.6%	95.3%	95.3%	87.6%	95.3%	95.3%	84.0%	95.3%
Study Power												
Probability of Not Meeting the Futility Criterion[b]	99.1%		96.1%		92.0%		99.9%		99.9%		73.0%	
Conditional Power to Establish Non-Inferiority at Week 48[c]	96.5%		92.2%		15.2%		~100%		99.8%		0.01%	
Unconditional Power to Establish Non-Inferiority at Week 48[c]	96.5%		91.6%		14.5%		~100%		99.9%		0.01%	

BIC=bictegravir; CI=confidence interval; DOR=doravirine; FTC=emtricitabine; HIV-1=human immunodeficiency virus type 1; ISL=islatravir; RNA=ribonucleic acid; TAF=tenofovir alafenamide.
The calculations assume 30 participants in each treatment group for the assessment of futility at Week 24 and 250 participants in each treatment group for the assessment of non-inferiority at Week 48.

[a] The assumptions for calculating power are based on observed rates in study MK-8591A-020 (P020) and the BIC/FTC/TAF treatment-naïve studies, Trials 1489 and 1490. Specifically, P020 showed a blinded rate (ie, pooled across the DOR/ISL and BIC/FTC/TAF treatment arms) <50 copies/mL at Week 48 of ~90% (based on ~450 participants with available Week 48 data as of September 2022). In the BIC/FTC/TAF Trials 1489 and 1490, the rates of HIV-1 RNA <50 copies/mL at Week 48 were 92% and 89%, respectively.

[b] Futility Criterion: Lower bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA <200 copies/mL at Week 24 (Group 1 minus Group 2) is less than -30 percentage points. Values for the probability of not meeting the futility criterion were calculated via simulation.

[c] Each value was calculated via 10,000 simulations to evaluate first whether the futility criterion was met and if not, evaluate non-inferiority between groups using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The non-inferiority margin is 10 percentage points and the Type I error is 0.02499 (1-sided). Calculations were performed in R 3.5.0.

9.9.2 Sample Size and Power for Safety Analyses

9.9.2.1 Evaluation of Adverse Events

The probability of observing at least 1 of a particular type of AE in this study depends on the number of participants treated and the underlying percentage of participants with that AE in the study population.

If the underlying incidence of a particular AE is 1%, there is a 91.9% chance of observing at least 1 AE among 250 participants in a treatment group. If no AE of that type is observed among 250 participants in a treatment group, this study will provide 97.5% confidence that the underlying percentage of participants with that particular AE is <1.5% (1 in every 69 participants) in the treatment group.

The point estimate and the upper bound of the corresponding 2-sided 95% CI for the underlying percentage of participants with an AE given various hypothetical observed numbers of participants with the AE within each treatment group are provided in Table 15. These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Table 15 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Participants with AEs

Number of Participants With Adverse Event	Estimate of Incidence	95% Upper Confidence Bound[a]
0	0.0%	1.5%
5	2.0%	4.6%
10	4.0%	7.2%
15	6.0%	9.7%
20	8.0%	12.1%
25	10.0%	14.4%
30	12.0%	16.7%

AE=adverse event; CI=confidence interval.
250 Participants Per Group
[a] Based on the 2-sided exact 95% CI for a binomial proportion (Clopper and Pearson method [Clopper, C. J. and Pearson, E. S. 1934]). In the 0-event case, it is 1-sided 97.5% CI.

Table 16 gives the difference in the incidence of an AE (Group 1 minus Group 2) that can be ruled out with different power levels and 95% confidence when there are 250 participants in each group. The underlying incidence of the AE is assumed to be the same for the 2 treatment groups. For example, for a reasonably common AE, which occurs in 20% of participants in both groups, the study has 80% power to declare with 95% confidence that the true difference between the treatment groups is no more than 10.9 percentage points. The calculations are based on an asymptotic method proposed by Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985].

Table 16 Difference in Incidence (Percentage Points) of AEs (Group 1 Minus Group 2) That Can Be Ruled Out With 250 Participants Per Group

Target Power	Underlying AE Incidence Rate						
	1%	5%	10%	20%	30%	40%	50%
80%	4.4	7.0	8.8	10.9	12.0	12.5	12.4
85%	4.9	7.6	9.5	11.7	12.9	13.3	13.3
90%	5.5	8.3	10.4	12.7	14.0	14.4	14.3
95%	6.5	9.5	11.7	14.3	15.6	16.0	15.8

AE=adverse event; CI=confidence interval.
Values represent the upper bound of the 2-sided 95% CI (unstratified Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985]) for the difference in AE incidences (Group 1 minus Group 2) assuming the incidences are the same.

9.9.2.2 Evaluation of Change in Weight

Table 17 gives the hypothetical minimal treatment differences in the mean change from baseline in weight that can be detected between the DOR/ISL and BIC/FTC/TAF treatment groups with given power at Weeks 48 and 96 assuming varying values of the underlying standard deviation and accounting for potential participant dropout. The calculations incorporate the testing strategy specified in Section 9.8, which allows for the transfer of alpha back and forth between the Week 48 and Week 96 hypotheses based on whether hypotheses (H2) and (H3) are retained (ie, the null hypothesis is not rejected) or rejected. Note that the probability that the Week 48 and Week 96 hypotheses are retained or rejected are not estimated or accounted for in the power calculations. For example, if the standard deviation of the mean change in weight from baseline in both treatment groups at Week 96 is 8 kg and the number of participants in each treatment group at Week 96 is 200, then this study will provide 90% power to detect a difference at least as large as 2.77 kg at Week 96 assuming that the Week 48 hypothesis (H2) was retained.

While the mean change in weight will be compared between treatment groups using a cLDA model, for simplicity, the power calculations in Table 17 are based on the pooled 2-sample t-test. The minimal treatment differences that could be detected with given power using the cLDA model would be smaller than those in Table 17 due to the increased precision of the cLDA approach relative to the pooled 2-sample t-test.

Table 17 Hypothetical Minimal Treatment Differences (Group 1 minus Group 2) in the Mean Change From Baseline in Weight That Can Be Detected With Given Power at Weeks 48 and 96

Week 48 Hypothesis (H2) is Tested at $\alpha_1 = 0.01$			
Power	n = 217 Participants per Group[a]		
	Standard Deviation of Mean Change in Weight From Baseline[b]		
	4 kg	5 kg	6 kg
80%	1.22	1.53	1.83
85%	1.30	1.62	1.94
90%	1.39	1.74	2.08
If Week 48 Hypothesis (H2) is Rejected, Week 96 Hypothesis (H3) is Tested at $\alpha_1 + \alpha_2 = 0.025$			
Power	n = 200 Participants per Group[a]		
	Standard Deviation of Mean Change in Weight From Baseline[b]		
	8 kg	10 kg	12 kg
80%	2.25	2.81	3.37
85%	2.40	3.00	3.60
90%	2.60	3.25	3.90
If Week 48 Hypothesis (H2) is Retained, Week 96 Hypothesis (H3) is Tested at $\alpha_2 = 0.015$			
Power	n = 200 Participants per Group[a]		
	Standard Deviation of Mean Change in Weight From Baseline[b]		
	8 kg	10 kg	12 kg
80%	2.42	3.02	3.62
85%	2.57	3.22	3.86
90%	2.77	3.46	4.15
If Week 48 Hypothesis (H2) is Retained and Week 96 Hypothesis (H3) is Rejected, Week 48 Hypothesis (H2) is Retested at $\alpha_2 = 0.015$			
Power	n = 217 Participants per Group[a]		
	Standard Deviation of Mean Change in Weight From Baseline[b]		
	4 kg	5 kg	6 kg
80%	1.16	1.45	1.74
85%	1.23	1.54	1.85
90%	1.33	1.66	1.99

3TC=lamivudine; DOR=doravirine; ISL=islatravir; TDF=tenofovir disoproxil fumarate.
Values are computed using the pooled 2-sample t-test.

[a] The calculations account for potential participant dropout prior to the Week 48 and Week 96 time points. A dropout rate of 13% at Week 48 and 20% at Week 96 was assumed in the calculations based on data from MK-1439A-021. As such, the number of participants per group is assumed to be 217 at Week 48 and 200 at Week 96.

[b] Values of the standard deviation of the mean change in weight from baseline are based on experience with MK-8591-011. In this study, the standard deviation of the mean change in weight from Day 1 through Week 48 ranged from approximately 4.1 kg (DOR/3TC/TDF treatment group) to 5.9 kg (ISL[0.75 mg]+DOR+3TC treatment group). Assuming the mean change in weight from Week 48 through Week 96 would be consistent with the observed mean change in weight from Day 1 through Week 48, the 96-week mean weight change standard deviations range from approximately 8 kg to 12 kg.

α_1=1% 1-sided Type I error for the Week 48 weight hypothesis (H2).
A_2=1.5% 1-sided Type I error for the Week 96 weight hypothesis (H3).
Note: “Retained” means the corresponding null hypothesis is not rejected.
Note: The probability that the Week 48 and Week 96 hypotheses are retained or rejected are not estimated or accounted for in the power calculations.

9.10 Subgroup Analyses

To assess whether the treatment effect with respect to the primary efficacy endpoint of the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48 is consistent across various subgroups of the study population, the between-treatment group effect (with a nominal 95% CI based on the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]) will be estimated within each subgroup of the following classification variables:

- Age category (<50 years of age, ≥50 years of age)
- Sex at birth (female, male)
- Gender identity (boy/man, girl/woman, transgender boy/man, transgender girl/woman, genderqueer/non-binary/gender non-conforming, other)
- Region (North America, South America, Europe, Asia, Africa, etc.)
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Chronic hepatitis C status (HCV-infected, HCV-uninfected)
- Baseline CD4+ T-cell count category (<200 cells/mm^3, ≥200 cells/mm^3)
- Screening HIV-1 RNA (≤100,000 copies/mL, >100,000 copies/mL)
- Baseline HIV-1 RNA (≤100,000 copies/mL, >100,000 copies/mL)
- Baseline HIV-1 RNA (≤500,000 copies/mL, >500,000 copies/mL)
- HIV-1 subtype

The snapshot approach will be used to handle missing values in these subgroup analyses.

9.11 Compliance (Medication Adherence)

In this study, as part of the routine recording of the amount of study intervention taken by each participant, the number of tablets remaining in study packaging will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate participant compliance.

For the main analysis of compliance in this study, a day within the study will be considered an “On Therapy” day if the participant takes at least 1 tablet from any bottle provided for this study.

In the base study period, the “Number of Days Should be On Therapy” is the total number of days from start date of the blind study intervention to the last dose date of the blinded study intervention for each participant. As such, the “Number of Days Should be On Therapy” will be the number of days from start date of the blind study intervention to the time point of interest (ie, Week 48, Week 96, or Week 144) for those participants who are on the blinded

study intervention for the entire blinded study period of interest. For participants who discontinue the blinded study intervention prior to or within the blinded study period of interest, the "Number of Days Should be On Therapy" will be the number of days from start date of the blind study intervention to the date of discontinuation of the blinded study intervention.

For each participant and each blinded study period of interest, percent compliance will be calculated using the following formula:

$$Percent\ Compliance = \frac{Number\ of\ Days\ on\ Therapy}{Number\ of\ Days\ Should\ be\ on\ Therapy} \times 100$$

For the secondary analysis of compliance, a day within the study will be considered an "On Therapy" day if the participants take at least 1 tablet from the bottle containing the active study intervention. The definition of the "Number of Days Should be On Therapy" and the formula for calculating percent compliance are the same as defined above for the main analysis of compliance. This secondary compliance measure will be used to identify exclusions from the PP population (see Section 9.5.1).

Summary statistics will be provided for percent compliance by treatment group for the FAS population.

9.12 Extent of Exposure

The extent of exposure to study intervention for all randomized and treated participants will be summarized in the base study period. The number of participants exposed to various doses (actual total daily dose) for defined periods of time will be tabulated, along with a summary of the mean (range) duration participants were exposed to various doses.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and

healthcare providers to ensure operational feasibility. Trial design also includes proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide their financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this

process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 Interim Analysis) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.3 Scientific Advisory Committee (SAC)

This study was developed in collaboration with an SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on

various aspects of the clinical trial and/or development, which may include study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. For studies conducted under the EMA Clinical Trials Regulation 536/2014, a summary of the study results will be submitted in compliance with the regulation**.** MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection,

copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the study). No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- Local laboratory tests may be utilized for screening and to determine study eligibility as noted in Section 1.3.1.

- The tests detailed in Table 18 will be performed by the central laboratory at Day 1 and all subsequent visits.
  Note: In rare instances, if central laboratory use is not feasible, local laboratory tests may be used at scheduled study visits after consultation with the Sponsor. Plasma HIV-1 RNA quantification requires use of a validated PCR assay with a lower limit of detection of <50 copies/mL (see Appendix 10). In these cases, central laboratory samples should not be collected in parallel.

- Unscheduled local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time if feasible. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

The amount of blood collected from each participant over the duration of the study is provided in Table 19 through Table 22.

- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

- Pregnancy testing:

  - Pregnancy testing requirements for study inclusion are described in Section 5.1.

  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during participation in the study.

  - Participants who become pregnant during the study must be managed per Section 8.11.6.

Table 18 Protocol-required Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCH Concentration RDW	WBC Count with Differential[a]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
TBNK Panel/ CD4+ T-cell Count	T and B Lymphocyte, and Natural Killer Cell profile that includes: CD3+CD4+ Percent CD3+CD4+ Value/Absolute Count CD3+CD8+ Percent CD3+CD8+ Value/Absolute Count CD4/CD8 Ratio and the following exploratory assessments (which, do not need to be evaluated by the investigator): CD3+ Percent CD3+ Value/Absolute Count CD3-CD19+ Percent CD3-CD19+ Value/Absolute Count CD16+CD56+ Percent CD16+CD56+ Value/Absolute Count CD3+CD4+CD8+ Percent CD3+CD4+CD8+ Value/Absolute Count			
Coagulation	PT/INR			
Chemistry (nonfasting)	BUN	Potassium	AST/SGOT	Total bilirubin Direct bilirubin Indirect bilirubin
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (nonfasting)	Calcium	ALP	CrCl
	CK	Lipase	Amylase	Mg
	eGFR by MDRD equation (Appendix 8)			
Additional Chemistry at Fasting Visits (fasting for at least 8h)	Glucose HbA1c (collected regardless of participant's fasting status) HDL-C LDL-C TGs TC Non-HDL-C Insulin[b] HOMA-IR (calculation)			

Laboratory Assessments	Parameters
Routine Urinalysis (with microscopic exam as needed)	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
Pregnancy Testing	Highly sensitive serum and urine hCG (as needed for POCBP)
Hepatitis B Serology[c]	HBsAg Anti-HBs Anti-HBc
HBV DNA (reflex)[c]	HBV DNA (perform if HBsAg or Anti-HBc positive)
Hepatitis C Serology	Hepatitis C antibody (if positive perform plasma HCV quantitative test) (at screening only)
HIV-1 and HIV-2 Serology	HIV-1 and HIV-2 antibody test HIV-1/HIV-2 antibody differentiation assay
Virology	HIV-1 RNA quantification (validated PCR assay with a lower limit of detection of <50 copies/mL) HIV-1 viral drug resistance
Inflammatory Markers	D-dimer IL-6 sCD-163 hs-CRP
Energy and Metabolism Markers	Adipokines: Leptin Adiponectin
Renal Markers	Urinary analysis: Albumin/Cr Protein B-2 M/Cr RBP/Cr Serum analysis: Cystatin-C Creatinine Clearance by Cockcroft-Gault equation (Appendix 8) eGFR by MDRD equation (Appendix 8)
PK	Plasma ISL PK
	Plasma Investigational ISL (PK samples will be collected from all participants. Analysis of these samples will be performed by the Sponsor as needed).
	Plasma ISL and DOR PK (Only participants on DOR/ISL who become pregnant during the study)

Laboratory Assessments	Parameters
ALP=alkaline phosphatase; ALT=alanine aminotransferase; anti-HBc= hepatitis B core antibody; anti-HBs= hepatitis B surface antibody AST=aspartate aminotransferase; B-2M/Cr=beta-2-microglobulin/creatinine ratio; BUN=blood urea nitrogen; CK=creatine kinase; CrCl=creatinine clearance; DNA=deoxyribonucleic acid; DOR=doravirine; eGFR=estimated glomerular filtration rate; FBR=future biomedical research; HbA1c=hemoglobin A1c; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HDL-C=high-density lipoprotein; HIV-1=human immune-deficiency virus 1; HIV-2=human immune-deficiency virus type 2; HOMA-IR=Homeostatic Model Assessment of Insulin Resistance; hs-CRP=high-sensitivity C-reactive protein; IL-6=interleukin-6; INR= international normalized ratio; ISL=islatravir; LDL-C=low-density lipoprotein; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; MDRD=Modification of Diet in Renal Disease; Mg=magnesium; PCR=real time polymerase chain reaction; PK=pharmacokinetic(s); POCBP=participant/participants of childbearing potential; PT =prothrombin time; RBC=red blood cell; RBP/Cr=retinol binding protein/creatinine ratio; RDW=red cell distribution width; sCD-163=soluble CD-163; SGOT=serum glutamic-oxaloacetic transaminase; RNA=ribonucleic acid; SGPT=serum glutamic-pyruvic transaminase; TBNK=T and B lymphocyte and natural killer cell; TC=total cholesterol; TG=triglyceride; WBC=white blood cell. Notes: [a] The central laboratory may reflex to manual differential to further identify atypical or immature forms of leukocytes. [b] Participants with type 1 diabetes mellitus should not fast and should not have insulin levels tested. Participants with type 2 diabetes mellitus taking medications that may result in hypoglycemia should delay their morning dose of diabetic medication while fasting and take it after the blood draw for testing. [c] All participants will be screened and assessed for HBsAg, anti-HBs, and anti-HBc (with reflex HBV DNA testing) per the SoA (Section 1.3.1). Repeat serology with reflex HBV DNA testing at Weeks 48, 96, 144, 192, and 240 is required. In the OLE, Group 2 participants who are anti-HBc-positive, but HBV DNA-negative will have HBsAg and HBV DNA monitored. Pregnant participants (on DOR/ISL only) will have hepatitis serology (with reflex HBV DNA testing if indicated) performed once either centrally or site will report local results, after pregnancy is confirmed.	

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Table 19 Blood Volumes (Efficacy, Safety, and PK) in the Base Study

Study Period	**Screening**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**															**Viremia Confirmation**	**Total Lymphocyte/ CD4+ T-cell Confirmation**	**Total Lymphocyte/ CD4+ T-cell Monitor (DOR/ISL Only)[a]**	**Early Discontinuation of Treatment**	**End of Treatment Follow-Up (Base Study)[b]**
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**																				
Plasma HIV-1 RNA Quantification (PCR)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			6	6
TBNK Panel/CD4+ T-cell Count	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		6	6	6	
Blood (Plasma) for HIV-1 Viral Drug Resistance Testing	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12			12	
Whole Blood for HIV-1 Viral Drug Resistance Testing		4																			
HIV Serology[c]	1																				
HIV-1/HIV-2 Antibody Differentiation Assay	1																				
Hepatitis B with Reflex HBV DNA and Hepatitis C (Screening only) Serologies[c]	10							10				10				10					
Hepatitis B Serology with Reflex HBV DNA in Pregnant Participants[d]		< ----------(10)---------- >																			
Plasma HCV PCR Quantitative Test (only perform if antibody positive)	6																				

Study Period	**Screening**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**															**Viremia Confirmation**	**Total Lymphocyte/ CD4+ T-cell Confirmation**	**Total Lymphocyte/ CD4+ T-cell Monitor (DOR/ISL Only)[a]**	**Early Discontinuation of Treatment**	**End of Treatment Follow-Up (Base Study)[b]**
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**																				
PT/INR	3																				
Chemistry (includes Serum Pregnancy at Screening and Early Discontinuation of Treatment)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6				6	
Hematology	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	(2)
Fasting Lipids		2				2		2		2		2		2							
Fasting Insulin[e]		1				1		1		1		1		1							
HbA1c		2				2		2		2		2		2							
Blood for Inflammatory Markers		11				11		11				11				11					
Blood for Energy and Metabolism		6				6		6		6		6				6					
Cystatin-C		2				2		2				2				2					
Blood (Plasma) for ISL PK		4	4	4	4	4		4									4			4	
Blood (Plasma) for Investigational ISL (and DOR, if applicable) PK[f]							4		4	4	4	4					4	4			
Blood (Plasma) for DOR and ISL PK During Pregnancy[g]		< ----------(4 or 12 as indicated)---------- >															(4)			(4)	(4)
Total Blood Volume per Visit	**53**	**64**	**36**	**36**	**36**	**60**	**36**	**70**	**36**	**47**	**36**	**70**	**32**	**37**	**32**	**61**	**22**	**12**	**8**	**36**	**6**

Study Period	Screening	Blinded Intervention (Base Study) (Group 1 and Group 2)														Viremia Confirmation	Total Lymphocyte/ CD4+ T-cell Confirmation	Total Lymphocyte/ CD4+ T-cell Monitor (DOR/ISL Only)[a]	Early Discontinuation of Treatment	End of Treatment Follow-Up (Base Study)[b]
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 8	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**																			

anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; DNA= deoxyribonucleic acid; DOR=doravirine; HbA1c= hemoglobin A1c; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus type 1; INR=international normalized ratio; ISL=islatravir; mL=milliliter; PCR=polymerase chain reaction; PK=pharmacokinetic; POCBP=participant/participants of childbearing potential; PT=prothrombin time; RNA=ribonucleic acid; TBNK=T and B lymphocyte and natural killer cells.

[a] Blood volumes collected at the Total Lymphocyte Count/CD4+ T-cell Count Monitoring visit represent single monitoring visits every 10 to 14 weeks after discontinuing study intervention.

[b] For the End of Treatment Follow-Up visit, the approximate total volume to be collected is for the assessments in Section 1.3.1 or 1.3.2. Hematology and TBNK to be collected per Section 1.3.3, as indicated.

[c] All participants will be screened for HBsAg, anti-HBs, anti-HBc, (with reflex HBV DNA testing if indicated) as well as hepatitis C antibody (with reflex plasma HCV quantitative test if indicated) at screening. Repeat serology and reflex HBV DNA testing at Weeks 48, 96, and 144 is required.

[d] Not included in total blood volume per visit; pregnant participants (on DOR/ISL only) will have hepatitis serology (with reflex HBV DNA testing if indicated) performed once either centrally or site will report local results, after pregnancy is confirmed.

[e] Participants with type 1 diabetes mellitus should not fast and should not have insulin levels tested. Participants with type 2 diabetes mellitus taking medications that may result in hypoglycemia should delay their morning dose of diabetic medication while fasting and take it after the blood draw for testing.

[f] Investigational ISL PK samples will be collected from all participants. Analysis of these samples will be performed by the Sponsor as needed. See Section 8.6.1.

[g] Not included in total blood volume per visit; during pregnancy, blood samples will be collected for PK sampling per Section 8.11.6.1 during the 1st trimester (4 mL), 2nd trimester (12 mL), 3rd trimester (12 mL), and Postpartum (4 mL) visits. For participants whose pregnancy and/or postpartum visit(s) extends beyond Week 144, see Table 22.

Table 20 Blood Volumes (Genetic Analysis and FBR) in the Base Study

Study Period	**Screening**	**Blinded Intervention (Base Study) (Group 1 and Group 2)**													**Viremia Confirmation**	**Total Lymphocyte/ CD4+ T-Cell Confirmation**	**Total Lymphocyte/ CD4+ T-Cell Monitoring**	**Early Discontinuation of Treatment**	**End of Treatment Follow-Up (Base Study)**
Scheduled Day/Week	Screening	Day 1 (fasting)	Week 4	Week 12	Week 24 (fasting)	Week 36	Week 48 (fasting)	Week 60	Week 72 (fasting)	Week 84	Week 96 (fasting)	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood for Genetic Analysis		9																		
Whole Blood for FBR		8			8		8				8		8		8	8			8	
Total Blood Volume per Visit (mL)		**17**			**8**		**8**				**8**		**8**		**8**	**8**			**8**	
FBR=future biomedical research.																				

Table 21 Blood Volumes (Efficacy and Safety) in the OLE

Study Period	**Optional OLE**					**Viremia Confirmation**	**Total Lymphocyte/ CD4+ T-Cell Confirmation**	**Total Lymphocyte/ CD4+ T-Cell Monitoring**	**Discontinuation of Treatment (OLE)[a, b, or c]**	**End of Treatment Follow-Up (OLE)[a, b, or d]**		
Scheduled Day/Week	Week 148 (Group 2)	Week 168	Week 192	Week 216	Week 240	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**											
Plasma HIV-1 RNA Quantification (PCR)	6	6	6	6	6	6			6	6		6
TBNK Panel/CD4+ T-cell Count	6	6	6	6	6		6	6	6		6	6
Blood (Plasma) for HIV-1 Viral Drug Resistance Testing	12	12	12	12	12	12			12			12
Hematology	2	2	2	2	2		2	2	2		2	2
Chemistry												6
Hepatitis B Serology with Reflex HBV DNA			10		10							
HBsAg and HBV DNA (Group 2 participants with positive anti-HBc)	(10)	(10)	(10)	(10)	(10)							
Blood (Plasma) for Investigational ISL (and DOR, if applicable) PK						4	4	4	4	4		
Blood (Plasma) for DOR and ISL PK (pregnant participants on DOR/ISL)						(4)			(4)	(4)		4
Total Blood Volume per Visit[e]	**26**	**26**	**36**	**26**	**36**	**22**	**12**	**12**	**26[a, b, or c]**	**10[a]**	**8[b]**	**36[d]**

HIV-1=human immunodeficiency virus type 1; ISL=islatravir; mL=milliliter; OLE=open-label extension; PCR=polymerase chain reaction; PK=pharmacokinetic(s); RNA=ribonucleic acid; SoA=Schedule of Activities; TBNK=T and B lymphocyte and natural killer cells.

[a] See Section 1.3.2.
[b] See Section 1.3.3.
[c] See Section 1.3.5.
[d] See Section 1.3.4.
[e] Collection of samples noted in parentheses is conditional, therefore, volumes are not included in Total Blood Volume for that visit.

The assessments in Table 22 are for any participant who is pregnant at the last scheduled study visit (ie, Week 144) and whose visit schedule will be extended through the duration of the pregnancy, to allow assessments through each trimester and postpartum.

Table 22 Blood Volumes: Participants Whose Pregnancy and/or Postpartum Visit(s) Extends Beyond Week 144

Study Period	**Pregnancy**			**Postpartum**	**End of Treatment**
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Scheduled Week	**Pregnancy 1[a]**	**Pregnancy 2[a]**	**Pregnancy 3[a]**	**Pregnancy 4[a] Postpartum**	**End of Treatment Follow-Up[a]**
Visit Timing		12 weeks from Pregnancy 1	12 weeks from Pregnancy 2	≤8 weeks after delivery	42 +7 days after end of treatment
Blood Parameter	**Approximate Blood Volume (mL)**				
Plasma HIV-1 RNA Quantification (PCR)	6	6	6	6	6
TBNK Panel/CD4+ T-cell Count	6	6	6	6	6
Plasma for HIV-1 Viral Drug Resistance Testing	12	12	12	12	12
Hepatitis B Serology and reflex HBV DNA (DOR/ISL Only)[b]	<----------(10)---------->			--	10
Chemistry	6	6	6	6	6
Hematology	2	2	2	2	2
Blood (Plasma) for DOR and ISL PK[c]	4	12	12	4	4
Approximate Blood Volume per Visit (mL)	**36**	**44**	**44**	**36**	**46**

DNA=deoxyribonucleic acid; DOR=doravirine; HBsAg= hepatitis B surface antigen; HBV=hepatitis B virus; HIV-1=human immunodeficiency virus type 1; ISL=islatravir; PCR=polymerase chain reaction; PK=pharmacokinetic(s); RNA=ribonucleic acid.; TBNK=T and B lymphocyte and natural killer cells.

[a] If pregnancy visit occurs at the timeframe of a scheduled OLE study visit, collection of laboratory samples should occur per this SoA. Collection of laboratory samples should not be duplicated.

[b] Pregnant participants (DOR/ISL only) will have 1 sample collected once after pregnancy is confirmed or local laboratory results reported for HBsAg, anti-HBs, anti-HBc (with reflex HBV DNA if indicated) during pregnancy.

[c] Collect PK samples during pregnancy per Section 8.11.6.1.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is

diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
   - All potential or confirmed DILI events will be reported as an ECI and SAE with OME criteria in the absence of other serious criteria.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) by recording the grade according to the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1. Any AE that changes DAIDS grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1 Mild event: Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
  - Grade 2 Moderate event: Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.
  - Grade 3 Severe event: Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
  - Grade 4 Potentially life-threatening event: Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.
  - Grade 5 Death: Deaths related to an AE.

Assessment of causality

- Did the study intervention cause the AE?

- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose drug study; or (3) study intervention (s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

- Premenarchal
- Premenopausal with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Participants of Nonchildbearing Potential (PONCBP)

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, are considered PONCBP:

- Premenopausal with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant[b] • IUS[c] • Nonhormonal IUD • Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
• Azoospermic partner (vasectomized or secondary to medical cause, confirmed by medical history) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[b] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[b] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Penile/external or vaginal/internal condom with or without spermicide[d] • Cervical cap, diaphragm, or sponge with spermicide • A combination of penile/external condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
[a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly) [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation [c] IUS is a progestin releasing IUD [d] Vaginal/internal condom used for contraceptive purposes Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM • Penile/external and vaginal/internal condom should not be used together (due to risk of failure with friction)[d]

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Requirements for EU Countries

Note: Additional country-specific requirements for Germany are in Section 10.7.2 and for France in Section 10.7.3.

For sites participating in EU countries, the following changes apply:

Exclusion Criteria (Section 5.2)

Dependents

Exclusion Criterion #13: Individuals who are or have an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study may not participate in this clinical trial in EU countries.

Discontinuation of Study Intervention (Section 7.1)

Table 4 has been CCI [redacted] (Table 23).

Table 23 CCI [redacted]

CCI [redacted]

10.7.2 Country-specific Requirements for Germany

Throughout the Protocol

Legally Acceptable Representative

Persons of legal age, who are incapable of comprehending the nature, significance and implications of the clinical trial and of determining their will, are excluded from the trial at German sites; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

DEXA Scans

Participants who enroll in Germany will not have DEXA scans as indicated in the SoA. This procedure will be omitted, and participants in Germany will not be included in the applicable analyses.

Exclusion Criteria (Section 5.2)

Exclusion Criterion #14: **Exclusion of persons who per order of court or authorities have been accommodated in an institution (as per German Drug Law (AMG) § 40 (1) sentence 3 no. 4)**

Persons who have been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities are excluded from participation in this clinical trial in Germany.

10.7.3 Country-specific Requirements for France

Exclusion Criteria (Section 5.2)

Exclusion Criterion #15: In addition to all exclusion criteria listed in Section 5.2, the general principles relating to research involving human beings (French Public Health Code Art. L. 1121-6, Art. L. 1121-7, Art. L. 1121-8, Art. L. 1121-8-1) are to be followed.

Adults protected by laws, persons deprived of their liberty by a judicial or administrative decision, those hospitalized without consent in accordance with local law as further defined in the informed consent form, persons admitted to a health or social institution for purposes other than research and adults who are subject to a legal protection measure or who are unable to express their consent are not eligible to participate.

10.7.4 Country-specific Requirements for Turkey

In Turkey, if a participant becomes pregnant (has a positive serum pregnancy test), the participant must discontinue from study intervention (regardless of treatment assignment when known), and the participant's HIV-1 infection and treatment should be managed per local standard of care. All reported pregnancies must be followed to completion or termination so that the outcome of the pregnancy is reported. Additionally, pregnant participants who discontinue study intervention are encouraged, but not required, to consent to postnatal infant safety data collection.

The following protocol sections related to pregnancy remain applicable in Turkey:

- Section 8.1.1.4 Consent for Postnatal Infant Safety Data Collection Through One Year of Age
- Sections 8.4.5 Pregnancy and Exposure During Breastfeeding
- Section 8.11.6 Clinical Management of Participants Who Become Pregnant

  Note, the text within this protocol section (Section 8.11.6) advising the investigator/designee to discuss the appropriateness of continuing study intervention and requirement to obtain informed consent to continue study medication in pregnancy does not apply.
- Section 8.11.6.2 Discontinuing Study Intervention for Pregnancy
- Section 8.11.6.4 Infant Safety Data Collection
- Section 8.11.6.4.1 Schedule of Activities: Infant Safety Data Collection

The following protocol sections are not applicable in Turkey:

- Section 1.3.4 Schedule of Activities for Participants Whose Pregnancy and/or Postpartum Visit(s) Extends Beyond Week 144
- Section 4.2.7 Rationale for Continuing Study Intervention During Pregnancy
- Section 8.1.1.3 Consent for Continuation of Study Intervention During Pregnancy
- Section 8.11.6.1 Continuing Study Intervention in Pregnancy
- Section 8.11.6.3 Participants Who Choose to Breastfeed

10.7.5 Country-specific Requirements for Guatemala

In Guatemala, if a participant becomes pregnant (has a positive serum pregnancy test), the participant must discontinue from study intervention (regardless of treatment assignment when known), and the participant's HIV-1 infection and treatment should be managed per local standard of care. All reported pregnancies must be followed to completion or termination so that the outcome of the pregnancy is reported. Additionally, pregnant participants who discontinue study intervention are encouraged, but not required, to consent to postnatal infant safety data collection through one year of age.

The following protocol sections related to pregnancy remain applicable in Guatemala:

- Section 4.2.6 Rationale for Infant Safety Data Collection
- Section 8.1.1.4 Consent for Postnatal Infant Safety Data Collection Through One Year of Age
- Section 8.4.5 Pregnancy and Exposure During Breastfeeding
- Section 8.11.6 Clinical Management of Participants Who Become Pregnant

  Note, the text within this protocol section (Section 8.11.6) referring to required criteria to continue study medication, advising the investigator/designee to discuss the appropriateness of continuing study intervention, and requirement to obtain informed consent to continue study medication in pregnancy, does not apply.
- Section 8.11.6.2 Discontinuing Study Intervention for Pregnancy
- Section 8.11.6.3 Participants Who Choose to Breastfeed
- Section 8.11.6.4 Infant Safety Data Collection

The following protocol sections are not applicable in Guatemala:

- Section 1.3.4 Schedule of Activities for Participants Whose Pregnancy and/or Postpartum Visit(s) Extends Beyond Week 96
- Section 4.2.7 Rationale for Continuing Study Intervention During Pregnancy
- Section 8.1.1.3 Consent for Continuation of Study Intervention During Pregnancy
- Section 8.11.6.1 Continuing Study Intervention in Pregnancy

10.7.6 Country-specific Requirements for the Dominican Republic

In the Dominican Republic, if a participant becomes pregnant (has a positive serum pregnancy test), the participant must discontinue from study intervention (regardless of treatment assignment when known), and the participant's HIV-1 infection and treatment should be managed per local standard of care. All reported pregnancies must be followed to completion or termination so that the outcome of the pregnancy is reported. Additionally, pregnant participants who discontinue study intervention are encouraged, but not required, to consent to postnatal infant safety data collection through one year of age.

The following protocol sections related to pregnancy remain applicable in the Dominican Republic:

- Section 4.2.6 Rationale for Infant Safety Data Collection
- Section 8.1.1.4 Consent for Postnatal Infant Safety Data Collection Through One Year of Age
- Section 8.4.5 Pregnancy and Exposure During Breastfeeding
- Section 8.11.6 Clinical Management of Participants Who Become Pregnant

  Note, the text within this protocol section (Section 8.11.6) referring to required criteria to continue study medication, advising the investigator/designee to discuss the appropriateness of continuing study intervention, and requirement to obtain informed consent to continue study medication in pregnancy, does not apply.
- Section 8.11.6.2 Discontinuing Study Intervention for Pregnancy
- Section 8.11.6.3 Participants Who Choose to Breastfeed
- Section 8.11.6.4 Infant Safety Data Collection

The following protocol sections are not applicable in the Dominican Republic:

- Section 1.3.4 Schedule of Activities for Participants Whose Pregnancy and/or Postpartum Visit(s) Extends Beyond Week 96
- Section 4.2.7 Rationale for Continuing Study Intervention During Pregnancy
- Section 8.1.1.3 Consent for Continuation of Study Intervention During Pregnancy
- Section 8.11.6.1 Continuing Study Intervention in Pregnancy

10.8 Appendix 8: Calculation of Creatinine Clearance and eGFR

10.8.1 Cockcroft-Gault Equations

Cockcroft-Gault equations:

- If male:

$$Cr_{cl}\ (mL/min) = \frac{(140\text{-age [y]}) \times \text{weight [kg]})}{72 \times \text{serum creatinine (mg/dL)}}$$

- If female:

$$Cr_{cl}\ (mL/min) = \frac{(140\text{-age [y]}) \times \text{weight [kg]})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

10.8.2 MDRD Equation

eGFR estimated by MDRD-NKDEP:

eGFR (mL/min/1.73 m^2) = 175 × (serum creatinine [mg/dL])$^{-1.154}$ × (Age [years])$^{-0.203}$ × 0.742 (if female) × 1.212 (if Black)

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
3TC	lamivudine
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AIDS	acquired immunodeficiency syndrome
albumin/Cr	albumin/creatinine ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Anti-HBc	hepatitis B core antibody
Anti-HBs	hepatitis B surface antibody
APaT	all-participants-as-treated
APaT-E	all-participants-as-treated-extension
Art. L.	article de loi
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
B-2M/Cr	beta-2-microglobulin/creatinine ratio
BCRP	breast cancer resistance protein
BIC	bictegravir
BLOQ	below the limit of quantification
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
C24	concentration after 24 hours
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
cLDA	constrained longitudinal data analysis
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials

Abbreviation	Expanded Term
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
Cr	creatinine
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CTIS	Clinical Trials Information System
CTR	Clinical Trial Regulation
CTFG	Clinical Trial Facilitation Group
C_{trough}	lowest concentration reached before the next dose is administered
CYP	cytochrome P450
DAIDS	Division of AIDS
DAO	data as observed
DDI	drug-drug interaction
DEXA	dual x-ray absorptiometry
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	doravirine
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EEA	European Economic Area
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePROs	electronic patient-reported outcomes
EQ-5D-5L	EuroQol 5-dimensional descriptive system, 5-level version
EU	European Union
FAS	full analysis set
FAS-E	full analysis set-extension
FBR	future biomedical research

Abbreviation	Expanded Term
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDC	fixed-dose combination
FSH	follicle-stimulating hormone
FSR	first site ready
FTC	emtricitabine
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HBc	hepatitis B core
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HIV-SI/SDM	Human Immunodeficiency Virus Symptom Index/symptom distress module
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
HTA	Health Technology Assessment
IA(s)	interim analysis(ses)
IAS-USA	International Antiviral Society-United States of America
IB	Investigator's Brochure
IC_{50}	inhibitory concentration required for 50% inhibition
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICSR	individual case safety report

Abbreviation	Expanded Term
IEC	Independent Ethics Committee
IL-6	interleukin-6
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
InSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IRB	Institutional Review Board
IRT	interactive response technology
ISL	islatravir
ISL-TP	triphosphate form of islatravir
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhea method
LDL-C	low-density lipoprotein cholesterol
LLOQ	lower limit of quantification
M=F	missing data treated as treatment failure
MAR	missing at random
MCAR	missing completely at random
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	missing not at random
NCT	National Clinical Trial
NIMP	noninvestigational medicinal product
NKDEP	National Kidney Disease Education Program
NNRTI	non-nucleoside reverse transcriptase inhibitor
non-HDL-C	non-high-density lipoprotein cholesterol
NRTI	nucleos(t)ide analog reverse transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitor
OF	observed failure
OLE	open-label extension
OME	other important medical event
PCR	polymerase chain reaction

Abbreviation	Expanded Term
PDLC	predefined limit of change
PEP	post-exposure prophylaxis
PI	protease inhibitor
PK	pharmacokinetic(s)
PLWH	people living with HIV
POCBP	participant/participants of childbearing potential
PONCBP	participant/participants of nonchildbearing potential
PP	per-protocol
PrEP	pre-exposure prophylaxis
PRO	patient-reported outcome
PT	prothrombin time
PTs	preferred terms
QD	once-daily
QM	once-monthly
QW	once-weekly
RBC	red blood cell
RBP/Cr	retinol binding protein/creatinine ratio
RNA	ribonucleic acid
RR	respiratory rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
sCD-163	soluble CD-163
SD	standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SMQs	Standardized MedDRA Queries
SoA	schedule of activities
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide
TBNK	T and B lymphocyte and natural killer cell

Abbreviation	Expanded Term
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TG	triglyceride
TN	treatment-naïve
TP	triphosphate
ULN	upper limit of normal
US	United States
VS	virologically suppressed
WBC	white blood cell
WHO	World Health Organization

10.10 Appendix 10: Approved HIV-1 RNA Quantification Assays for Local Viral Load Monitoring

For this study, allowed US FDA-approved HIV-1 RNA quantification assays for local viral load monitoring are listed in Table 24.

This list represents the US FDA-approved nucleic acid testing assays for HIV-1 RNA detection and quantification that have a lower limit of detection of <50 copies/mL. Additional details can be found at: www.fda.gov/vaccines-blood-biologics/blood-blood-products/approved-blood-products and www.fda.gov/vaccines-blood-biologics/hiv-1.

Table 24 Approved HIV-1 RNA Quantification Assays for Local Viral Load Monitoring

Tradename	Infectious Agent	Format	Specimen	Use	Manufacturer
APTIMA HIV-1 Quant Assay **APTIMA HIV-1 Quant Dx Assay**	HIV-1	TMA	Plasma/ Serum	Patient Monitoring: Quantitation of HIV-1 RNA in plasma of HIV-1 infected individuals. Addition of claim for Qualitative detection HIV-1 RNA on Panther platform	Hologic Inc., San Diego, CA US License 1592
COBAS HIV-1		Quantitative PCR	Plasma	Patient Monitoring: Quantitation of HIV-1 RNA in plasma of HIV-1 infected individuals	Roche Molecular Systems, Inc., Pleasanton, CA US License 1636
Abbott RealTime HIV-1					ABBOTT Molecular, Inc., Des Plaines, IL US License NA
Amplicor HIV-1 Monitor Test					Roche Molecular Systems, Inc., Pleasanton, CA US License 1636
COBAS AmpliPrep/COBAS TaqMan HIV-1 Test					Roche Molecular Systems, Inc., Pleasanton, CA US License 1636

FDA=United States Food and Drug Administration; HIV-1=human immunodeficiency virus type 1; NA=not available; PCR=polymerase chain reaction; RNA=ribonucleic acid; TMA=transcription-mediated amplification; US=United States.

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