CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Randomized, Open-Label, Active Controlled Study Evaluating the Safety and Efficacy of an Oral Weekly Regimen of Islatravir in Combination with Lenacapavir in Virologically Suppressed People with HIV
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number: **EU CT Number:** **ClinicalTrials.gov Identifier:**	138311 Not Applicable NCT05052996
Indication:	HIV-1 Infection
Protocol ID:	GS-US-563-6041
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Amendment 6 02 December 2025
Amendment History:	Original: 09 June 2021 Amendment 1 07 September 2021 Amendment 2 20 July 2022 Amendment 3 26 October 2022 Amendment 4 21 February 2024 Amendment 5 19 November 2024 A high-level summary of the changes in each amendment is provided in Appendix 6.
Country-Specific Requirements:	Country-specific requirements, as applicable, are listed in Appendix 5.

This study will be conducted under United States Food and Drug Administration investigational new drug application regulations (21 Code of Federal Regulations Part 312).

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with

International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Gilead Sciences, Inc., and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable institutional review board or independent ethics committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Gilead Sciences, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

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3TC	lamivudine
AE	adverse event
ANCOVA	analysis of covariance
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BCRP	breast cancer resistance protein
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
BLQ	below the limit of quantification
BMI	body mass index
CD4	clusters of differentiation 4
CD8	clusters of differentiation 8
CI	confidence interval
CL_{cr}	creatinine clearance
CL/F	apparent oral clearance
C_{max}	maximum observed concentration of drug
COBI	cobicistat (Tybost®)
CSR	clinical study report
C_{tau}	observed drug concentration at the end of the dosing interval
CYP	cytochrome P450 enzyme
DAIDS	Division of AIDS
dCK	deoxycytidine kinase
DDI	drug-drug interaction
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRV	darunavir
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EFV	efavirenz
EQ-5D-5L	EuroQoL 5 dimension 5 level
ESDD	early study drug discontinuation
EU	European Union

FAM	famotidine
FAS	Full Analysis Set
FDA	Food and Drug Administration
CCI	[redacted]
FTC	emtricitabine
Gilead	Gilead Sciences, Inc.
GLSM	geometric least-squares mean
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIVDQoL	HIV Dependent Quality of Life
HIVTSQ12	HIV Treatment Satisfaction Questionnaires 12
HIVTSQc12	HIV Treatment Satisfaction Questionnaire change version
HIVTSQs12	HIV Treatment Satisfaction Questionnaire 12 status version
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IND	investigational new drug
IQ	inhibitory quotient
IRT	interactive response technology
ISL	islatravir
ISL-TP	triphosphate form of islatravir
LEN	lenacapavir
LLOQ	lower limit of quantification
M = F	missing = failure
MDZ	midazolam
MSD	Merck Sharp & Dohme LLC
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OATP	organic anion transporting polypeptide
OBR	optimized background regimen
P-gp	P-glycoprotein
PIT	pitavastatin
PK	pharmacokinetic(s)
PP-R	The Patient Perspective of Regimen

PP-RC	The Patient Perspective of Regimen Change
PrEP	pre-exposure prophylaxis
PRO	patient-reported outcome
PWH	people with HIV
Q1	first quartile
Q3	third quartile
QD	once daily
QM	once monthly
QW	once weekly
rBA	relative bioavailability
RIF	rifampin
RNA	ribonucleic acid
ROS	rosuvastatin
SAC	Safety Assessment Committee
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SSR	special situation report
TAF	tenofovir alafenamide (Vemlidy®)
T_{max}	time (observed time point) of C_{max}
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
US	United States
VL	viral load
VORI	voriconazole
WT	wild type

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title: A Phase 2 Randomized, Open-Label, Active Controlled Study Evaluating the Safety and Efficacy of an Oral Weekly Regimen of Islatravir in Combination with Lenacapavir in Virologically Suppressed People with HIV

Regulatory Agency Identifier Number(s):

IND Number: 138311

EU CT Number: Not Applicable

ClinicalTrials.gov Identifier: NCT05052996

Study Centers Planned:

Approximately 45 centers in the United States (US)

Objectives and Endpoints:

Primary Objective	Primary Endpoint
• To evaluate the efficacy of oral weekly islatravir (ISL, MK-8591) in combination with lenacapavir (LEN, GS-6207) in virologically suppressed people with HIV (PWH) at Week 24	• The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US Food and Drug Administration (FDA)-defined snapshot algorithm
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of oral weekly ISL in combination with LEN in virologically suppressed PWH at Weeks 12, 24, and 48	• The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 12 and 48 as determined by the US FDA-defined snapshot algorithm • The proportions of participants with HIV-1 RNA < 50 copies/mL at Weeks 12, 24, and 48 as determined by the US FDA-defined snapshot algorithm • The change from baseline in CD4+ T-cell count at Weeks 12, 24, and 48
• To evaluate the safety and tolerability of oral weekly ISL in combination with LEN	• The incidence of treatment-emergent adverse events (AEs) leading to study drug discontinuation
• To evaluate the pharmacokinetics (PK) of ISL and LEN administered as an oral weekly combination regimen	• ISL and LEN PK parameters (C_{max}, T_{max}, C_{tau}, AUC_{tau}, and $t_{1/2}$, as applicable)

CCI	

Study Design:

A schematic diagram of the study is provided in Figure 1.

This is a Phase 2, randomized, open-label, active-controlled, multicenter study to evaluate the safety, efficacy, and PK of ISL+LEN.

Cohort 1:

Virologically suppressed PWH who meet all eligibility criteria will be randomized in a 2:1 ratio to 1 of 2 treatment groups. Enrollment and dosing in Cohort 1 were stopped prematurely by the sponsor.

Treatment Group 1 (n = 50 planned)

Oral ISL 40 mg and LEN 600 mg loading on Days 1 and 2

Oral weekly ISL 20 mg administered with LEN 300 mg (ISL+LEN)

Treatment Group 2 (n = 25 planned)

Oral daily bictegravir/emtricitabine/tenofovir alafenamide (1 × 50/200/25 mg tablet) (B/F/TAF).

Participants in Cohort 1 will receive randomized study drugs for 48 weeks. Prior to the sponsor discontinuation of Cohort 1, it was planned that following completion of the Week 48 visit, participants receiving ISL+LEN in Treatment Group 1 were to continue ISL+LEN and attend visits every 12 weeks. Participants in Treatment Group 2 were to switch from B/F/TAF to the ISL+LEN regimen (starting with the loading doses over 2 days) and continue the study. Participants in Treatment Group 2 who did not switch from B/F/TAF to ISL+LEN at Week 48 were to be discontinued from the study.

After Week 48, participants taking ISL+LEN were to attend visits every 12 weeks until the product became accessible to participants commercially or Gilead Sciences, Inc. (Gilead) elected to discontinue the study.

Cohort 2:

Virologically suppressed PWH who meet all eligibility criteria will be randomized in a 1:1 ratio to 1 of 2 treatment groups:

Treatment Group 3 (n = 50 planned)

Day 1: LEN oral CCI and ISL CCI

Day 2: LEN oral CCI

Day 8 and weekly thereafter (ie, every 7 days): LEN oral CCI) and ISL CCI or ISL CCI tablet (when available)

Treatment Group 4 (n = 50 planned)

Oral daily B/F/TAF (1 × 50/200/25 mg tablet)

Randomization will be stratified by CD4+ T-cell count (350 to 499 [inclusive] cells/mm^3 or ≥ 500 cells/mm^3) at screening.

Participants in Cohort 2 will receive study drugs for at least 48 weeks during the Randomized Phase. At the Week 48 visit, all participants will be given an option to participate in an Extension Phase to receive ISL+LEN or ISL/LEN CCI tablet (when available). Participants in Treatment Group 3 may continue to receive ISL+LEN, while participants in Treatment Group 4 may switch from B/F/TAF to ISL+LEN, starting with the loading doses of LEN over 2 days. During the Extension Phase, participants who are receiving ISL+LEN will switch to ISL/LEN CCI when it becomes available and begin taking ISL/LEN CCI starting at their next scheduled dose. Participants who do not wish to participate in the Extension Phase will be discontinued from the study. Participants in the Extension Phase will attend visits every 12 weeks until Week 144; visits will occur every 24 weeks after Week 144 until ISL/LEN CCI becomes available to participants or Gilead elects to discontinue the study, whichever occurs first.

Number of Participants Planned:

Cohort 1: Approximately 75 virologically suppressed PWH will be enrolled in this cohort. Fifty participants may be enrolled in Treatment Group 1 and 25 participants may be enrolled in Treatment Group 2. Cohort 1 enrollment was stopped prior to reaching the target.

Cohort 2: Approximately 100 virologically suppressed PWH will be enrolled in this cohort. Fifty participants may be enrolled in each of Treatment Groups 3 and 4.

Target Population: Virologically suppressed PWH ≥ 18 years of age.

Duration of Treatment: Duration of treatment in the Randomized Phase is 48 weeks.

Diagnosis and Main Eligibility Criteria: Virologically suppressed PWH who meet the following criteria:

- Aged ≥ 18 years at screening
- Plasma HIV-1 RNA < 50 copies/mL for ≥ 24 weeks before and at screening
- Received B/F/TAF for ≥ 24 weeks prior to screening
- No nonnucleoside reverse transcriptase inhibitor (NNRTI) or nucleos(t)ide reverse transcriptase inhibitor (NRTI) resistance, including M184V/I (Cohort 2)
- CD4+ T-cells ≥ 200 cells/mm^3 (Cohort 1)
- CD4+ T-cells ≥ 350 cells/mm^3 (Cohort 2)

Study Procedures/Frequency:

Cohort 1:

The schedule of study procedures is presented in Table 1.

After screening, participants will have onsite visits on Day 1; at Weeks 4, 8, and 12; and then every 12 weeks thereafter. Participants in the PK substudy will have an additional onsite visit on Day 2. Participants in Treatment Group 1 will have telephone visits on Day 2 and at Week 2.

Cohort 2:

The schedule of study procedures is presented in Table 2.

After screening, participants will have onsite visits on Day 1; at Weeks 4, 8, and 12; and then every 6 weeks thereafter through Week 48 of the Randomized Phase. Participants in the PK substudy will have an additional onsite visit on Day 2 of the Randomized Phase. Participants in Treatment Group 3 and 4 will have a telephone visit at Day 2 and Week 2 of the Randomized Phase.

Participants in the Extension Phase will have onsite visits every 12 weeks through Week 144 and every 24 weeks thereafter. Participants in Treatment Group 4 who switch to ISL+LEN or ISL/LEN CCI (when available) in the Extension Phase will receive telephone calls to confirm adherence to the second day of the LEN loading dose and the second ISL+LEN or ISL/LEN CCI (when available) weekly dose.

Test Product, Dose, and Mode of Administration:

Cohort 1:

Treatment Group 1:

Oral ISL 40 mg (2 × 20 mg capsules) and oral LEN 600 mg (2 × 300 mg tablets) administered on the first and second days of the ISL+LEN regimen without regard to food.

Oral ISL 20 mg (1 × 20 mg capsule) and oral LEN 300 mg (1 × 300 mg tablet) administered on Day 8 of the ISL+LEN regimen and every week (7 days) thereafter (ie, on the same day of the week) without regard to food.

Cohort 2:

For Treatment Group 3 (and any Treatment Group 4 participant electing to start ISL+LEN in the Extension Phase), oral ISL and oral LEN are to be taken without regard to food and, where indicated, taken together. From Day 8 onward, ISL and LEN should be taken weekly on the same day of the week.

During the Extension Phase, participants who are receiving ISL+LEN will switch to the ISL/LEN CCI tablet (when available) administered orally on the same schedule, taken weekly on the same day of the week, without regard to food.

	LEN[a]	ISL[a]
Day 1	CCI	CCI
Day 2		No ISL
Day 8 (and weekly thereafter)		CCI

CCI

CCI; ISL = islatravir; LEN = lenacapavir

a Including participants in Treatment Group 4 who continue in the Extension Phase.

Reference Therapy, Dose, and Mode of Administration:

Treatment Groups 2 and 4: Oral daily B/F/TAF (1 × 50/200/25 mg tablet) administered without regard to food.

Statistical Methods: The primary efficacy endpoint is the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US FDA-defined snapshot algorithm. The 95% CI of the difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 between the ISL+LEN group and the B/F/TAF group within each cohort will be constructed based on an unconditional exact method using 2 inverted 1-sided tests.

The same methods used to analyze the primary efficacy endpoint, as determined by the US FDA-defined snapshot algorithm, will be used to assess the proportion of participants with HIV1 RNA ≥ 50 copies/mL at Weeks 12 and 48 and the proportion of participants with HIV-1 RNA <50 copies/mL at Weeks 12, 24, and 48.

Changes from baseline in CD4+ T-cell count at Weeks 12, 24, and 48 will be summarized by treatment group within each cohort using descriptive statistics. The differences in changes from baseline in CD4+ T-cell count between the ISL+LEN group and the B/F/TAF group within each cohort and the associated 95% CIs will be constructed using analysis of covariance (ANCOVA) models, including baseline CD4+ T-cell count as a covariate and treatment (ISL+LEN vs B/F/TAF) as a fixed-effect in the models.

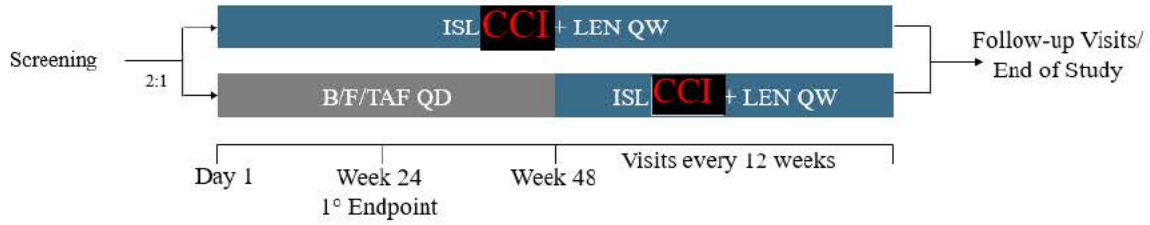
Incidence of treatment-emergent AEs, AEs leading to discontinuation of study drugs, and treatment-emergent laboratory abnormalities will be summarized using descriptive statistics by treatment group within each cohort.

For the general PK analyses, the PK of ISL and LEN may be evaluated using descriptive statistics or population analysis approaches. For the intensive PK substudy, plasma concentrations of ISL and LEN will be summarized by nominal sampling time. Pharmacokinetic parameters (C_{max}, T_{max}, C_{tau}, AUC_{tau}, and $t_{1/2}$, as appropriate) will be listed and summarized using descriptive statistics.

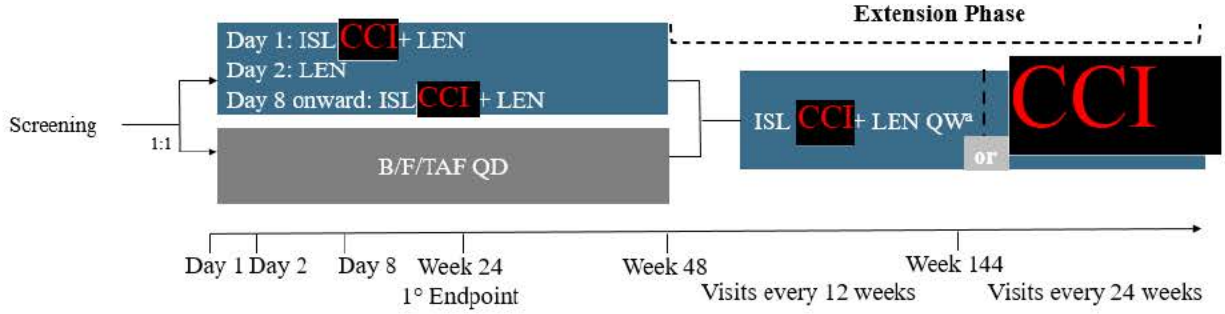
STUDY SCHEMA

Figure 1. Study Schema for Cohort 1 and Cohort 2

Cohort 1



Cohort 2



1° = primary; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CCI ISL = islatravir; LEN = lenacapavir; QD = once daily; QW = once weekly

The randomized treatment period is at least 48 weeks. At the Week 48 visit, all participants will be given the option to take ISL+LEN or ISL/LEN CCI in an Extension Phase until ISL/LEN CCI becomes available or until Gilead elects to discontinue the study, whichever occurs first.

a At the Week 48 visit, all participants will be given the option to take ISL+LEN in an Extension Phase until ISL/LEN CCI becomes available or until Gilead elects to discontinue the study, whichever occurs first.

STUDY PROCEDURES TABLE

Table 1. Study Procedures for Cohort 1

Enrollment and dosing in Cohort 1 were stopped prematurely by the sponsor in December 2021.

	Screening[a]	Day 1[b]	Day 2[c]	Week 2[d]	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48[e]	Week 60	Week 72	Week 84 and every 12 weeks thereafter	ESDD[f]	30- and 60-Day Follow-up[g]
Visit Window (Days)	**Within 35 days prior to Day 1**			**± 1 day**	**± 7 days**								**± 14 days**		**± 2 days**
Written informed consent	X														
PRO questionnaire administration[h]		X			X			X		X		X			
Obtain demographic information	X														
Medical history	X														
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[i] (including weight)	X	X			X	X	X	X	X	X	X	X	X	X	X
Height	X														
Complete physical examination[j]	X	X												X	
Symptom-directed physical examination					X	X	X	X	X	X	X	X	X		X
12-lead ECG (supine)	X														

Visit Window (Days)	Screening[a] Within 35 days prior to Day 1	Day 1[b]	Day 2[c]	Week 2[d] ± 1 day	Week 4 ± 7 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 24 ± 7 days	Week 36 ± 7 days	Week 48[e] ± 7 days	Week 60 ± 7 days	Week 72 ± 7 days	Week 84 and every 12 weeks thereafter ± 14 days	ESDD[f]	30- and 60-Day Follow-up[g] ± 2 days
Hematology, chemistry, urinalysis and urine chemistry, CD4+ T-cell count[k]	X	X			X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test[l]	X														
Serum FSH[m]	X														
Urine pregnancy test[l]		X			X	X	X	X	X	X	X	X	X	X	X
HBV, HCV tests[n]	X														
Plasma HIV-1 RNA	X	X			X	X	X	X	X	X	X	X	X	X	X
Plasma storage sample[o]	X	X			X	X	X	X	X	X	X	X	X	X	X
Whole blood storage sample[p]		X						X		X		X			
PK plasma collection[q]		X			X	X	X	X	X	X					
CCI															
Randomization[s]		X													
Oral ISL+LEN dispensation		X			X	X	X	X	X	X	X	X	X		
B/F/TAF dispensation		X			X	X	X	X	X						
Telephone visit			X[c]	X[d]						X[e]					
Study drug accountability					X	X	X	X	X	X	X	X	X		

AE = adverse event; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; CD4 = clusters of differentiation 4; CPK = creatine phosphokinase; ECG = electrocardiogram; EQ-5D-5L = 5-level EuroQoL (5 dimensions); ESDD = early study drug discontinuation; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIVDQoL = HIV Dependent Quality of Life; HIVTSQ12 = HIV Treatment Satisfaction Questionnaire 12; HIVTSQs12 = HIV Treatment Satisfaction Questionnaire 12 status version; HIVTSQc12 = HIV Treatment Satisfaction Questionnaire change version ICF = informed consent form; ISL = islatravir; LEN = lenacapavir; PK = pharmacokinetic(s); PRO = patient-reported outcome

a Screening evaluations must be completed within 35 days prior to Day 1. Conditions for participant rescreening are outlined in Section 6.2.

b Day 1 tests and procedures must be completed prior to administration of the dose of study drugs. Participants must begin dosing on the same day as Day 1.

c Participants in the PK substudy will come to the site for a study visit on Day 2 and will take their dose of study drugs at the site. All other participants in Treatment Group 1 will receive a telephone call to confirm adherence to the Day 2 ISL+LEN dose.

d Participants in Treatment Group 1 will have a telephone visit at Week 2 to assess AEs and concomitant medications, and to confirm adherence to weekly ISL+LEN dosing.

e Participants in Treatment Group 2 who switch to ISL+LEN at Week 48 will receive telephone calls to confirm adherence to the second day of the ISL+LEN loading dose and the first ISL+LEN weekly dose.

f Visit should occur within 3 days (+1 day) of permanently discontinuing study drugs. Participant should be counseled regarding the importance of resuming a complete ARV therapy in accordance with standard-of-care and referred to an appropriate HIV treatment facility.

g Participants who received ISL+LEN and discontinue study drugs are required to return to the clinic for follow-up visits 30 and 60 days after the last ISL+LEN dose. Participants who received only B/F/TAF (ie, did not switch to ISL+LEN) and discontinue study drugs will be required to return to the clinic for a follow-up visit 30 days after the last on-study B/F/TAF dose. Details are provided in Section 6.4.

h Before completion of other study procedures, participants in both treatment groups will complete the following questionnaires at the specified visits (if available): HIVDQoL at Day 1, Weeks 24 and 48; HIVTSQs12 at Day 1, Weeks 4, 24, and 48; HIVTSQc12 at Week 48; EQ-5D-5L at Day 1, Weeks 4, 24, and 48. The Patient Perspective of Regimen and the Patient Perspective of Regimen Change will be completed by participants in Treatment Group 1 at Weeks 24, 48, and 72, and by participants in Treatment Group 2 at Week 72 only.

i Vital signs include blood pressure, pulse, temperature, and weight.

j Complete physical examination is required at the screening, Day 1, and ESDD visits.

k Analyses to be performed by the central laboratory. Analytes are presented in Table 25.

l Women will have a serum test at screening. Urine pregnancy test will only be done for women of childbearing potential. If any pregnancy test is positive, study drugs should be immediately discontinued, and participant should come to the site for serum pregnancy test.

m FSH test is required for women who are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.

n HBcAb, HBsAg, HBV DNA, HCV RNA.

o For additional safety and virology testing (HIV-1 genotype and phenotype).

p To test for archived resistance. Sampling will occur at the Day 1, Week 24, and Week 48 visits, and every 24 weeks thereafter.

q PK collection: For Treatment Group 1, single anytime plasma PK sampling for ISL and LEN will occur at each onsite visit through Week 48. The date and time of the previous dose of ISL+LEN will be recorded.

r PK substudy: For Treatment Group 1, approximately 10 participants on Days 1 and 2, and at Week 12 on scheduled dosing days, with the dose taken at the site during the study visit. See Table 26 for PK substudy details.

s Participants will be randomized to 1 of the 2 treatment groups on Day 1 after the ICF has been signed, all screening and eligibility tests and assessments have been performed, and study eligibility has been confirmed.

Table 2. Study Procedures for Cohort 2

Study Procedures	Screening[a]	Randomized Phase									Extension Phase		ESDD[f]	Post-Study Drug Follow-up		
				Week							Week					
		Day 1[b]	Day 2[c]	2[d]	4, 8	12	18	24	30, 36, 42	48[e]	Week 60 and every 12 weeks Until Week 144	Week 168 and every 24 weeks thereafter	Within 3 Days of Last Dose	30-Day Follow-up[g]	60-Day Follow-up[g]	100-Day and 200-Day Follow-up[h]
Visit Window (Days)	**Within 35 Days Prior to Day 1**			**± 1 day**	**± 7 days**						**± 14 days**		**+ 1 day**	**± 7 days**		
Written informed consent	X															
Obtain demographic information	X															
Medical history	X															
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIVDQoL[i]		X						X		X						
HIVTSQs12[i]		X			X[i]			X		X						
HIVTSQc12[i]										X						
EQ-5D-5L[i]		X			X[i]			X		X						
HIV Patient Perspective of Regimen (PP-R)[j]		X			X	X		X	X[j]	X	X					
HIV Patient Perspective of Regimen Change (PP-RC)[k]					X	X		X	X[k]	X	X					
Vital signs[l] (including weight)	X	X			X	X	X	X	X	X	X	X	X	X	X	

Study Procedures	Screening[a]	Randomized Phase									Extension Phase		ESDD[f]	Post-Study Drug Follow-up		
				Week							Week					
		Day 1[b]	Day 2[c]	2[d]	4, 8	12	18	24	30, 36, 42	48[e]	Week 60 and every 12 weeks Until Week 144	Week 168 and every 24 weeks thereafter	Within 3 Days of Last Dose	30-Day Follow-up[g]	60-Day Follow-up[g]	100-Day and 200-Day Follow-up[h]
Visit Window (Days)	**Within 35 Days Prior to Day 1**			**± 1 day**	**± 7 days**						**± 14 days**		**+ 1 day**	**± 7 days**		
Height	X															
Complete physical examination[m]	X	X											X			
Symptom-directed physical examination					X	X	X	X	X	X	X	X		X	X	
12-lead ECG (supine)	X															
Hematology, chemistry, urinalysis and urine chemistry, CD4+ T-cell count/TBNK panel[n]	X	X			X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test[o]	X															
Serum FSH[p]	X															
Urine pregnancy test[o]		X				X		X	Week 36 only	X	X	X	X			
HBV, HCV tests[q]	X									X	X[q]	X[q]				
Plasma HIV-1 RNAs	X	X			X	X	X	X	X	X	X	X	X	X	X	
Plasma storage sample[r]	X	X			X	X	X	X	X	X	X	X	X	X	X	

Study Procedures	Screening[a]	Randomized Phase									Extension Phase		ESDD[f]	Post-Study Drug Follow-up		
				Week							Week					
		Day 1[b]	Day 2[c]	2[d]	4, 8	12	18	24	30, 36, 42	48[e]	Week 60 and every 12 weeks Until Week 144	Week 168 and every 24 weeks thereafter	Within 3 Days of Last Dose	30-Day Follow-up[g]	60-Day Follow-up[g]	100-Day and 200-Day Follow-up[h]
Visit Window (Days)	**Within 35 Days Prior to Day 1**			**± 1 day**	**± 7 days**						**± 14 days**		**+ 1 day**	**± 7 days**		
HIV-1 proviral genotype[s]	X															
Whole blood storage sample[t]		X						X		X	X[t]	X				
PK plasma collection[u]		X			X	X	X	X	X	X	X					
CCI																
Randomization[w]		X														
Oral ISL+LEN dispensation		X			X	X	X	X	X	X	X[x]	X[x]				
CCI																
B/F/TAF dispensation (Treatment Group 4)[y]		X			X	X	X	X	X							
Telephone visit			X[c]	X[d]												
Study drug accountability					X	X	X	X	X	X	X	X	X			

AE = adverse event; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; CD4 = clusters of differentiation 4; CPK = creatine phosphokinase; ECG = electrocardiogram; EQ-5D-5L = 5-level EuroQoL (5 dimensions); ESDD = early study drug discontinuation; CCI; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIVDQoL = HIV Dependent Quality of Life;

HIVTSQs12 = HIV Treatment Satisfaction Questionnaire 12 status version; HIVTSQc12 = HIV Treatment Satisfaction Questionnaire change version; ICF = informed consent form; ISL = islatravir; LEN = lenacapavir; PK = pharmacokinetic(s); PP-R = Patient Perspective of Regimen; PP-RC = Patient Perspective of Regimen Change; PRO = patient-reported outcome; TBNK = T, B, and natural killer cells

a Screening evaluations must be completed within 35 days prior to Day 1. Conditions for participant rescreening are outlined in Section 6.2. Participants in Treatment Group 3 must stop their B/F/TAF treatment on Day −1.

b Day 1 tests and procedures must be completed prior to administration of the dose of study drugs. Participants in Treatment Group 3 must begin dosing on Day 1 and will take their dose of study drug on site.

c Participants in the PK substudy will come to the site for a study visit on Day 2 and will take their dose of study drug at the site. All other participants in Treatment Group 3 will receive a telephone call to confirm adherence to the Day 2 LEN dose.

d Participants in Treatment Groups 3 and 4 will have a telephone visit at Week 2 to assess AEs and concomitant medications and, for Treatment Group 3 only, to confirm adherence to weekly ISL+LEN dosing.

e At the Week 48 visit, all participants will be given the option to take ISL+LEN or ISL/LEN [CCI] (when available) in an Extension Phase until ISL/LEN [CCI] becomes available or until Gilead elects to discontinue the study, whichever occurs first. Participants in Cohort 2 who complete the study through the Week 48 visit and do not wish to participate in the Extension Phase will be required to return to the clinic after the Week 48 visit for a 30-day follow-up visit, and participants in Treatment Group 3 will also return for a 60-day follow-up visit. Then the participants will be considered to have completed the study. Participants in Treatment Group 4 who switch to ISL+LEN or ISL/LEN [CCI] (when available) in the Extension Phase will receive telephone calls to confirm adherence to the second day of the LEN loading dose and the second ISL+LEN or ISL/LEN [CCI] (when available) weekly dose.

f Visit should occur within 3 days (+1 day) of permanently discontinuing study drugs. Participant should be counseled regarding the importance of resuming a complete ARV therapy in accordance with standard-of-care and referred to an appropriate HIV treatment facility.

g Participants who received ISL+LEN or ISL/LEN [CCI] and discontinue study drugs are required to return to the clinic for follow-up visits 30 and 60 days after the last ISL+LEN or ISL/LEN [CCI] dose. Participants who received only B/F/TAF (ie, did not switch to ISL+LEN or ISL/LEN [CCI]) and discontinue study drugs will be required to return to the clinic for a follow-up visit 30 days after the last on-study B/F/TAF dose. Details are provided in Section 6.4.

h Participants in Treatment Group 3 or any Cohort 2 participant in the Extension Phase who were discontinued on ISL+LEN due to decrease in CD4 or lymphocytes. Day 200 follow-up visit to be completed only as needed, per Section 6.4.1.

i Participants will complete the questionnaires at the specified visits before completion of other study procedures. Questionnaires are to be completed at Week 4 and not completed at Week 8.

j The PP-R will be completed by participants in Treatment Groups 3 and 4 on Day 1, Weeks 4, 8, 12, 24, 36, 48, 60, and every 12 weeks until Week 144.

k The PP-RC will be completed at Weeks 4, 8, 12, 24, 36, 48, 60, and every 12 weeks thereafter. Participants in Treatment Group 4 will complete the PP-RC every 12 weeks after switching to ISL+LEN in the Extension Phase until Week 144.

l Vital signs include blood pressure, pulse, temperature, and weight.

m Complete physical examination is required at the screening, Day 1, and ESDD visits.

n Analyses to be performed by the central laboratory. Analytes are presented in Table 25.

o Women of childbearing potential will have a serum pregnancy test at screening and urine pregnancy test at Day 1, Weeks 12, 24, 36, 48, and Post Week 48-Every 12 Weeks in Randomized Phase, in Extension Phase (every 12 weeks until Week 144 and every 24 weeks thereafter), and at ESDD. If any pregnancy test is positive, study drugs should be immediately discontinued, and participant should come to the site for serum pregnancy test.

p FSH test is required for women who are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.

q HBcAb, HBsAg, HBsAb, HBV DNA, HCV RNA. Testing will occur in the Extension Phase at Week 96 and every 48 weeks thereafter.

r For additional safety and virology testing (HIV-1 genotype and phenotype).

s Whole blood sample collected at screening visit for proviral genotype analysis of archived resistance.

t Whole blood sample storage to test for archived resistance. Sampling will occur at the Day 1, Week 24, and Week 48 visits, and every 24 weeks thereafter.

u PK collection: For Treatment Group 3, single anytime plasma PK sampling for ISL and LEN will occur at each onsite visit through Week 72 except at Day 1. Day 1 PK sample will be collected 1 hour (± 30 minutes) postdose after onsite study drug administration. The date and time of the previous dose of ISL+LEN will be recorded. PK samples collected at Week 60 and 72 will be stored and analyzed only if deemed necessary by the sponsor.

[redacted]

w Participants will be randomized to 1 of the 2 treatment groups in Cohort 2 on Day 1 after the ICF has been signed, all screening and eligibility tests and assessments have been performed, and study eligibility has been confirmed. Participants in Treatment Group 3 will stop B/F/TAF on Day −1.

x Participants will switch to ISL/LEN[redacted] in the Extension Phase when [redacted] is available. ISL+LEN will no longer be dispensed once a participant switches.

y B/F/TAF dispensation applies only to participants randomized to Treatment Group 4.

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus type 1 (HIV-1) infection is a life-threatening and serious disease of major public health significance, with approximately 39 million people with HIV (PWH) worldwide and approximately 29.8 million taking antiretroviral (ARV) treatment {UNAIDS 2023}. Advances in combination ARV therapy (ART) for HIV have led to significant improvements in morbidity and mortality by suppressing viral replication, preserving immunologic function, and averting disease progression to AIDS. Standard-of-care for the treatment of HIV-1 infection involves the use of a combination of oral ARV drugs (ie, 2 nucleoside reverse transcriptase inhibitors [NRTI] plus a third agent) to suppress viral replication to below detectable limits, increase CD4+ T-cell counts, and delay disease progression.

While combination ART for the treatment of HIV-1 infection is efficacious and well-tolerated, these agents need to be taken every day and require near perfect adherence to minimize the emergence of drug resistant variants. In addition, "treatment fatigue" can occur, defined as "decreased desire and motivation to maintain vigilance in adhering to a treatment regimen" among PWH prescribed chronic or life-long treatment {Claborn 2015}, which can lead to nonadherence and treatment failure. As such, there remains a significant medical need for ARVs that can be administered less frequently (ie, long-acting drug products), thereby providing an alternative treatment option for PWH.

1.2. Background on Study Interventions

Islatravir (ISL, MK-8591)/lenacapavir (LEN, GS-6207) fixed-dose combination (CCI) is being developed for the treatment of HIV-1 in collaboration with Merck Sharp & Dohme LLC (MSD).

1.2.1. Information About Islatravir

Islatravir is a nucleotide reverse transcriptase translocation inhibitor (NRTTI) with potent ARV activity, including activity against common NRTI-resistant variants, and favorable nonclinical toxicity and pharmacokinetic (PK) profiles.

1.2.1.1. General Information

For further information on ISL, including information on the following, refer to the current investigator's brochure (IB) for ISL:

- Nonclinical pharmacology
- Pharmacokinetics and product metabolism in animals
- Nonclinical toxicology and toxicokinetics

- Clinical experience
- Changes in absolute lymphocyte and lymphocyte subset counts (see Section 1.6 for additional details).

1.2.2. Information About Lenacapavir

Lenacapavir is a novel, first-in-class, selective inhibitor of HIV-1 capsid function, which has potent antiviral activity, low human clearance, and physiochemical properties well suited for extended-release parenteral or oral formulations.

1.2.2.1. General Information

For further information on LEN, including information on the following, refer to the IB for LEN:

- Nonclinical PK
- Nonclinical pharmacology and toxicology
- Clinical experience

1.2.2.2. Clinical Studies of Lenacapavir

Clinical data from studies not presented in the LEN IB are presented in this section.

1.2.2.2.1. GS-US-563-6148

Study GS-US-563-6148 is a Phase 1, open-label, parallel-design, single-dose, 3-cohort study examining potential DDIs between ISL and LEN following oral coadministration. Fifty-five healthy participants received single oral doses of coadministered ISL 20 mg and LEN 600 mg (test: N = 18), ISL 20 mg only (reference: N = 18), or LEN 600 mg only (reference: N = 19) under fasted conditions.

Preliminary PK results based on nominal times for percentage geometric least-squares mean (%GLSM) ratios of PK parameters AUC_{inf} and C_{max} for ISL were 105% and 87.9%, respectively, and for LEN were 88.6% and 80.1%, respectively (Table 3). Higher percentage coefficient of variation (%CV) was observed for LEN compared with ISL resulting in wider 90% CI.

Table 3. GS-US-563-6148: Summary Statistics and Statistical Comparisons of ISL and LEN PK Parameters

	Mean PK Parameter (%CV)	ISL+LEN (N=18)	Reference: ISL Only (N=16) or LEN Only (N=18)	ISL+LEN vs Reference %GLSM Ratio (90% CI)
ISL	$C_{max,}$ ng/mL	145 (41.3)	165 (42.2)	87.9 (68.7, 113)
	$AUC_{inf,}$ h•ng/mL	674 (25.4)	642 (25.8)	105 (90.2, 123)
	$T_{max,}$ h[a]	0.75 (0.50, 2.00)	0.75 (0.50, 2.00)	ND
	Apparent terminal $t_{1/2,}$ h	121 (18.7)	99.1 (14.6)	ND
LEN	$C_{max,}$ ng/mL	33.7 (77.7)	37.9 (57.0)	80.1 (50.9, 126)
	$AUC_{inf,}$ h•ng/mL	9840 (51.0)	10,800 (56.9)	88.6 (60.5, 130)
	$T_{max,}$ h[a]	8.00 (1.00, 48.0)	10.0 (2.00, 312)	ND
	Apparent terminal $t_{1/2,}$ h	296 (23.5)	308 (24.7)	ND

%CV = percentage coefficient of variation; CI = confidence interval; GLSM = geometric least-squares mean; ISL = islatravir; LEN = lenacapavir; ND = not determined; PK = pharmacokinetic(s)
Data are shown to 3 significant digits; results based on nominal time.
a T_{max} is presented as median (min, max).

Overall, oral coadministration of ISL and LEN showed similar PK compared with when administered alone and no clinically meaningful PK DDIs were present.

1.2.2.2.2. GS-US-200-4333

Study GS-US-200-4333 is a Phase 1, open-label, parallel-design, single- and multiple-dose, multiple-cohort study in healthy volunteers evaluating the drug-drug interaction (DDI) potential of LEN. The objectives were to evaluate the clinical effects of strong cytochrome P450 enzyme (CYP) 3A, P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) inhibitors and inducers on LEN exposure; LEN coadministration on sensitive P-gp, breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP), and CYP3A substrates using tenofovir alafenamide (TAF, Vemlidy®), rosuvastatin (ROS), pitavastatin (PIT), and midazolam (MDZ), respectively; and increased gastric pH on LEN exposure. Available preliminary data are presented below. Final PK and safety data analyses are ongoing.

Cohort 1 served as a reference arm for Cohorts 2 and 3; participants in Cohort 1 received a single dose of LEN 300 mg capsule alone (N = 30). Participants in Cohorts 2 and 3 received up to 90 days of cobicistat (COBI) 150 mg once daily (mixed CYP3A/P-gp inhibitor), and darunavir (DRV)/COBI 800/150 mg once daily (mixed CYP3A/P-gp inhibitor and inducer), respectively, with a single dose of LEN 300 mg capsule coadministered in the morning on Day 11 (N = 29 per cohort). All doses were administered in the morning under fed conditions. Preliminary PK data are presented in Table 4. Median maximum plasma concentrations of LEN (C_{max}) occurred between 6 to 8 hours (T_{max}), and the median $t_{1/2}$ of LEN administered alone was 11.5 days and ranged from 15.4 to 17.9 days following administration with DRV/COBI or COBI.

Coadministration of DRV/COBI or COBI with LEN resulted in an approximate 2-fold increase in C_{max} and AUC_{inf}. This 2-fold increase in LEN exposure was not deemed clinically relevant, based on safety data from ongoing Phase 1 studies at or above exposures anticipated to be achieved following administration of LEN with strong CYP3A/P-gp inhibitors. Accordingly, the use of strong CYP3A and P-gp inhibitors is permitted with LEN.

Table 4. GS-US-200-4333: Preliminary Plasma PK Parameters of LEN 300 mg Oral Capsule Following Administration Alone or with DRV/COBI (800/150 mg QD) or COBI (150 mg QD)

PK Parameter Mean (%CV)	LEN Alone 300 mg (N = 30)	LEN 300 mg + COBI (N = 29)	LEN 300 mg + DRV/COBI (N = 29)
C_{max} (ng/mL)	30.6 (74.4)	57.8 (53.6)	61.5 (42.4)
AUC_{last} (h•ng/mL)	10,300 (77.9)	16,100 (61.3)	14,200 (47.3)
AUC_{inf} (h•ng/mL)	10,600 (77.2)	22,600 (64.1)	18,700 (49.5)
T_{max} (hours)	8.00 (6.00, 48.00)	6.00 (6.00, 8.00)	6.00 (4.00, 6.00)
$t_{1/2}$ (days)	11.5 (9.46, 15.0)	17.9 (15.1, 20.2)	15.4 (14.2, 17.4)

%CV = percentage coefficient of variation; COBI = cobicistat; DRV = darunavir; LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; QD = once daily
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits.

Cohort 4 served as a reference arm for Cohort 5; participants in Cohort 4 received a single dose of LEN 300 mg tablet alone (N = 27). Participants in Cohort 5 received voriconazole (VORI), a CYP3A inhibitor, for 24 days (400 mg twice daily on Day 1, followed by 200 mg twice daily on Days 2 through 24), with LEN 300 mg tablet administered on Day 2. All doses were administered in the morning under fasted conditions.

The median $t_{1/2}$ of LEN administered alone was 13.7 days (Table 5). Coadministration of VORI with LEN resulted in an approximate 1.4-fold increase in AUC_{inf}. This increase in LEN exposure was not deemed clinically relevant, and further supports the above recommendation permitting use of strong CYP3A and P-gp inhibitors with LEN.

Table 5. GS-US-200-4333: Preliminary Plasma PK Parameters of LEN 300 mg Oral Tablet Following Administration Alone or with VORI (400/200 mg BID)

PK Parameter Mean (%CV)	LEN Alone 300 mg (N = 27)	LEN 300 mg + VORI (N = 25)
C_{max} (ng/mL)	20.4 (102)	20.5 (62.8)
AUC_{last} (h•ng/mL)	3640 (70.9)[a]	5060 (58.6)
AUC_{inf} (h•ng/mL)	5290 (61.1)[a]	7300 (51.9)
T_{max} (hours)	4.00 (4.00, 6.00)	4.00 (4.00, 8.00)
$t_{1/2}$ (days)	13.7 (9.63, 16.2)	12.5 (10.4, 16.7)

%CV = percentage coefficient of variation; BID = twice daily; LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; VORI = voriconazole
a N = 24
Pharmacokinetic parameters are presented as mean (%CV) except T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits.

Cohort 6 served as a reference arm for Cohort 7; participants in Cohort 6 received a single dose of LEN 300 mg tablet alone (N = 25). Participants in Cohort 7 received up to 60 days of atazanavir (ATV)/COBI 300/150 mg once daily, a mixed CYP3A/P-gp/UGT1A1 inhibitor, with LEN 300 mg tablet administered on Day 10. All doses were administered in the morning under fed conditions.

The median $t_{1/2}$ of LEN administered alone was 11.9 days (Table 6). Coadministration of ATV/COBI with LEN resulted in an approximate 6.6-fold and 4.2-fold increase in C_{max} and AUC_{inf}, respectively. In the absence of additional data, coadministration of LEN and strong UGT1A1 inhibitors is not recommended.

Table 6. GS-US-200-4333: Preliminary Plasma PK Parameters of LEN 300 mg Oral Tablet Following Administration Alone or with ATV/COBI (300/150 mg QD)

PK Parameter Mean (%CV)	LEN Alone 300 mg (N = 25)	LEN 300 mg + ATV/COBI (N = 21)
C_{max} (ng/mL)	17.6 (51)	120 (55.7)
AUC_{last} (h•ng/mL)	5000 (56.6)	20300 (56.4)
AUC_{inf} (h•ng/mL)	5430 (54.4)	23700 (55.5)
T_{max} (hours)	6.00 (4.05, 6.00)	4.00 (4.00, 4.00)
$t_{1/2}$ (days)	11.9 (11.0, 13.4)	14.9 (13.5, 18.5)

%CV = percentage coefficient of variation; ATV = atazanavir; COBI = cobicistat; LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; QD = once daily
Pharmacokinetic parameters are presented as mean (%CV) except T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits.

Cohort 4 served as a reference arm for Cohorts 8, 9, and 10; participants in Cohort 4 received a single dose of LEN 300 mg tablet alone (N = 27). Participants in Cohorts 8 and 9 received rifampin (RIF), a strong CYP3A and P-gp/UGT inducer, and efavirenz (EFV), a moderate inducer, respectively, for 25 days (600 mg once daily) with LEN 300 mg tablet administered on Day 14 for both cohorts. Participants in Cohort 10 received a single dose of 40 mg famotidine (FAM) 2 hours prior to a dose of LEN 300 mg tablet on Day 1. All LEN doses were administered in the morning under fasted conditions.

The median $t_{1/2}$ of LEN administered alone was 13.7 days (Table 7). Following coadministration with RIF, LEN C_{max} and AUC_{inf} were approximately 2.5 fold and 6.5 fold lower, respectively, with an approximately 5-fold decrease in $t_{1/2}$. Following coadministration with EFV, LEN C_{max} and AUC_{inf} were approximately 1.5 fold and 2 fold lower, respectively, with an approximate 2-fold decrease in $t_{1/2}$. These data support the recommendations to disallow use of strong and moderate CYP3A and P-gp/UGT inducers with LEN.

Following coadministration with FAM, no change in LEN exposure or $t_{1/2}$ was observed; accordingly, use of FAM and other acid-reducing agents is permitted with LEN.

Table 7. GS-US-200-4333: Preliminary Plasma PK Parameters of LEN 300 mg Tablet Following Administration Alone or with RIF (600 mg QD), EFV (600 mg QD), or FAM (40 mg)

PK Parameter Mean (%CV)	LEN Alone 300 mg (N = 27)	LEN 300 mg + RIF (N = 25)	LEN 300 mg + EFV (N = 18)	LEN 300 mg + FAM (N = 25)
C_{max} (ng/mL)	20.4 (102)	8.20 (59.5)	13.3 (76.1)	18.6 (60.2)
AUC_{last} (h•ng/mL)	3640 (70.9)[a]	720 (51.6)	1690 (73.5)	4610 (58.3)
AUC_{inf} (h•ng/mL)	5290 (61.1)[a]	784 (47.5)	2480 (80.2)	6590 (56.5)
T_{max} (hours)	4.00 (4.00, 6.00)	24.0 (24.0, 48.0)	4.00 (4.00, 6.00)	10.0 (4.00, 48.0)
$t_{1/2}$ (days)	13.7 (9.63, 16.2)	2.61 (2.36, 2.98)	6.96 (5.38, 7.75)	12.3 (10.7, 16.6)

%CV = percentage coefficient of variation; EFV = efavirenz; FAM = famotidine; LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; QD = once daily; RIF = rifampin
a N = 24
Pharmacokinetic parameters are presented as mean (%CV) except T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits.

In Cohort 11, participants received PIT, ROS, TAF, and MDZ alone, or coadministered with oral LEN 600 mg tablet. Agents were either codosed with LEN to evaluate the worst-case scenario (coadministration; PIT, ROS, TAF, and MDZ), or up to 3 days after the last dose of LEN (PIT, MDZ) to evaluate the systemic drug interaction liability of LEN. Mean concentrations of LEN were at, or above clinically relevant C_{max} concentrations (> 100 ng/mL) throughout the drug interaction evaluation (data not shown). Preliminary PK data are presented in Table 8, Table 9, Table 10, and Table 11.

Table 8. GS-US-200-4333: Preliminary Plasma PK Parameters of PIT (2 mg) Following Administration Alone or with LEN

PK Parameter Mean (%CV)	PIT Alone (N = 31)	PIT + LEN (Day 15; Coadministration) (N = 30)	PIT + LEN (Day 27; 3 Days Post LEN Dose) (N = 28)
C_{max} (ng/mL)	31.4 (52.8)	31.0 (48.1)	26.8 (50.5)
AUC_{last} (h•ng/mL)	83.6 (47.5)	96.8 (47.8)	73.1 (41.3)
AUC_{inf} (h•ng/mL)	90.8 (43.8)[a]	102 (47.0)	81.3 (36.3)[b]
T_{max} (hours)	1.00 (1.00, 1.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)
$t_{1/2}$ (hours)	11.7 (8.62, 13.5)[a]	10.9 (6.82, 14.6)	14.1 (10.5, 16.3)[b]

%CV = percentage coefficient of variation; LEN = lenacapavir; PIT = pitavastatin; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile
a N = 30
b N = 26
Pharmacokinetic parameters are presented as mean (%CV) except T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits.

Table 9. GS-US-200-4333: Preliminary Plasma PK Parameters of ROS (5 mg) Following Administration Alone or with LEN

PK Parameter Mean (%CV)	ROS Alone (N = 30)	ROS + LEN (Day 18; Coadministration) (N = 30)
C_{max} (ng/mL)	1.10 (39.1)	1.90 (65.7)
AUC_{last} (h•ng/mL)	10.2 (41.7)	13.7 (52.2)
AUC_{inf} (h•ng/mL)	12.5 (34.1)[a]	16.5 (42.7)[b]
T_{max} (hours)	5.00 (5.00, 5.00)	4.00 (2.00, 4.00)
$t_{1/2}$ (hours)	13.1 (9.14, 20.0)[a]	17.1 (13.4, 24.4)[b]

%CV = percentage coefficient of variation; LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; ROS = rosuvastatin
a N = 28
b N = 29
Pharmacokinetic parameters are presented as mean (%CV) except T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits.

Table 10. GS-US-200-4333: Preliminary Plasma PK Parameters of TAF (25 mg) and its Metabolite, TFV, Following Administration Alone or with LEN

PK Parameter Mean (%CV)	TAF Alone (N = 30)	TAF + LEN (Day 21; Coadministration) (N = 28)
TAF		
C_{max} (ng/mL)	248 (52.5)	322 (52.6)
AUC_{last} (h•ng/mL)	256 (54.3)	328 (35.3)
AUC_{inf} (h•ng/mL)	262 (54.4)[a]	361 (27.6)[b]
T_{max} (hours)	1.00 (0.50, 1.00)	1.00 (0.50, 1.55)
$t_{1/2}$ (hours)	0.38 (0.34, 0.42)[a]	0.41 (0.35, 0.43)[b]
TFV		
C_{max} (ng/mL)	6.30 (30.3)	8.00 (34.1)
AUC_{last} (h•ng/mL)	171 (26.3)	250 (29.2)
AUC_{inf} (h•ng/mL)	207 (26.2)	314 (27.7)
T_{max} (hours)	2.00 (2.00. 2.00)	2.00 (1.50, 2.99)
$t_{1/2}$ (hours)	37.3 (34.8, 40.7)	39.8 (36.0, 45.8)

%CV = percentage coefficient of variation; LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; TAF = tenofovir alafenamide; TFV = tenofovir
a N = 28
b N = 22
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits.

Table 11. GS-US-200-4333: Preliminary Plasma PK Parameters of MDZ (2.5 mg) and its Metabolite, 1-OH-MDZ, Following Administration Alone or with LEN

PK Parameter Mean (%CV)	MDZ Alone (N = 30)	MDZ + LEN (Day 24; Coadministration) (N = 28)	MDZ + LEN (Day 25; 1 Day Post LEN Dose) (N = 28)
MDZ			
C_{max} (ng/mL)	9.50 (29.1)	17.7 (22.7)	19.7 (23.8)
AUC_{last} (h•ng/mL)	50.5 (35.0)	151 (26.9)	171 (27.7)
AUC_{inf} (h•ng/mL)	53.0 (36.3)	185 (33.0)	210 (35.6)
T_{max} (hours)	2.00 (1.00, 2.00)	2.00 (1.49, 3.98)	2.00 (1.00, 2.00)
$t_{1/2}$ (hours)	5.16 (4.20, 7.18)	9.36 (7.00, 11.3)	9.38 (7.20, 11.8)
1-OH-MDZ			
C_{max} (ng/mL)	2.60 (44.5)	1.40 (34.7)	1.30 (36.8)

PK Parameter Mean (%CV)	MDZ Alone (N = 30)	MDZ + LEN (Day 24; Coadministration) (N = 28)	MDZ + LEN (Day 25; 1 Day Post LEN Dose) (N = 28)
AUC_{last} (h•ng/mL)	13.1 (39.3)	8.80 (32.3)	9.70 (35.8)
AUC_{inf} (h•ng/mL)	14.0 (39.2)	10.4 (23.5)	11.6 (43.2)
T_{max} (hours)	2.00 (1.00, 2.00)	1.99 (1.00, 2.00)	2.00 (2.00, 2.00)
$t_{1/2}$ (hours)	4.21(3.15, 4.90)	6.95 (4.15, 9.85)	7.18 (5.07, 10.1)

%CV = percentage coefficient of variation; 1-OH-MDZ = 1-hydroxymidazolam; LEN = lenacapavir; MDZ = midazolam; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits.

PIT AUC and C_{max} were not affected following administration with LEN, suggesting LEN does not inhibit OATP transporters (Table 8). ROS AUC and C_{max} were approximately 1.3 to 1.6 fold higher following coadministration with LEN (Table 9), suggesting LEN inhibits BCRP transporters. TAF and TFV AUC and C_{max} were 1.2- to 1.5-fold higher following coadministration with LEN (Table 10), suggesting LEN is a weak inhibitor of P-gp transporters. MDZ AUC_{inf} and C_{max} were approximately 2- to 4-fold higher, and 1-OH-MDZ AUC and C_{max} were lower following coadministration with LEN (Table 11), suggesting LEN is a moderate inhibitor of CYP3A. Caution is advised if LEN is coadministered with sensitive CYP3A substrates, but not for P-gp, BCRP, or OATP substrates.

1.2.2.2.3. GS-US-200-4330

Study GS-US-200-4330 was a Phase 1, open-label, single-dose, parallel-group study to evaluate the PK of oral LEN in participants with impaired renal function and matched healthy control participants. The objectives were to evaluate the single-dose PK of LEN and to evaluate the safety and tolerability of single-dose LEN in participants with severe renal impairment and matched healthy control participants with normal renal function.

Disposition and Baseline Characteristics

The study enrolled 20 participants: 10 participants with severe renal impairment (15 ≤ creatinine clearance [CL_{cr}] ≤ 29 mL/min using the Cockcroft-Gault equation) and 10 matched healthy control participants (CL_{cr} ≥ 90 mL/min). Participants received a single dose of LEN (1 × 300 mg tablet) administered orally on Day 1. All 20 participants completed study drug dosing and completed the study. No participants prematurely discontinued the study.

The majority of participants were male (70.0%, 14 participants), 19 participants were White and 1 participant was Black, and most participants were Hispanic or Latino (60.0%, 12 participants). Overall, the median age of participants was 61 years (range: 18 to 77), and the median (Q1, Q3) body mass index (BMI) was 26.6 (24.0, 29.2) kg/m².

Safety Results

Treatment-emergent AEs were reported in 5 of 20 participants. Four participants in the severe renal impairment group had at least 1 AE and 1 participant in the normal renal function group had an AE. No AE was reported in more than 1 participant in either group (Table 12).

Four participants had AEs that were Grade 1 or 2 in severity. One Grade 3 AE of hypertension was reported in a participant in the severe renal impairment group.

Table 12. GS-US-200-4330: Treatment-Emergent Adverse Events by Preferred Term (Safety Analysis Set)

Preferred Term	Severe Renal Impairment (N = 10)	Normal Renal Function (N = 10)
Number (%) of Participants with Any Treatment-Emergent Adverse Event	4 (40.0%)	1 (10.0%)
Diarrhoea	1 (10.0%)	0
Hyperglycaemia	0	1 (10.0%)
Hypertension	1 (10.0%)	0
Infusion site extravasation	1 (10.0%)	0
Melena	1 (10.0%)	0
Pain in extremity	1 (10.0%)	0
Prehypertension	1 (10.0%)	0

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term
Adverse events were coded according to MedDRA Version 23.1. Treatment-emergent events began on or after the study drug start date, or led to premature study drug discontinuation. Multiple AEs were counted only once per participant for each PT. Preferred terms were presented by descending order of total frequencies.

One AE of hyperglycemia was considered related to study drug and was reported in the normal renal function group. One SAE of melena occurred and resolved in the severe renal impairment group. No deaths, Grade 4 or Grade 5 AEs, or AEs leading to premature discontinuation of study drug or study participation were reported.

There were no clinically relevant changes from predose in median values for hematology or clinical chemistry parameters (including metabolic parameters) in either treatment group. Laboratory abnormalities were reported in 19 of 20 participants (10 in the severe renal impairment group; 9 in the normal renal function group). The majority of laboratory abnormalities were Grade 1 or 2 in severity. Grade 3 or 4 laboratory abnormalities were reported for 5 participants in the severe renal impairment group and 3 participants in the normal renal function group. Creatinine increase was the most common laboratory abnormality occurring in 3 participants. One participant in each group had a Grade 3 occurrence and 1 participant in the severe renal impairment group had a Grade 4 occurrence.

Pharmacokinetic Evaluation

Intensive PK sampling occurred relative to the morning dose of LEN at the following time points for each cohort:

- Day 1: 0 (predose, ≤ 5 minutes before dose), 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours postdose
- Days 4, 6, 8, 15, 22, 29, 36, 43, and 50: A single anytime PK sample was collected

LEN PK parameters with associated exposure comparisons following a single oral dose of 300 mg under fed conditions in participants with severe renal impairment and their matched healthy controls are presented in Table 13. There were no observable differences in the T_{max} between participants with severe renal impairment and matched healthy controls; the $t_{1/2}$ values were comparable in participants with severe renal impairment compared with their matched healthy controls. Lenacapavir exposures increased in participants with severe renal impairment as indicated by GLSM ratios for C_{max} and AUC. Lenacapavir C_{max} and AUC_{inf} increased 162% and 84%, respectively, in participants with severe renal impairment (N = 10) compared with their matched healthy controls (N = 10).

Table 13. GS-US-200-4330: Summary Statistics and Statistical Comparison of Plasma PK Parameters (LEN PK Analysis Sets)

PK Parameter	Severe Renal Impairment (N = 10)	Matched Healthy Control (N = 10)	Severe Renal Impairment/Matched Healthy Control % Geometric Least-Squares Mean Ratio (90% CI)
C_{max} (ng/mL)[a]	118 (129)	22.1 (43.6)	262 (112, 614)
AUC_{last} (h•ng/mL)[a]	18335 (101)	6844 (48.8)	189 (95.2, 377)
AUC_{inf} (h•ng/mL)[a]	18997 (98.3)	7401 (47.6)	184 (93.6, 360)
CL/F (mL/h)[a]	44063 (138.3)	51822 (56.3)	—
T_{max} (h)[b]	8.00 (6.00, 24.0)	6.00 (6.00, 8.00)	—
$t_{1/2}$ (h)[b]	234 (178, 354)	319 (270, 357)	—

%CV = percentage coefficient of variation; CI = confidence interval; LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile
a Data presented as mean (%CV).
b $t_{1/2}$ and T_{max} are presented as median (Q1, Q3).

Unbound fractions (plasma protein binding) of LEN were measured in predose samples spiked with the analyte of interest. Unbound fractions of LEN were similar in the severe renal impairment group relative to the matched healthy control group (%unbound fraction [%CV] of 0.246 [35.3] and 0.206 [27.2], respectively).

The observed increases in LEN exposure with severe renal impairment (< 2 fold) were not deemed clinically meaningful and results from this study do not indicate the necessity for dose adjustment in participants with renal impairment.

1.2.2.2.4. GS-US-200-4334

Study GS-US-200-4334 is an ongoing Phase 2, randomized, open-label, active-controlled, multicenter study evaluating the safety and efficacy of subcutaneous (SC) and oral LEN in combination with other ARV agents in ARV-naive PWH. Participants were randomized in a 2:2:2:1 ratio to 1 of 4 treatment groups (Table 14).

Table 14. GS-US-200-4334: Study Treatments

Treatment Group	Time Period	Study Treatments
1	Induction (Day 1 through Week 27)	• Oral LEN 600 mg (2 × 300 mg tablet) on Days 1 and 2; 300 mg (1 × 300 mg tablet) on Day 8 • Oral daily F/TAF (200/25 mg) from Day 1 onwards for a total of 28 weeks[a] • SC LEN 927 mg (3 mL of 309 mg/mL) on Day 15
	Maintenance (Week 28 through Week 80)	• SC LEN 927 mg (3 mL of 309 mg/mL) at Week 28 and every 26 weeks thereafter • Oral daily TAF (25 mg)
2	Induction (Day 1 through Week 27)	• Oral LEN 600 mg (2 × 300 mg tablet) on Days 1 and 2; 300 mg (1 × 300 mg tablet) on Day 8 • Oral daily F/TAF (200/25 mg) from Day 1 onwards for a total of 28 weeks[b] • SC LEN 927 mg (3 mL of 309 mg/mL) on Day 15
	Maintenance (Week 28 through Week 80)	• SC LEN 927 mg (3 mL of 309 mg/mL) at Week 28 and every 26 weeks thereafter • Oral daily BIC (75 mg)
3	Day 1 through Week 80	• Oral LEN 600 mg (2 × 300 mg tablet) on Days 1 and 2; 50 mg (1 × 50 mg tablet) daily from Day 3 onwards • Oral daily F/TAF (200/25 mg)
4	Day 1 through Week 80	• Oral daily B/F/TAF (50/200/25 mg)

BIC, B = bictegravir; F = emtricitabine; LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide

a Treatment Group 1 participants with < 50 copies/mL of HIV-1 RNA at Week 16 and Week 22 stopped F/TAF at Week 28 and initiated oral daily TAF.

b Treatment Group 2 participants with < 50 copies/mL of HIV-1 RNA at Week 16 and Week 22 stopped F/TAF at Week 28 and initiated oral daily BIC.

Participants are treated for at least 80 weeks. Participants in Treatment Group 4 will complete the study at Week 80.

Disposition and Baseline Characteristics

As of 11 February 2021, 182 participants were randomized and dosed (n = 52, 53, 52, and 25 in Treatment Groups 1 to 4, respectively). Most participants were male (93.4%, 170 of 182) and the majority were Black (54.4%, 99 of 182) or White (40.7%, 74 of 182). The median age was 29 years (range: 19 to 72). Mean baseline viral load (VL) was 4.30 $\log_{10}$ copies/mL and 15% had VL > 100,000 copies/mL. The mean baseline CD4+ T-cell count was 495 cells/µL (range: 175 to 1846).

Virologic Efficacy Results

At Week 16, 92.3% (48 of 52), 94.3% (50 of 53), and 94.2% (49 of 52) of the participants in the LEN Treatment Groups 1, 2, and 3, respectively, had HIV RNA < 50 copies/mL versus 100% in Treatment Group 4 (25 of 25) as assessed by the missing = failure (M = F) analysis.

Preliminary Safety Results

Lenacapavir was generally well tolerated. There were no deaths and no participant discontinued study drug due to AEs. Serious adverse events (SAEs) were reported in 7 participants in LEN Treatment Groups 1 to 3; none were considered related to study drug.

Grade 3 or higher AEs were reported in 8 participants (5.1%) in LEN Treatment Groups 1, 2, and 3 (none in Treatment Group 1, 3 in Treatment Group 2, and 5 in Treatment Group 3) and 1 participant in Treatment Group 4. None of the Grade 3 or higher AEs were reported in more than 1 participant. None of the Grade 3 or higher AEs were considered related to study drug. The most frequent AEs were injection site erythema (12.7%), and injection site pain and injection site swelling (12.1% each).

All treatment-related AEs of injection site reactions (approximately 36%) were mild or moderate. Treatment-related AEs that were reported in > 5% of participants in LEN Groups 1 and 2 are summarized in Table 15; no events were reported in > 5% of participants in Group 3.

Table 15. GS-US-200-4334: Treatment-Related, Treatment-Emergent Adverse Events in > 5% of Participants Overall Receiving SC LEN by Preferred Term

	SC LEN + (F/TAF →TAF) (N = 52)	SC LEN + (F/TAF →BIC) (N = 53)	SC LEN Total 1+2 (N = 105)
Injection site erythema	10 (19.2%)	6 (11.3%)	16 (15.2%)
Injection site pain	9 (17.3%)	5 (9.4%)	14 (13.3%)
Injection site swelling	7 (13.5%)	7 (13.2%)	14 (13.3%)
Injection site nodule	5 (9.6%)	4 (7.5%)	9 (8.6%)
Injection site induration	5 (9.6%)	3 (5.7%)	8 (7.6%)

BIC = bictegravir; F = emtricitabine; LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide

1.2.2.2.5. GS-US-200-4625

Study GS-US-200-4625 is a Phase 2/3, placebo-controlled, multicenter study of LEN together with an optimized background regimen (OBR) in heavily treatment experienced PWH with multidrug resistant infection.

Participants in Cohort 1 were randomized to receive blinded oral LEN or placebo, while also continuing their failing regimen during a 14-day Functional Monotherapy Period. After this period, participants who received oral LEN switched to open-label SC LEN (927 mg; 309 mg/mL; 2 × 1.5 mL) and OBR, and participants who had received placebo then received open-label oral LEN and OBR for 14 days prior to switching to open-label SC LEN (927 mg; 309 mg/mL; 2 × 1.5 mL) and OBR. Participants in Cohort 2 received open-label oral LEN and OBR for 14 days before switching to open-label SC LEN and OBR. Cohort 2 includes participants who did not meet the criteria for randomization in Cohort 1 or who joined the study after Cohort 1 was fully enrolled.

Disposition and Baseline Characteristics

As of 02 February 2021, 72 participants enrolled in Cohorts 1 and 2 and were included in the safety analysis set (Cohort 1: LEN 24 participants, placebo 12 participants; Cohort 2: LEN + OBR 36 participants). A total of 70 participants completed the Functional Monotherapy (Cohort 1: 36 participants) or Oral Lead-in Period (Cohort 2: 34 participants), and all received SC LEN.

Overall in Cohorts 1 and 2, the majority of participants were male (75.0%), 38.0% were Black, and the median age was 52 years (range: 23 to 78). Mean baseline VL was 4.17 $\log_{10}$ copies/mL. The median (range) baseline CD4+ T-cell count was 150 (3 to 1296) cells/µL. The baseline disease characteristics were consistent with the profile of the heavily treatment experienced population, and the median (Q1, Q3) number of prior ARV medications taken by participants was 11 (8, 16).

Of the 72 participants in Cohorts 1 and 2 who received oral LEN, 70 participants received SC LEN. In Cohort 2, 2 participants remained in the Oral Lead-in Period at the time of the data cut. Overall, 25 participants received Week 26 SC LEN and 1 participant received Week 52 SC LEN.

Virologic Efficacy Results

The primary efficacy endpoint was the proportion of participants in Cohort 1 achieving ≥ 0.5 $\log_{10}$ copies/mL reduction from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period.

At the primary endpoint, a significantly greater proportion of participants receiving LEN had a VL reduction of at least 0.5 $\log_{10}$ copies/mL from baseline compared with those receiving placebo (87.5% vs 16.7%, $P < 0.0001$). Additionally, the LEN group achieved a statistically significant greater mean change in VL versus the placebo group (−1.93 $\log_{10}$ copies/mL vs −0.29 $\log_{10}$ copies/mL, $P < 0.0001$).

At Weeks 16, 22, and 26, the proportion of participants who received LEN in Cohorts 1 and 2 and had HIV-1 RNA < 50 copies/mL, as assessed using the M = F approach, were: 75.0% (30 of 40), 71.0% (22 of 31), and 73.1% (19 of 26), respectively.

Preliminary Safety Results

Lenacapavir was generally well tolerated. Overall, 81.9% (59 of 72) of participants who received LEN in Cohorts 1 and 2 had AEs. One participant with a low baseline CD4+ T-cell count (7 cells/μL) had an SAE of pneumonia with a fatal outcome; the primary cause of the death is unknown at this time; the same participant had a previous SAE of dizziness. Another participant had SAEs of abdominal pain and pancreatic mass. No SAEs were considered related to study drug. No participant discontinued study drug due to AEs.

Grade 3 or higher AEs were reported for 10 participants (13.9%). Grade 3 or higher AEs that were reported for > 1 participant were as follows: injection site erythema (4.2%, 3 participants), injection site edema (2.8%, 2 participants each); 2 of the 3 injections site erythema and both injection site edema AEs were attributed to enfuvirtide. One participant had Grade 3 injection site swelling and injection site erythema that was considered related to study drug. Another participant had Grade 3 AE of rash that was considered related to study drug.

Injection site reactions related to LEN were reported in 32 of 70 participants (45.7%) (Table 16); the majority were Grade 1 (37.1%, 26 of 70); 7.1% were Grade 2 (5 of 70); and 1.4% were Grade 3 (1 of 70). The most commonly reported treatment-related AEs were as follows: injection site swelling (22.9%, 16 participants), injection site erythema (18.6%, 13 participants), and injection site nodule (18.6%, 13 participants).

Table 16. GS-US-200-4625: Treatment-Related, Treatment-Emergent Adverse Events in > 5% of Participants Overall by Preferred Term

	Total (N = 70)
Any injection site reaction	32 (45.7%)
Injection site swelling	16 (22.9%)
Injection site erythema	13 (18.6%)
Injection site nodule	13 (18.6%)
Injection site pain	10 (14.3%)
Injection site induration	6 (8.6%)

1.2.3. Clinical Studies of Coadministered ISL and LEN and ISL/LEN Fixed-dose Combination

For information on clinical studies of coadministered ISL and LEN, including the Phase 1 relative bioavailability (rBA) study for ISL/LEN CCI (GS-US-563-6192), refer to the current ISL/LEN IB.

1.2.4. Information About B/F/TAF

Bictegravir/emtricitabine/tenofovir alafenamide is a tablet approved for the treatment of HIV-1 infection {BIKTARVY 2021}. The B/F/TAF tablet is a safe and highly effective INSTI-based treatment regimen, offering minimal pill burden, once-daily dosing, and excellent tolerability. The B/F/TAF is a recommended initial treatment for PWH {Department of Health and Human Services (DHHS) 2013}.

1.2.4.1. General Information

For further information on B/F/TAF, including information on the following, refer to the B/F/TAF IB:

- Nonclinical pharmacology
- Nonclinical PK and in vitro metabolism
- Nonclinical toxicology
- Clinical experience

1.3. Rationale for This Study

Oral ISL administered with oral LEN has the potential to offer a safe, efficacious, and well-tolerated once weekly regimen to treat HIV-1 infection. The 2 agents in combination are predicted to be effective for treatment of HIV-1 infection because they have different mechanisms of action. Weekly oral dosing is supported by their individual PK profiles. Further, clinical evaluation of oral ISL CCI and LEN CCI coadministration showed no clinically meaningful PK drug-drug interactions.

The data from this study are intended to support the ongoing clinical development of an oral weekly regimen of ISL and LEN, including Phase 3 studies.

In the Extension Phase, participants receiving ISL+LEN will switch to ISL/LEN CCI when the CCI becomes available. PK data in the single-dose rBA Study GS-US-563-6192 showed comparable LEN exposures and a similar extent of ISL exposure with a slower rate of absorption for ISL between ISL/LEN CCI CCI tablet and LEN CCI tablet administered with ISL CCI capsule, supporting the use of ISL/LEN CCI tablets in this Phase 2 and in Phase 3 studies. For more information, refer to the current ISL/LEN IB.

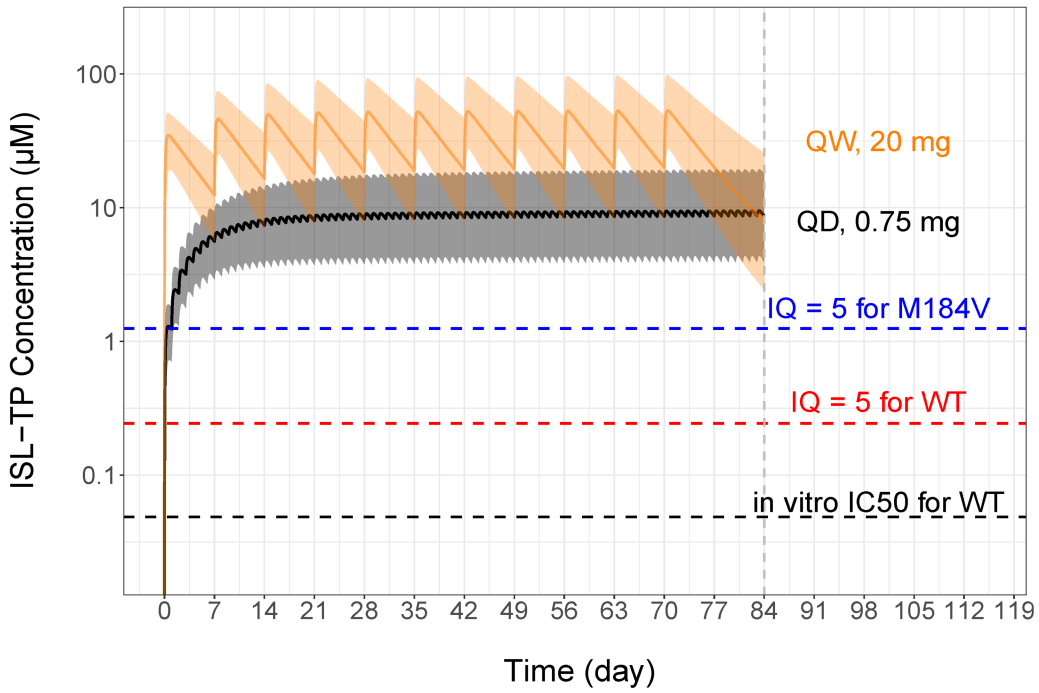
An active control group of B/F/TAF is included as a current standard-of-care comparator allowing those participants not randomized to ISL+LEN to continue to receive highly effective treatment.

1.4. Rationale for Dose Selection of Islatravir

Cohort 1: ISL 20 mg once weekly (enrollment and dosing in Cohort 1 were stopped prematurely by the sponsor [see Section 1.6]).

The once weekly dose of 20 mg chosen for ISL in this study is supported by antiviral efficacy, PK, and safety data from Phase 1 and 2 oral ISL studies. A single dose of ISL 20 mg once weekly achieves a trough concentration comparable to the triphosphate form of islatravir (ISL-TP) steady-state levels for a dose of 0.75 mg once daily (the dose selected for the doravirine/ISL once daily clinical development program), providing coverage for wild-type (WT) and M184V viruses (Figure 2). In addition, ISL 20 mg once weekly provides forgiveness for an entire dosing interval, addressing concerns with a late or missed dose.

Figure 2. ISL-TP Concentrations, Achieved with an ISL 20 mg Once-Weekly Regimen, Provide Coverage for Both Wild-type and M184V Mutant Virus



IC_{50} = half-maximal inhibitory concentration; IQ = inhibitory quotient; ISL = islatravir; ISL-TP = triphosphate form of islatravir; NRTI = nucleoside reverse transcriptase inhibitor; QW = once weekly; WT = wild type
The solid lines (black and orange) and the shaded region (grey and orange) correspond to the median and 95% prediction interval, respectively (based on simulations, N = 1000). Inhibitory Quotient is defined as Trough Concentration/IC_{50}. The black dashed line corresponds to the in vitro intracellular IC50 against WT virus. The red and the blue dashed lines correspond to an IQ of 5 based on proof-of-concept monotherapy data for WT virus and a variant bearing the common NRTI M184V resistance-associated mutation, respectively. No ISL QW dose is given post Day 70 to demonstrate forgiveness of a missed dose (denoted by the vertical dashed line).

Plasma ISL exposures on Day 1 and Day 2

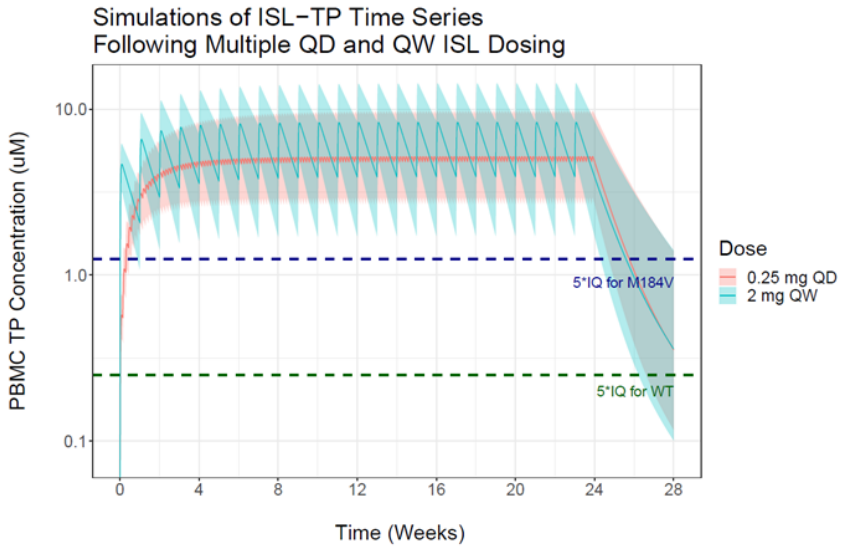
To reach therapeutic levels quickly, loading doses are required for LEN. Loading doses of both ISL 40 mg and LEN 600 mg on Day 1 and 2 will be evaluated in this study. While AUC and C_{max} of plasma ISL following administration of ISL 40 mg on Day 1 and Day 2 are higher than the steady-state plasma ISL exposures following ISL 20 mg once weekly, 3 doses of ISL 100 mg once weekly (MK-8591-002) and 120 mg once monthly (QM) for 6 months (MK-8591-016) have been well-tolerated, and no dose-related toxicities have been identified. Based on available data to date, clinically meaningful systemic DDIs with LEN are not expected. The sponsor stopped the dosing of ISL+LEN in Cohort 1 due to the laboratory findings of decreases in total lymphocyte and CD4+ T-cell counts observed in clinical studies with ISL 60 to 120 mg QM for HIV-1 pre-exposure prophylaxis (PrEP), ISL 20 mg (with MK-8507, a nonnucleoside reverse transcriptase inhibitor [NNRTI]) once weekly, and ISL 0.75 mg daily (with doravirine 100 mg) for HIV-1 treatment.

Cohort 2: ISL 2 mg once weekly

The once weekly dose of ISL 2 mg chosen for this study is supported by antiviral efficacy, PK, predicted CD4+ T-cell increases, and absolute lymphocyte count increases similar to approved ART regimens and safety data from Phase 1, 2, and 3 oral ISL studies.

Robust antiviral efficacy was observed down to 0.5 mg in the single-dose, proof-of-concept study in treatment-naive participants. Additionally, no M184V/I selection was observed across any of the doses. In a Phase 2 clinical study, the 0.25 mg once daily dose fully suppressed treatment-naive participants through to the end of the study. Predictions from the population PK model show 2 mg QW dosing achieves a trough concentration comparable to the ISL-TP steady-state trough levels for a dose of 0.25 mg QD (the dose selected for the DOR/ISL QD clinical development program), providing coverage for WT and M184V viruses (Figure 3).

Figure 3. Simulations of ISL-TP Time Series Following Multiple QD and QW ISL Dosing



ISL = islatravir; ISL-TP = triphosphate form of islatravir; PBMC = peripheral blood mononuclear cells; QD = once daily; QW = once weekly; TP = triphosphate; WT = wild type

A PK/pharmacodynamic model capturing the changes in lymphocytes and CD4+ T-cells for ISL across the oral Phase 2 and 3 programs was developed. A 2 mg QW oral dose of ISL, in combination with LEN, is expected to be well tolerated and will not have a negative effect on lymphocytes in participants with HIV-1 who are treatment naive or virologically suppressed.

Table 17 and Table 18 present the corresponding predicted change from baseline at Week 48 for mean absolute lymphocyte cell count in virologically suppressed and treatment-naive participants, respectively. At ISL doses below 3 mg QW, the confidence interval for mean change from baseline ratio of ISL versus control includes 1, and at doses below 3 mg QW, the confidence interval for the mean change from baseline ratio overlaps with the confidence interval for participants receiving standard ART.

Table 19 and Table 20 present the corresponding predicted change from baseline at Week 48 for mean CD4+ T-cell count in virologically suppressed and treatment-naive participants, respectively. At ISL doses below 3 mg QW, the confidence interval for the mean change from baseline ratio of ISL versus control includes 1, and at doses below 3 mg QW, the confidence interval for the mean change from baseline ratio overlaps with the confidence interval for participants receiving standard ART.

Table 17. Week 48 Predicted Mean Absolute Lymphocyte Cell Count and Predicted Change From Baseline Ratio Following Once Weekly Dosing, Islatravir Versus Control, Virologically Suppressed Population

ISL QW Dose (mg)	Predicted ISL Mean Absolute Lymphocyte Cell Count (10^3 cells/mm^3) (95% CI) 48 Weeks	Predicted Change From Baseline Ratio of ISL vs Control (95% CI) 48 Weeks
Standard ARV	1.98 (1.88, 2.07)	—
0.5	1.96 (1.87, 2.06)	0.992 (0.948, 1.05)
1	1.93 (1.85, 2.02)	0.978 (0.920, 1.03)
2	1.87 (1.78, 1.96)	0.948 (0.900, 1.01)
3	1.82 (1.74, 1.93)	0.923 (0.875, 0.971)
5	1.72 (1.64, 1.79)	0.872 (0.823, 0.915)
20	1.12 (1.04, 1.21)	0.560 (0.505, 0.610)

ARV = antiretroviral; CI = confidence interval; ISL = islatravir; QW = once weekly
Mean (95% CI) for the predicted lymphocyte cell count at baseline in the virologically suppressed group was 1.98 (1.87, 2.06).

Table 18. Week 48 Predicted Mean Absolute Lymphocyte Cell Count and Predicted Change From Baseline Ratio Following Once Weekly Dosing, Islatravir Versus Control, Treatment-Naive Population

ISL QW Dose (mg)	Predicted ISL Mean Absolute Lymphocyte Cell Count (10^3 cells/mm^3) (95% CI) 48 Weeks	Predicted Change From Baseline Ratio of ISL vs Control (95% CI) 48 Weeks
Standard ARV	2.09 (1.97, 2.19)	—
0.5	2.08 (1.92, 2.19)	0.995 (0.945, 1.04)
1	2.06 (1.91, 2.18)	0.990 (0.941, 1.02)
2	2.03 (1.85, 2.17)	0.972 (0.928, 1.02)
3	1.98 (1.87, 2.11)	0.954 (0.908, 1.00)
5	1.91 (1.80, 2.00)	0.918 (0.872, 0.959)
20	1.40 (1.27, 1.52)	0.672 (0.625, 0.719)

ARV = antiretroviral; CI = confidence interval; ISL = islatravir; QW = once weekly
Mean (95% CI) for the predicted lymphocyte cell count at baseline in the treatment-naive group was 1.98 (1.87, 2.06).

Table 19. Week 48 Predicted Mean CD4+ T-Cell Count and Predicted Change From Baseline Ratio Following Once Weekly Dosing, Islatravir Versus Control, Virologically Suppressed Population

ISL QW Dose (mg)	Predicted Mean CD4+ T-Cell Count (cells/mm^3) (95% CI) 48 Weeks	Predicted Change From Baseline Ratio of ISL vs Control (95% CI) 48 Weeks
Standard ARV	750 (706, 799)	—
0.5	746 (709, 795)	0.994 (0.933, 1.04)
1	738 (683, 787)	0.982 (0.916, 1.05)
2	725 (683, 775)	0.959 (0.905, 1.04)
3	713 (669, 747)	0.948 (0.885, 1.01)
5	692 (655, 726)	0.922 (0.858, 0.983)
20	568 (513, 618)	0.742 (0650, 0.819)

ARV = antiretroviral; CD4 = clusters of differentiation 4; CI = confidence interval; ISL = islatravir; QW = once weekly
Mean (95%CI) for the predicted CD4+ T-cell count at baseline in the virologically suppressed group was 717 (673, 763).

Table 20. Week 48 Predicted Mean CD4+ T-Cell Count and Predicted Change From Baseline Ratio Following Once Weekly Dosing, Islatravir Versus Control, Treatment-Naive Population

ISL QW Dose (mg)	Predicted Mean CD4+ T-Cell Count (cells/mm^3) (95% CI) 48 Weeks	Predicted Change From Baseline Ratio of ISL vs Control (95% CI) 48 Weeks
Standard ARV	715 (670, 759)	—
0.5	711 (669, 751)	0.991 (0.936, 1.04)
1	705 (667, 758)	0.987 (0.931, 1.03)
2	699 (660, 742)	0.975 (0.929, 1.02)
3	687 (648, 730)	0.962 (0.908, 1.01)
5	671 (624, 713)	0.932 (0.885, 0.980)
20	563 (511, 620)	0.769 (0.703, 0.827)

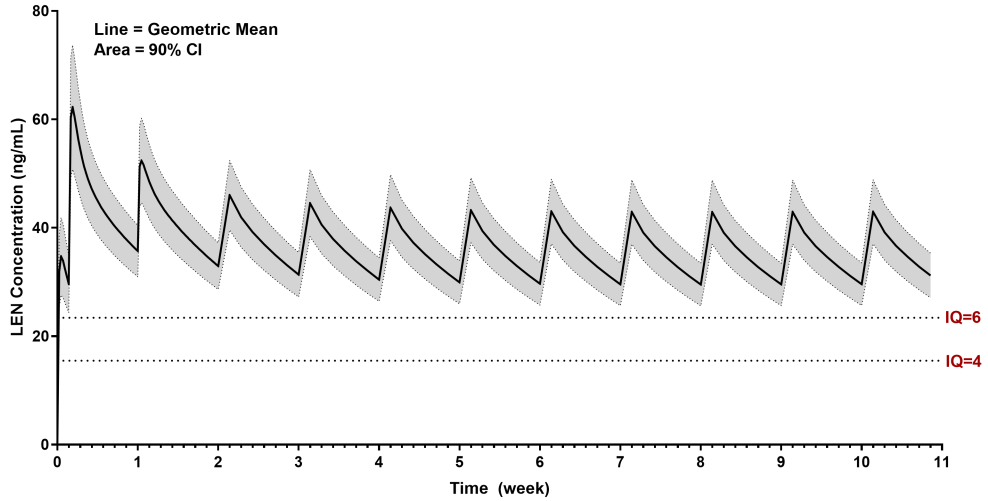
ARV = antiretroviral; CD4 = clusters of differentiation 4; CI = confidence interval; ISL = islatravir; QW = once weekly
Mean (95% CI) for the predicted CD4+ T-cell count at baseline in the treatment-naive group was 589 (548, 628).

To reach therapeutic levels quickly, loading doses are required for LEN but not for ISL. In Cohort 2, no extra doses of ISL will be administered during the loading of LEN. Clinically meaningful systemic DDIs with ISL were not observed in a recent clinical DDI study.

1.5. Rationale for Dose Selection of Lenacapavir

The dose selection for LEN is supported by antiviral activity, PK, and safety data from a Phase 1b proof-of-concept study (GS-US-200-4072) and 2 ongoing Phase 2 and 2/3 studies (GS-US-200-4334 and GS-US-200-4625), as well as PK and safety data from 2 Phase 1 studies in healthy volunteers (GS-US-200-4071 and GS-US-200-4333). Phenotypic analyses and modeling indicate that LEN plasma concentration of 15.5 ng/mL, corresponding to inhibitory quotient (IQ) of 4, or higher would provide near maximal antiviral activity. The proposed oral regimen targets an exposure where the lower bound of the 90% CI of predicted geometric mean for LEN C_{tau} is rapidly achieved and maintained above IQ4 (Figure 4). Participants will receive 2 loading doses of LEN 600 mg on Day 1 and Day 2 followed by LEN 300 mg on Day 8 and once weekly thereafter. LEN has been administered orally at doses up to 1800 mg (Study GS-US-200-4701). Preliminary safety data from all ongoing LEN studies indicate that all treatments are generally safe and well tolerated. Clinically meaningful systemic DDIs with ISL were not observed in a recent clinical DDI study.

Figure 4. Target Exposures are Rapidly Achieved and Maintained with An Oral LEN Once-Weekly Regimen



CI = confidence interval; IQ = inhibitory quotient; LEN = lenacapavir; QW = once weekly
The solid line and the shaded region correspond to the geometric mean and 90% CI, respectively (based on simulations, N = 100). Inhibitory Quotient is defined as Trough Concentration/in vitro protein-adjusted EC95 (paEC95) against wild-type virus. Horizontal dashed lines correspond to target IQ values of 4 and 6 based on phenotypic analyses and modeling.

1.6. Risk/Benefit Assessment for the Study

Potential risks associated with the study include unknown AEs associated with each of the investigational drugs, ISL and LEN, and with the novel combination of ISL+LEN, general risks associated with frequent clinic visits and laboratory blood draws, and the associated pain and discomfort of multiple phlebotomies. Strategies to mitigate these risks include close monitoring of laboratory values and AEs. Parameters for monitoring of AEs will be well-defined and closely followed.

In addition, potential risks to PWH include virologic breakthrough with exposure to subtherapeutic concentrations of ISL+LEN or unrecognized preexisting resistance to ISL and/or LEN. These risks could lead to development of resistance to either ISL, LEN, or both. Strategies to mitigate these risks include resistance testing of each participant's latent viral reservoir to minimize the risk of enrolling participants with preexisting resistance, and frequent assessments of HIV-1 RNA to ensure that virologic breakthrough is rapidly identified, thus limiting the time during which drug resistance mutations could emerge. Each component of the study regimen has a novel mechanism without predicted cross-resistance with currently approved ART. CCI [redacted] Participants will be advised to initiate alternative therapy for HIV if they discontinue from the study.

Decreases in total lymphocyte and lymphocyte subset (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 December 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.

Merck 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 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 ARVs in any ISL 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 virologically suppressed 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 virologically suppressed 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 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 the lymphocyte counts available at this point was from the studies involving administration of ISL QW (20 mg) and QM (60 to 120 mg), as detailed below. Data on recovery to baseline following discontinuation of DOR/ISL 100 mg/0.75mg QD in virologically suppressed adults (Studies MK-8591A-017 and MK-8591A-018) are not yet available.

  — Approximately 6 months after discontinuation of ISL 20 mg QW in adult virologically suppressed 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 of 40 (25%) and 15of 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 MK8591-024 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 suggests that the decrease in mean total lymphocyte and lymphocyte subset counts is ISL dose-dependent, with lower doses less likely to cause decreases. A return toward baseline in lymphocyte and lymphocyte subset counts has been observed.

As a result of these findings and after a review of the totality of the ISL data, Cohort 1 was discontinued, and a decreased ISL dose is being implemented in Cohort 2 and loading of ISL has been eliminated (see below). Based on modeling and simulation, it is believed that the newly selected dose of ISL for Cohort 2 (2 mg once weekly) is unlikely to cause any decrease in CD4+ T-cell or absolute lymphocyte counts. Any residual risk for ISL-associated CD4+ T-cell

or absolute lymphocyte count decreases will be further mitigated by exclusion of participants with CD4+ T-cell count < 350 cells/mm^3 or absolute lymphocyte counts < 900 cells/mm^3, close monitoring and stopping criteria for CD4+ T-cell/absolute lymphocyte count decreases, and periodic review of safety and efficacy by an independent data monitoring committee (DMC). Details of the planned DMC analyses are provided in Section 8.2.1.2.

The weekly LEN 300 mg dose selected for evaluation in this study requires that loading doses of LEN 600 mg be administered on Days 1 and 2 in order to rapidly achieve exposures predicted to be efficacious. In Cohort 1, ISL 40 mg loading doses along with the LEN 600 mg loading doses will be evaluated. While the safety profile of ISL under this dosing regimen has not been directly studied, the projected exposures were within those observed to be well tolerated in the once-monthly oral ISL 120 mg dose administered in the Phase 2 PrEP study (MK-8591-016), which supported selection of the ISL 60 mg once-monthly dose for Phase 3 PrEP studies (MK-8591-022 and MK-8591-024). However, given the ISL dose-dependent decreases in both CD4+ T-cells and absolute lymphocyte counts, ISL loading has been eliminated for Cohort 2 participants while LEN loading will be maintained.

Lack of adherence or accidental overdose due to weekly dosing for the treatment of HIV is a potential risk in this study, as participants have no experience with an HIV treatment regimen of this dosing frequency. Participants will be followed during the first 2 weeks of ISL+LEN dosing with phone calls and throughout the study via clinic site visits and may be offered other means of adherence support and other medication guides through the remainder of the study.

Potential benefits of participation in the study include receiving a long-acting weekly regimen, thus freeing participants from daily ARV medication, with potentially improved adherence leading to improved efficacy and immunologic control. Participants will also be contributing to an understanding of the safety and tolerability of a novel long-acting treatment regimen, including the PK of the regimen, thus contributing to the development of ART with novel mechanisms of action with potential applications for HIV-1 treatment, prevention, and cure. Those randomized to receive B/F/TAF the first 48 weeks of the study are not anticipated to have any additional therapeutic benefit while taking B/F/TAF but may benefit from increased contact with health care providers and close monitoring during this time.

An infectious disease pandemic may pose additional risks to study drug availability, the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 2 for further details on the risks and risk mitigation strategy.

Considering the above, the benefit-risk balance for this study is considered positive.

1.7. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoint
• To evaluate the efficacy of oral weekly ISL in combination with LEN in virologically suppressed PWH at Week 24	• The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of oral weekly ISL in combination with LEN in virologically suppressed PWH at Weeks 12, 24, and 48	• The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 12 and 48 as determined by the US FDA-defined snapshot algorithm • The proportions of participants with HIV-1 RNA < 50 copies/mL at Weeks 12, 24, and 48 as determined by the US FDA-defined snapshot algorithm • The change from baseline in CD4+ T-cell count at Weeks 12, 24, and 48
• To evaluate the safety and tolerability of oral weekly ISL in combination with LEN	• The incidence of treatment-emergent AEs leading to study drug discontinuation
• To evaluate the PK of ISL and LEN administered as an oral weekly combination regimen	• ISL and LEN PK parameters (C_{max}, T_{max}, C_{tau}, AUC_{tau}, and $t_{1/2}$, as applicable)
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the development of resistance to ISL and LEN administered as an oral weekly combination regimen	• Identification of mutations conferring resistance to ISL and/or LEN in participants with virologic failure
• To assess the effect of treatment with ISL and LEN administered as an oral weekly combination regimen on patient-reported outcomes (PROs)	• Participant scores on the PRO questionnaires HIV Dependent Quality of Life (HIVDQoL), EuroQoL 5 dimension 5 level (EQ-5D-5L), HIV Treatment Satisfaction Questionnaires (HIVTSQc12 and HIVTSQs12), the Patient Perspective of Regimen and the Patient Perspective of Regimen Change

3. STUDY DESIGN

3.1. Study Design Overview

A schematic diagram of the study is provided in Figure 1.

This is a Phase 2, randomized, open-label, active-controlled, multicenter study to evaluate safety, efficacy, and PK of a regimen of ISL+LEN in virologically suppressed PWH.

Cohort 1 (Enrollment and dosing in Cohort 1 were stopped prematurely by the sponsor):

For Cohort 1, participants who meet all eligibility criteria will be randomized in a 2:1 ratio to receive oral weekly ISL+LEN (Treatment Group 1) or oral daily B/F/TAF (Treatment Group 2) for 48 weeks. Enrollment and dosing were stopped prematurely by the sponsor. Prior to the sponsor discontinuation of Cohort 1, it was planned that following completion of the Week 48 visit, participants receiving ISL+LEN in Treatment Group 1 were to continue ISL+LEN and attend visits every 12 weeks. Participants in Treatment Group 2 were to switch from B/F/TAF to the ISL+LEN regimen (starting with the loading doses over 2 days) and continue the study. Participants in Treatment Group 2 who did not switch from B/F/TAF to ISL+LEN at Week 48 were to be discontinued from the study.

After Week 48, participants taking ISL+LEN were to attend visits every 12 weeks until the product became accessible to participants commercially or Gilead Sciences, Inc. (Gilead) elected to discontinue the study.

Cohort 2:

For Cohort 2, participants who meet all eligibility criteria will be randomized in a 1:1 ratio to receive oral weekly ISL (2 mg) capsule + LEN (300 mg) tablet (Treatment Group 3) or oral daily B/F/TAF (Treatment Group 4) for 48 weeks.

At the Week 48 visit, all participants will be given an option to participate in an Extension Phase to receive ISL+LEN or ISL/LEN CCI (when available). Participants in Treatment Group 3 may continue to receive ISL+LEN, while participants in Treatment Group 4 may switch from B/F/TAF to ISL+LEN, starting with the loading doses of LEN over 2 days. During the Extension Phase, participants who have started ISL+LEN will switch to ISL/LEN CCI when it becomes available and begin taking ISL/LEN CCI starting at their next scheduled dose. Participants who do not wish to participate in the Extension Phase will be discontinued from the study. Participants in the Extension Phase will attend visits every 12 weeks until Week 144; visits will occur every 24 weeks after Week 144 until ISL/LEN CCI becomes available to participants or Gilead elects to discontinue the study, whichever occurs first.

3.2. Study Treatments

Details regarding the doses and dosing regimens for ISL+LEN, B/F/TAF, and ISL/LEN CCI are provided in Sections 5.6 and 5.7, respectively. Details regarding the formulation, packaging, and labeling of study drugs are provided in Sections 5.2 to 5.4.

3.3. Duration of Treatment

Durations of treatment in the Randomized Phases of this study for Cohort 1 and Cohort 2 are 48 weeks.

3.4. Discontinuation Criteria

3.4.1. Early Discontinuation from Study Treatment

Study drugs may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a meaningful degree. Following resolution of intercurrent illness, the participant may resume study dosing at the discretion of the investigator
- Reactivation of hepatitis B virus (HBV) infection
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the participant's best interest
- Lack of efficacy
- Participant request to discontinue for any reason
- Participant noncompliance
- Pregnancy during the study; refer to Appendix 3
- Discontinuation of the study at the request of Gilead or a regulatory agency or institutional review board (IRB)
- Meeting the stopping criteria for changes in CD4+ T-cell or absolute lymphocyte count (Treatment Group 3 or Extension Phase only) – see Section 7.7.

Procedures for participants who discontinue study drugs early are described in Section 6.4.1.

The Gilead medical monitor should be consulted prior to study drug discontinuation when medically feasible. After study drug discontinuation, participants should be switched to an appropriate alternative ARV regimen.

3.4.2. Early Discontinuation from the Study

A participant may permanently discontinue from the study for reasons including but not limited to the following:

- Death
- Investigator decision to remove a participant from the study
- Withdrawal of consent by the participant
- Participant lost to follow-up (see Section 3.4.3)
- Study terminated by the sponsor

Procedures for participants who discontinue the study early are described in Section 6.4.

3.4.3. Lost to Follow-up

Should the participant fail to return to the investigational site for a scheduled protocol-specific visit, sites will need to make at least 2 attempts by a combination of telephone and certified mail to contact the participant. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule. If the participant does not respond within 1 month after the second contact, the participant will be considered lost to follow-up and no additional contact will be required. Sites must document all attempts to contact the participant.

3.5. Definitions for Time of Primary Endpoint and End of Study

3.5.1. Primary Endpoint

The date of the last participant's last visit for the primary endpoint is the date of the last visit to perform assessments for the primary analysis.

3.5.2. End of Study

The end of this study will be the last participant's last observation (or visit).

3.6. Poststudy Care

After the participant has completed/terminated their participation in the study, long-term care of the participant will remain the responsibility of their primary treating physician.

3.7. Source Data

The source data for this study will be obtained from electronic data capture (EDC), central laboratory, specialty laboratory (eg, for PK and/or pharmacodynamic data), interactive response technology (IRT), and electronic clinical outcome assessments

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

For Cohort 1, approximately 75 virologically suppressed PWH who meet the eligibility criteria will be randomized in a 2:1 ratio to receive ISL+LEN or B/F/TAF. Enrollment and dosing in Cohort 1 were stopped prematurely by the sponsor.

For Cohort 2, approximately 100 virologically suppressed PWH who meet the eligibility criteria will be randomized in a 1:1 ratio to receive ISL 2 mg + LEN 300 mg or B/F/TAF.

4.1.1. Participant Replacement

Participants who discontinue before the end of the study will not be replaced.

4.2. Inclusion Criteria (Applicable to Both Cohorts, Unless Specified Otherwise)

Participants must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Willing and able to provide written informed consent prior to performing study procedures

2) Aged ≥ 18 years at screening

3) Received B/F/TAF for HIV-1 infection for ≥ 24 weeks prior to screening

4) Documented plasma HIV-1 RNA < 50 copies/mL (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL) for ≥ 24 weeks before screening

5) Plasma HIV-1 RNA < 50 copies/mL at screening

4.3. Exclusion Criteria (Applicable to Both Cohorts, Unless Specified Otherwise)

Participants who meet *any* of the following exclusion criteria are not eligible to be enrolled in this study:

1) History of prior virologic failure while receiving treatment for HIV-1

2) Prior use of, or exposure to, ISL or LEN

3) Active, serious infections requiring parenteral therapy < 30 days before randomization

4) Active tuberculosis infection

5) Acute hepatitis < 30 days before randomization

6) Active or occult HBV coinfection, defined as hepatitis B core antibody (HBcAb) positive, hepatitis B surface antigen (HBsAg) positive, or HBV DNA positive (regardless of prior HBsAb status) as determined by the central laboratory

7) Active hepatitis C virus (HCV) coinfection, defined as detectable HCV RNA.
Note: Participants with prior/inactive HCV infection (defined as undetectable HCV RNA) may be enrolled

8) History of or current clinical decompensated liver cirrhosis (eg, ascites, encephalopathy, or variceal bleeding)

9) Treatment < 3 months prior to screening or anticipated treatment during the study period with immunosuppressant therapies, hydroxyurea, foscarnet, radiation, or cytotoxic chemotherapeutic agents without approval from sponsor prior to randomization. Agents disallowed in Section 5.8 may not be considered for approval

10) Active malignancy requiring acute systemic therapy

11) Abnormal electrocardiogram (ECG) at the screening visit that is clinically significant as determined by the investigator

12) Any of the following laboratory values at screening

    a) $CL_{cr} \leq 30$ mL/min according to the Cockcroft-Gault formula {Cockcroft 1976}

    b) Alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN)

    c) Direct bilirubin > 1.5 × ULN

    d) Platelets < 50,000/mm^3

    e) Hemoglobin < 8.0 g/dL

    f) CD4+ T-cells < 200 cells/mm^3 (Cohort 1); CD4+ T-cells < 350 cells/mm^3 (Cohort 2)

    g) Absolute lymphocyte count < 900 cells/mm^3 (Cohort 2)

13) Participation or planned participation in any other clinical study (including observational studies) without prior approval from the sponsor

14) Known hypersensitivity to any of the study drugs, their metabolites, or formulation excipients

15) Ongoing therapy or anticipated frequent use of any prohibited medications listed in Section 5.8

16) Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the participant unsuitable for the study or unable to comply with dosing requirements

17) Participants of childbearing potential who engage in heterosexual intercourse and do not agree to use protocol-specified methods of contraception (Appendix 3)

18) Participants of childbearing potential (as defined in Appendix 3) who have a positive serum pregnancy test at screening or positive urine and serum pregnancy tests at Day 1 prior to study drug administration

19) Participants who plan to continue breastfeeding during the study

20) Documented historical (if available) or screening (proviral genotype analysis) resistance reports showing NRTI or NNRTI resistance mutations in reverse transcriptase, including M184V/I (Cohort 2)

    The following substitutions in HIV-1 reverse transcriptase will be considered NRTI resistance mutations: M41L, K65E/N/R, D67N, T69 insertions, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, Q151M, M184I/V, L210W, T215F/Y, K219E/N/Q/R. The following substitutions in HIV-1 reverse transcriptase will be considered NNRTI resistance mutations: L100I, K101E/H/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/Q/S, H221Y, P225H, F227C, M230I/L

5. STUDY DRUGS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Participants will be assigned a screening number in the IRT system at the time of consent.

Once eligibility has been confirmed, the investigator or designee will randomize the participant using the IRT system. Once a participant number has been assigned to a participant, it will not be reassigned to any other participants. The participant number assignment and randomization may be performed up to 3 days prior to the Day 1 visit provided all screening procedures have been completed and participant eligibility has been confirmed.

For Cohort 1, participants who meet eligibility criteria will be randomized in a 2:1 ratio to Treatment Group 1 (ISL+LEN) or Treatment Group 2 (B/F/TAF). Enrollment and dosing in Cohort 1 were stopped prematurely by the sponsor.

For Cohort 2, participants who meet all eligibility criteria will be randomized in a 1:1 ratio to Treatment Group 3 (ISL 2 mg + LEN) or Treatment Group 4 (B/F/TAF). Randomization will be stratified by CD4+ T-cell count (350 to 499 [inclusive] cells/mm^3 or ≥ 500 cells/ mm^3) at screening.

The IRT will assign study drug bottle numbers of open-label study drugs at Day 1 and subsequent visits for each participant.

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this study.

5.2. Description and Handling of Islatravir

5.2.1. Formulation

Cohort 1: Islatravir capsules, 20 mg, are white opaque capsules. Each capsule contains 20 mg ISL drug substance. In addition to the active ingredient, ISL capsules contain the following inactive ingredients: gelatin, titanium dioxide, mannitol, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

Cohort 2: Islatravir capsules, 1 mg, are white opaque capsules. Each capsule contains 1 mg ISL drug substance. In addition to the active ingredient, ISL capsules contain the following inactive ingredients: gelatin, titanium dioxide, mannitol, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

5.2.2. Packaging and Labeling

Cohort 1: Islatravir capsules, 20 mg, are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 4 capsules. Each bottle is enclosed with a white, continuous-thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Cohort 2: Islatravir capsules, 1 mg, are packaged in white, HDPE bottles. Each bottle contains 4 capsules. Each bottle is enclosed with a white, continuous-thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, European Union (EU) Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

Cohort 1: Islatravir capsules, CCI , should be stored at 2 °C to 30 °C (36 °F to 86 °F). Storage conditions are specified on the label. Until dispensed to participants, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

Cohort 2: Islatravir capsules, 1 mg, should be stored at 2 °C to 30 °C (36 °F to 86 °F). Storage conditions are specified on the label. Until dispensed to participants, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drugs should not be stored in a container other than the container in which they were supplied. Keep the bottle tightly closed to protect from moisture.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Description and Handling of Lenacapavir

5.3.1. Formulation

Lenacapavir tablets, 300 mg, are capsule-shaped, film-coated beige tablets, debossed with “GSI” on 1 side of the tablet and “62L” on the other side of the tablet. Each tablet core contains the equivalent of 300 mg LEN in the form of LEN sodium. In addition to the active ingredient, LEN tablets, 300 mg, contain the following inactive ingredients: copovidone, poloxamer 407, mannitol, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, iron oxide black, and iron oxide red.

5.3.2. Packaging and Labeling

Lenacapavir tablets, 300 mg, are packaged in white, HDPE bottles. Each bottle contains 4 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous-thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.3.3. Storage and Handling

Lenacapavir tablets, CCI , should be stored below 30 °C (86 °F). Storage conditions are specified on the label. Until dispensed to participants, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drugs should not be stored in a container other than the container in which they were supplied. Keep the bottle tightly closed to protect from moisture.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.4. Description and Handling of B/F/TAF

5.4.1. Formulation

B/F/TAF 50/200/25 mg tablets are capsule-shaped, film-coated, purplish-brown tablets, debossed with “GSI” on one side of the tablet and “9883” on the other side of the tablet. Each tablet core contains 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide. In addition to the active ingredients, B/F/TAF tablets contain the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red, and iron oxide black.

5.4.2. Packaging and Labeling

B/F/TAF 50/200/25 mg tablets are packaged in white, HDPE bottles. Each bottle contains 30 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous-thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.4.3. Storage and Handling

B/F/TAF 50/200/25 mg tablets should be stored at 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F). Storage conditions are specified on the label. Until dispensed to participants, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drugs should not be stored in a container other than the container in which they were supplied. Keep the bottle tightly closed to protect from moisture.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.5. Description and Handling of ISL/LEN CCI

5.5.1. Formulation

ISL/LEN CCI CCI tablets are capsule-shaped, film-coated gray tablets.

ISL/LEN CCI CCI tablets are capsule-shaped, debossed, film-coated pink tablets.

5.5.2. Packaging and Labeling

ISL/LEN CCI tablets are packaged in white, HDPE bottles. Each bottle contains 4 tablets, silica gel desiccant, and with or without polyester packing material. Each bottle is enclosed with a white, continuous-thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.5.3. Storage and Handling

ISL/LEN CCI tablets should be stored below 30 °C (86 °F). Storage conditions are specified on the label. Until dispensed to participants, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

5.6. Dosage and Administration of Islatravir and Lenacapavir

Cohort 1 (enrollment and dosing in Cohort 1 were stopped prematurely by the sponsor):

Participants in Treatment Group 1 will take oral ISL 40 mg (2 × 20 mg capsules) and oral LEN 600 mg (2 × 300 mg tablets) on Days 1 and 2 without regard to food. On Day 8 and once a week thereafter (ie, on the same day of the week together with LEN), participants will take oral ISL 20 mg (1 × 20 mg capsule) and oral LEN 300 mg (1 × 300 mg tablet) without regard to food.

After 48 weeks of on-study B/F/TAF, participants in Treatment Group 2 will take ISL+LEN beginning with the loading doses over 2 days and continuing with dosing 7 days after the first loading dose and then once a week thereafter.

Cohort 2

For Treatment Group 3, oral ISL and oral LEN are to be taken without regard to food and, where indicated, taken together. From Day 8 onward, ISL and LEN should be taken weekly on the same day of the week.

During the Extension Phase, participants who are receiving ISL+LEN will switch to the ISL/LEN CCI tablet (when available) administered orally on the same schedule, taken weekly on the same day of the week, without regard to food.

Table 21. Cohort 2: Treatment Group 3 Dosing Schedule

	LEN[a]	ISL[a]
Day 1	CCI	
Day 2		
Day 8 (and weekly thereafter)		
CCI		

CCI; ISL = islatravir; LEN = lenacapavir
a Including participants in Treatment Group 4 who continue in the Extension Phase.

After 48 weeks of on-study B/F/TAF, participants in Treatment Group 4 will be offered to switch from B/F/TAF to ISL+LEN, starting with the loading doses of LEN over 2 days.

Missed dose recommendations for ISL, LEN, and ISL/LEN CCI for Cohort 2 are provided in Table 22 and Table 23. These recommendations apply to missing both ISL and LEN as well as to missing only ISL, only LEN, or ISL/LEN CCI The scheduled dosing day of the week should not change due to the missed dose of ISL and/or LEN or ISL/LEN CCI

Table 22. Cohort 2: Missed Dose Recommendations for ISL and LEN

Number of Days Since Initial Missed Scheduled Dose	Recommendation	Examples
1 to 6 days (1 missed dose)	For both ISL and LEN, take 1 dose each (ie, 2 capsules of 1 mg ISL and 1 tablet of 300 mg LEN) as soon as possible, then resume normal schedule, taking 1 dose on the next scheduled day.	Participant forgets to take dose on Monday (scheduled) but remembers before the next scheduled dose day (ie, Tuesday-Sunday). Take 1 dose as soon as possible, then take 1 dose on the following Monday as scheduled.
7 to 14 days (1 – 2 missed doses)	NOTE: Separate instructions for ISL and LEN ISL: Take 1 dose (ie, 2 capsules of 1 mg ISL) as soon as possible, then resume normal schedule, taking 1 dose on the next scheduled day. If participant remembers on scheduled dosing day, then take 1 dose only. Do not take 2 doses on the same day. LEN: Take 2 doses (ie, 2 tablets of 300 mg LEN) as soon as possible, then resume normal schedule on the next scheduled day. If participant remembers on scheduled dosing day, then take 2 doses only. Never take 3 doses on the same day.	Participant forgets to take both doses on Monday (scheduled) but remembers the following Monday. Take 1 dose of ISL and 2 doses of LEN on that Monday and resume dosing schedule (1 dose each on Mondays). Participant forgets to take both doses on 2 consecutive Mondays (scheduled) but remembers a few days later (ie, Tuesday-Sunday following second missed dose) before the third Monday. Take 1 dose of ISL and 2 doses of LEN as soon as possible, then resume dosing schedule (1 dose each the next Monday as scheduled). Participant forgets to take both doses on 2 consecutive Mondays (scheduled) but remembers on the third Monday. Take 1 dose of ISL and 2 doses of LEN on the third Monday and resume dosing schedule (1 dose on Mondays). Do not take 2 doses of ISL or 3 doses of LEN on the same day.
More than 14 days (3 or more missed doses)	Assess whether clinically appropriate to restart oral weekly regimen. Consider checking HIV-1 RNA.	Participant forgets to take dose on 3 consecutive Mondays (scheduled). Clinical assessment needed.

HIV-1 = human immunodeficiency virus type 1; ISL = islatravir; LEN = lenacapavir; RNA = ribonucleic acid

Table 23. Cohort 2: Missed Dose Recommendations for ISL/LEN CCI

Number of Days Since Initial Missed Scheduled Dose	Recommendation	Examples
1 to 6 days (1 missed dose)	Take the usual maintenance dose (ie, 1 tablet of ISL/LEN CCI 2/300 mg) as soon as possible, then resume normal schedule, taking 1 dose on the next scheduled day.	Participant forgets to take dose on Monday (scheduled) but remembers before the next scheduled dose day (ie, Tuesday-Sunday). Take 1 dose as soon as possible, then take 1 dose on the following Monday as scheduled.
7 days (1 full missed dose)	Take the usual maintenance dose (ie, 1 tablet of ISL/LEN CCI 2/300 mg) on that day, then resume normal schedule, taking 1 dose on the next scheduled day.	Participant has been taking doses every Monday. Participant forgets to take dose on Monday (scheduled) but does not realize this until the following Monday. The participant should take a single dose on that Monday and resume the previous dosing schedule (1 dose on each Monday).
More than 7 days (2 or more missed doses)	Participant to contact the clinic. Investigator to consider checking HIV-1 RNA and assess whether clinically appropriate to restart oral weekly regimen. If appropriate, initiate reloading (ie, 2 tablets of ISL/LEN 0.5/300 mg or CCI on 2 consecutive days) as soon as possible followed by once weekly maintenance doses. The site should contact the sponsor medical monitor.	Participant has been taking doses every Monday. Participant forgets to take dose on 2 consecutive Mondays. Participant should contact the clinic. If clinically appropriate, participant will be asked for a clinic visit to restart the loading regimen (ie, 2 tablets of ISL/LEN 0.5/300 mg or CCI on 2 consecutive days) as soon as possible, followed by once weekly maintenance doses.

CCI ; HIV-1 = human immunodeficiency virus type 1; ISL = islatravir; LEN = lenacapavir; RNA = ribonucleic acid

CCI

CCI

ISL/LEN CCI CCI tablet administered orally should be taken weekly on the same day of the week, without regard to food.

5.7. Dosage and Administration of B/F/TAF

Participants in Treatment Groups 2 and 4 will take oral daily B/F/TAF (1 × 50/200/25 mg tablet) without regard to food.

If a participant misses a dose of B/F/TAF and notices within 18 hours of the usual dosing time, the participant should take the missed dosed as soon as possible, then take the next dose at the next usual dosing time. If a participant misses a dose of B/F/TAF and notices after 18 hours or more past the usual dosing time, the participant should skip the missed dose and wait to take the next dose at the next usual dosing time.

5.8. Prior and Concomitant Medications

Medications in Table 24 are prohibited or should be used with caution while participants are taking study drugs. Should participants have a need to initiate treatment with any prohibited concomitant medication, the Gilead medical monitor must be consulted, and approval granted before initiation of the new medication. In instances where a prohibited medication is initiated before discussion with the Gilead medical monitor, the investigator must notify Gilead as soon as he/she/they is/are aware of the use of the prohibited medication.

For guidance on prior and concomitant medications for participants in Treatment Groups 2 and 4, the investigator is directed to refer to the FDA-approved B/F/TAF product labeling package insert for complete information {BIKTARVY 2021}.

Islatravir metabolism occurs primarily via adenosine deaminase, a non–cytochrome P450 enzyme (CYP)-mediated process. Given the very low propensity for people with HIV-1 to require an adenosine deaminase inhibitor (eg, pentostatin), the likelihood of ISL being a victim of DDI is low. Islatravir is not metabolized by CYP enzymes and, therefore, is not expected to be a victim of CYP-mediated drug interactions. In vitro studies show that ISL is not an inhibitor of major CYP enzymes, transporters, or UGT1A1, nor a time-dependent inhibitor of CYP3A4 at clinically meaningful concentrations. No clinically significant interactions were seen in DDI studies of ISL and dolutegravir/tenofovir disoproxil fumarate, ISL and levonorgestrel/ethinyl estradiol, ISL and doravirine, or ISL and pantoprazole, ISL and methadone, or ISL and metformin/atorvastatin. Islatravir, like many other nucleosides, is phosphorylated initially by deoxycytidine kinase (dCK), an enzyme for which ISL has relatively low affinity and, therefore, is not converted to ISL-TP when exogenous nucleosides with a higher affinity for dCK (eg, lamivudine [3TC], emtricitabine [FTC]) are also administered. Islatravir has the potential to be an object of a dCK-mediated interaction when coadministered with 3TC or FTC, or other high affinity substrates of dCK. Coadministration of 3TC or FTC with ISL/LEN CCI is prohibited.

Clinical data indicate LEN is a substrate of CYP3A, P-gp, and UGT1A1, a moderate inhibitor of CYP3A, and a weak inhibitor of P-gp and BCRP. Current clinical recommendations for LEN allow coadministration of LEN with strong CYP3A or CYP3A/P-gp inhibitors without dose modification, but coadministration with strong UGT1A1 inhibitors or UGT1A1/CYP3A/P-gp inhibitors is not recommended. Strong and moderate inducers of CYP/P-gp/UGT should also be avoided with LEN. Caution is advised if LEN is coadministered with sensitive CYP3A substrates, but not P-gp, BCRP, or OATP substrates.

Concomitant use of LEN with medications or herbal/natural supplements that are substrates of CYP3A may result in increased exposure of these medications. Representative medications and herbal/natural supplements listed in Table 24 are currently excluded or should be used with caution while participating in this study; this table is not exhaustive. For medications not listed below that may be sensitive substrates of CYP3A, strong or moderate inducers, strong UGT1A1/CYP3A/P-gp inhibitors, or strong UGT1A1 inhibitors, the investigator should reach out to Gilead for guidance.

Participants should discontinue disallowed concomitant medications 30 days prior to initiation of study drugs, except for their baseline B/F/TAF regimen.

Table 24. Examples of Prior and Concomitant Medications That are to be Used With Caution or That Are Prohibited due to the Potential for PK DDI With Islatravir or Lenacapavir[a]

Medication Class	Medications to be Used With Caution	Prohibited Medications
Adenosine deaminase inhibitors		Pentostatin
Anticonvulsants		Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
Antihyperlipidemic agents (HMG-CoA reductase inhibitors)	Coadministration may increase certain statin concentrations, which is associated with increased risk of myopathy, including rhabdomyolysis. Start with the lowest dose and titrate to clinical response with careful monitoring. In particular, Gilead recommends maximum doses for the following statins: simvastatin 10 mg, lovastatin 20 mg, and atorvastatin 20 mg.	
Antimycobacterials		Rifampin, rifabutin, rifapentine
ARV		Any nonstudy HIV-1 ARV
Corticosteroids		Any chronic systemic corticosteroid (> 2 weeks)
dCK substrates	Coadministration with cladribine, clofarabine, cytarabine, fludarabine, and gemcitabine is not recommended.	Coadministration is contraindicated with 3TC or FTC.
Ergot derivatives		Ergotamine, dihydroergotamine, methylergonovine, ergometrine
Herbal/natural supplements		St. John's wort, echinacea, milk thistle
Immunomodulators		Interferons
Phosphodiesterase-5 inhibitors	Recommended maximum doses are as follows: sildenafil 25 mg in 24 hours, vardenafil 5 mg in 24 hours, and tadalafil 10 mg in 72 hours.	
Sedatives/hypnotics	Midazolam, triazolam	

3TC = lamivudine; ARV = antiretroviral; dCK = deoxycytidine kinase; DDI = drug-drug interactions; FTC = emtricitabine; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; PK = pharmacokinetic(s)

a This table represents examples of the most common concomitant medications and is not meant to be exhaustive. If the investigator is unsure if a medication is allowed per protocol, he/she/they should consult with the sponsor.

5.9. Accountability for Study Drugs

The investigator is responsible for ensuring adequate accountability of all used and unused study drug supplies (drugs and bottles). This includes acknowledgment of receipt of each shipment of study drug supplies (quantity and condition). All used and unused study drug supplies dispensed to participants must be returned to the site.

Each investigational site must keep accountability records that capture the following:

- The date received, quantity, and condition of study drug bottles
- The date, participant number, and the study drug bottle numbers or lots dispensed
- The date, quantity of used and unused study drug bottles returned, along with the initials of the person recording the information

5.9.1. Study Drug Return or Disposal

Gilead recommends that used and unused study drugs, which includes bottles, be destroyed at the site. If the site has an appropriate standard operating procedure for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug bottles in accordance with that site's approved procedural documents. A copy of the site's approved procedural document will be obtained for the electronic trial master file. If the study drug supply is destroyed at the site, the investigator must maintain accurate records for all study drug supplies destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug supplies. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be provided to Gilead.

If the site does not have an appropriate standard operating procedure for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform study drug accountability.

6. STUDY PROCEDURES

The study procedures to be conducted for each participant screened or enrolled in the study are presented in tabular form in Table 1, Table 2, and described in the sections below.

The investigator must document any deviation from the protocol procedures and notify Gilead or the contract research organization.

6.1. Informed Consent

Written informed consent must be obtained from each participant before initiation of any study-related procedures. Refer to Section 9.1.4 for further information regarding informed consent.

6.2. Screening, Participant Enrollment, and Treatment Assignment

Participants will be screened within 35 days before enrollment in the study. Each participant will be assigned a unique screening number using the IRT. Participants meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 35 days for randomization into the study. It is the responsibility of the investigator to ensure that participants are eligible to participate in the study prior to enrollment and continue to remain eligible throughout the study. The medical monitor may be contacted regarding any questions related to eligibility.

If the screening window is exceeded in an otherwise eligible participant, the participant is allowed to rescreen 1 time after approval from the sponsor. Once a participant has started the rescreening process, a new screening window (35 days) will begin, during which time screening procedures will be repeated.

Participants who are considered screen failures because the duration of baseline B/F/TAF was < 24 weeks are allowed to rescreen if they have continued to receive B/F/TAF therapy.

For all participants, the last day of baseline B/F/TAF prior to randomization will be Day −1.

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study wide at any time.

Once the informed consent form (ICF) has been signed, all screening and eligibility tests and assessments have been assessed, and study eligibility has been confirmed, participants will be randomized to receive study drugs on Day 1.

Participants will receive the study treatments as described in Sections 5.6 and 5.7.

6.3. Instructions for Study Procedures

Study procedures and assessments are outlined in Table 1 and Table 2.

6.3.1. Adverse Events

From the time informed consent is obtained through the first administration of study drugs, record all SAEs, as well as any AEs related to protocol-required procedures on the AE electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. After study drug administration, report all AEs and SAEs. Additional details are provided in Section 7.

6.3.2. Concomitant Medications

Review of concomitant medications will occur at the time points presented in Table 1 and Table 2. Further information about concomitant medications is provided in Sections 4.3 and 5.8.

6.3.3. Electrocardiograms

Participants should rest quietly in the supine position for a minimum of 10 minutes before ECG acquisition and should remain in that position until the recording is complete.

The investigator or other qualified individual at the study center will review the ECG for abnormalities.

6.3.4. Medical History and Demographic Information

Medical history and demographic information are to be collected for each participant at screening as follows:

- Review medical history including HIV-1 disease-related events, available historical genotype/phenotype reports, available HIV-1 treatment history, substance (ie, illicit drug) use, and medications taken within 30 days of the screening visit
- Obtain demographic information, including sex at birth, sexual orientation, and gender identity
- If available, investigators are asked to document prior resistance data from available HIV-1 genotype and/or phenotype reports (see Exclusion Criterion 20 in Section 4.3)

6.3.5. Physical Examination

Physical examinations conducted throughout the study will be complete or symptom driven (Table 1 and Table 2).

The complete physical examination will include source documentation of general appearance, and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes; abdomen; skin, hair, nails; musculoskeletal; neurological. Genito-urinary and breast examinations should not be conducted unless clinically indicated.

6.3.6. Clinical Laboratory Assessments

Blood and urine samples will be collected throughout the study as outlined in Table 1 and Table 2. Laboratory assessments are listed in Table 25.

Table 25. Laboratory Assessments

Safety Laboratory Measurements			
Chemistry (Serum or Plasma)	**Hematology**	**Urinalysis**	**Other Laboratory Measurements**
ALT AST Albumin Alkaline phosphatase Creatine kinase Creatinine[a] Direct bilirubin Total bilirubin Glucose Lipase Phosphorus Potassium Sodium	Hemoglobin Platelets White cell count 5-part differential[b]	Color & clarity Specific gravity pH Glucose Protein Blood and microscopic (reflex if positive) Leukocyte esterase and microscopic (reflex if positive) Pregnancy test[c]	Serum pregnancy test[c] Serum FSH[d] CD4+ T-cell/TBNK panel (Cohort 2) Plasma HIV-1 RNA HBcAb, HBsAg, HBsAb, HBV DNA, HCV Ab (Cohort 2), HCV RNA Plasma storage samples Whole blood storage sample Pharmacokinetics HIV-1 proviral genotype[e] HIV-1 genotype and phenotype at virologic failure

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CD4+ = clusters of differentiation 4; CL_{cr} = creatinine clearance; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HCV Ab = hepatitis C antibody; TBNK = T, B, and natural killer cells

a Creatinine clearance to be calculated according to the Cockcroft-Gault formula for Creatinine clearance: male: [(140 – age in years) × (weight in kg)]/[72 × (serum creatinine in mg/dL)] = CL_{cr} (mL/min); female: [(140 – age in years) × (weight in kg) × 0.85]/[72 × (serum creatinine in mg/dL)] = CL_{cr} (mL/min).

b Count and percent (neutrophils, lymphocytes, monocytes, basophils, eosinophils).

c For participants of childbearing potential.

d For participants who were female sex at birth and are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.

e For all participants enrolled in Cohort 2, to be performed at the screening visit.

Refer to Table 1 and Table 2 for collection time points.

HIV-1 RNA will be measured using the COBAS Ampliprep/COBAS Taqman v. 2.0 assay. Gilead reserves the right to use alternate assays for HIV-1 RNA should this assay become unavailable.

6.3.7. Pharmacokinetics Assessments

6.3.7.1. Single Anytime Plasma PK Sampling

Single anytime plasma PK sampling for ISL and LEN will occur in Treatment Group 1 and Treatment Group 3 participants at each onsite visit through Week 72 except Day 1. Day 1 PK sample will be collected 1 hour (± 30 minutes) postdose after onsite drug administration. The date and time of ISL and LEN dosing on Day 1 and previous ISL and LEN dosing for subsequent visits will be recorded. PK collections after Week 48 will be stored and analyzed only if deemed necessary by sponsor.

6.3.7.2. Pharmacokinetics Substudy

A PK substudy will be conducted in approximately 10 participants in Treatment Group 1 and approximately 15 participants in Treatment Group 3 who provide consent. Samples will be collected on Day 1, Day 2, and Week 12 at the time points presented in Table 26. Study drugs will be administered during the onsite visits on Day 1, Day 2, and Week 12. For Day 2, only LEN samples will be collected; both ISL and LEN samples will be collected for Day 1 and Week 12. Week 12 PK substudy sample collection may be performed at Week 18 if the participant took the Week 12 study drugs prior to the clinic visit instead of administered onsite.

Additional single anytime PK sampling will not be collected for participants in the substudy during PK substudy visits (Day 1, Week 12, or Week 18).

Table 26. PK Substudy Sample Collection Time Points

Visit[a]	Sampling Time Points
Day 1	predose (within 30 minutes prior to dosing), 0.5, 1, 2, 4, 6, and 8 hours postdose
Day 2 [b]	predose (within 30 minutes prior to dosing), 0.5, 1, 2, 4, 6, and 8 hours postdose
Week 12[c, d]	predose (within 30 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 72, 120, and 168 hours postdose

LEN = lenacapavir; PK = pharmacokinetic(s)
a The study drugs will be administered at the site during the study visit.
b For Day 2, only LEN samples will be collected after LEN only (2 × 300 mg) administration onsite.
c Week 12 PK substudy sample collection may be performed at Week 18 if the participant took the Week 12 study drugs prior to the clinic visit instead of administered onsite.
d 168-hour sample must be collected prior to next dose to capture trough concentration.

6.3.8. Clinical Virology Analyses

6.3.8.1. Virology Testing

6.3.8.1.1. Virology Samples to Address Study Objectives

Stored plasma and whole blood samples may be used to assess HIV-1 genotype at baseline HIV-1 genotype and phenotype in confirmed cases of virologic failure as defined in Section 6.3.8.2.

6.3.8.2. Virologic Failure

Virologic failure is defined as virologic rebound, as defined below, or having HIV-1 RNA ≥ 50 copies/mL at study discontinuation or at last visit.

6.3.8.2.1. Management of Virologic Rebound

Participants who meet the criteria listed below will be considered to have virologic rebound:

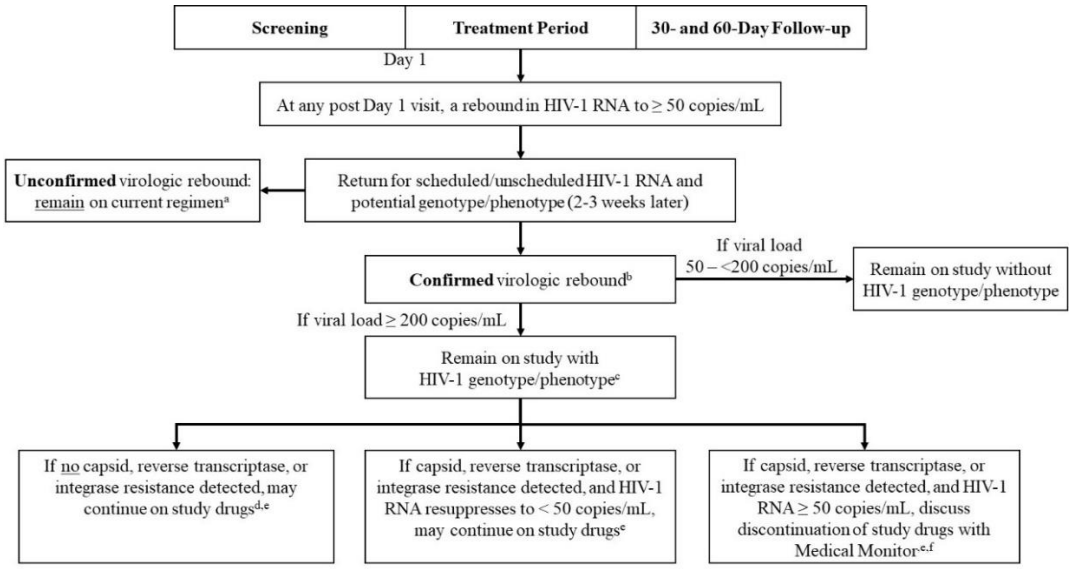
- At any post Day 1 visit, a rebound in HIV-1 RNA ≥ 50 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit; OR
- Any participant with HIV-1 RNA ≥ 50 copies/mL at study drug discontinuation or at the last visit

At Day 1 visit or any post Day 1 visit, if the HIV-1 RNA is ≥ 50 copies/mL and < 200 copies/mL, a reflex HIV-1 RNA repeat test will be conducted on stored plasma samples, if available. If the repeat result is < 50 copies/mL, no further action is required. If the repeat result is ≥ 50 copies/mL, participants will be asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 3 weeks after the date of the original test with HIV-1 RNA ≥ 50 copies/mL) for confirmation of virologic rebound. If virologic rebound is confirmed and HIV-1 RNA is ≥ 200 copies/mL, the plasma sample from the confirmation visit will be the primary sample used for HIV-1 genotypic and phenotypic testing. After a participant's first post Day 1 resistance test, additional testing will be conducted on a case-by-case basis.

If no resistance is detected from the genotype or phenotype, the participant may remain on study drugs and the HIV-1 RNA test should be repeated (2 to 3 weeks after the date of confirmed test with HIV-1 RNA ≥ 50 copies/mL). If genotypic or phenotypic resistance to study drug is documented and the participant resuppresses HIV-1 RNA to < 50 copies/mL at a subsequent visit, the participant may continue on study drugs. If resistance to study drug is detected and HIV-1 RNA levels remain ≥ 50 copies/mL, investigators should carefully evaluate the benefits and risks of remaining on study drugs for each individual participant and document this assessment in the onsite medical record. Investigators who opt to discontinue study drugs for an individual participant must discuss with the medical monitor prior to study drug discontinuation.

Refer to Figure 5 for the management of participants who meet the criteria for virologic rebound.

Figure 5. Virologic Rebound Schema



ARV = antiretroviral; HIV-1 = human immunodeficiency virus type 1; RNA = ribonucleic acid

a If virologic rebound is not confirmed, the participant will remain on their current regimen.

b If virologic rebound is confirmed and the HIV-1 RNA is ≥ 200 copies/mL, the HIV-1 genotype and phenotype (capsid, reverse transcriptase, and integrase) will be analyzed.

c Based on the results of the genotypic and phenotypic assays, the participant will remain on study drugs or study drugs will be discontinued. If the genotyping or phenotyping assay shows resistance, a new ARV regimen may be configured at the discretion of the investigator, in consultation with the medical monitor.

d If no resistance is detected, HIV-1 RNA will be repeated (2 to 3 weeks later).

e Investigator reviews study drug continuation/discontinuation options and discusses with the medical monitor prior to study drug discontinuation.

f If study drugs are discontinued, a new ARV regimen will be configured, at the investigator's discretion, and the participant will remain in the study through the 30- and 60-day (as applicable) follow-up visits.

6.3.8.3. Resistance Analysis at a Participant's Last Visit

Participants with HIV-1 RNA ≥ 50 copies/mL at their last study visit while taking study drugs (ie, rebound not confirmable) will be considered to have virologic failure. Participants with HIV-1 RNA ≥ 200 copies/mL at the last visit will be evaluated for resistance.

6.3.9. Patient-Reported Outcomes

Patient-reported outcome questionnaires (if available) will be completed by participants in both cohorts at the visits specified in Table 1 and Table 2, and include HIVDQoL, the HIV Treatment Satisfaction Questionnaires (HIVTSQc12 and HIVTSQs12), EQ-5D-5L, the Patient Perspective of Regimen (PP-R), and the Patient Perspective of Regimen Change (PP-RC). The PP-R and PP-RC questionnaires are novel 10-item treatment preference questionnaire developed by MSD, following the FDA PRO development guidance and are intended to explore patient perceptions of weekly oral ART and how those perceptions may differ from perceptions of those taking daily oral ART. The PP-R will be administered to participants in Treatment Groups 3 and 4; for Treatment Group 3, participants will also be administered the PP-RC after completing the PP-R.

6.4. Assessments for Early Discontinuation from Study Treatment or from the Study

If a participant discontinues study drugs, every attempt should be made to keep the participant in the study and continue to perform the required 30- and 60-day (as applicable) follow-up visit procedures. If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study.

6.4.1. Assessments for Early Discontinuation from Study Treatment

Participants who permanently discontinue study drugs before the end of the study are required to return to the investigational site to complete an early study drug discontinuation (ESDD) visit within 3 days (+1 day) after their last dose. If early discontinuation occurs during the timeframe of a scheduled study visit, the assessments for the ESDD visit should be conducted. Assessments and procedures for the ESDD visit are specified in Table 1 and Table 2.

At the ESDD visit, any assessment showing abnormal results (except those meeting stopping criteria due to CD4+ T-cell and/or absolute lymphocyte count declines) that the investigator determines to have a possible or probable causal relationship with the study drugs, will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

Participants in Treatment Group 3 or any Cohort 2 participant in the Extension Phase who has been discontinued from the study due to CD4+ T-cell declines will have the laboratory test repeated as specified in the study procedures (Section 7.7) until it is at least 75% (or higher) of the average baseline (based on screening and Day 1 values, with average baseline equal to 100%) or until the 200-day follow-up visit, whichever comes first. Participants who have been discontinued from the study due to absolute lymphocyte count declines will have the laboratory test repeated as specified in the study procedures until it is above the lower limit of normal based on age (per central laboratory) or until the 200-day follow-up visit, whichever comes first.

For participants who discontinued study drugs and are confirmed to have HIV-1 RNA ≥ 50 copies/mL at the ESDD visit, the participant will be followed until resuppression of HIV-1 RNA to < 50 copies/mL or for 3 months, whichever occurs first.

6.4.2. Assessments for End of Study

Participants who received ISL+LEN or ISL/LEN[CCI] are required to return to the clinic for follow-up visits 30 and 60 days after the last ISL+LEN or ISL/LEN[CCI] dose. Participants who received only B/F/TAF (ie, did not switch to ISL+LEN or ISL/LEN[CCI]) are required to return to the clinic for a follow-up visit 30 days after the last on-study B/F/TAF dose. Assessments and procedures for the 30- and 60-day follow-up visits are specified in Table 1 and the 100- and 200-day follow-up visits in Table 2.

At the 30- and 60-day follow-up visits, as applicable, any assessment showing abnormal results that the investigator determines to have a possible or probable causal relationship with the study drugs, will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

6.5. Poststudy Care

After the participant has completed/terminated their participation in the study, long-term care of the participant will remain the responsibility of their primary treating physician.

6.6. Sample Storage

The stored biological samples may be used by Gilead or its research partner for additional testing to provide supplemental data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period up to 15 years or per country requirements.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a study drug, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.4).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, or transfusion. The condition that led to the procedure may be an AE and must be reported
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.1.4)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- A life-threatening situation (Note: 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 that hypothetically might have caused death if it were more severe)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse

7.1.3. Adverse Events of Special Interest

Not applicable.

7.1.4. Study Drugs and Gilead Concomitant Medications Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit or falsified medicine, and pregnancy regardless of an associated AE. Any sequelae from a special situation event must be reported as an AE/SAE in accordance with Sections 7.3 and 7.4 in addition to being captured in the SSR.

Below are the definitions for special situation events that require reporting in accordance with Section 7.4.3.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, participant, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a participant.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only

when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the participant has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, drug/alcohol, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is reasonable possibility that the adverse event may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.

- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs and laboratory abnormalities will be graded using the Division of AIDS (DAIDS) Toxicity Grading Scale, Version 2.1 dated July 2017, available as follows:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale.

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Before Study Drug Initiation

After informed consent, but before initiation of study drug, the following types of events must be reported on the applicable eCRF: all SAEs and any AEs that are related to protocol-required procedures.

7.3.2. Adverse Events

Following initiation of study drug, collect all AE, regardless of cause or relationship, until the end of the protocol-defined follow-up period and report the AEs on the eCRF as instructed.

All AEs and clinically significant laboratory abnormalities should be followed until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the participant first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit(s), must be reported on the applicable electronic case report forms and to Gilead Patient Safety as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed. The investigator must report the primary cause of death as an SAE for any participant who dies during the follow-up period to the sponsor. The primary cause of death will be reported as the SAE term(s) unless the cause of death cannot be obtained.

Any SAEs and deaths that occur after the posttreatment follow-up visit(s) until the end of the protocol-defined follow-up period, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead Patient Safety.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Adverse Events of Special Interest

Not applicable.

7.3.5. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit(s), must be reported to Gilead Patient Safety (Section 7.4.3). Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.3).

7.3.6. Concomitant Medications Reports

7.3.6.1. Gilead Concomitant Medications Special Situations Report

Special situation reports involving a Gilead concomitant medication (not considered study drug), that occurs after the participant first consents to participate in the study (ie, signing of the ICF) and throughout the duration of the study, including the posttreatment follow-up visit(s), must be reported to Gilead Patient Safety utilizing the paper SSR (Section 7.4.3.1).

7.3.6.2. Non-Gilead Concomitant Medications Report

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE eCRF.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE eCRF. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events, Adverse Events of Special Interest, and Special Situations Reports

7.4.1. Serious Adverse Event Reporting Process

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant’s eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

Site personnel will record all initial or follow-up SAE data (including updates to the reported event term[s]) on the applicable CRFs within 24 hours of the investigator's knowledge of the initial event/update in order for the SAE information to be transmitted timely to Gilead Patient Safety. Serious adverse event information must be reported from the time of the ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason it is not possible to record and transmit the SAE information electronically, site personnel must record the SAE on the paper Initial or Follow-up SAE Report Form and transmit by emailing or faxing the report within 24 hours of the investigator's knowledge of the initial event/update using the contact information below:

Gilead Patient Safety
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to Gilead Patient Safety.

7.4.2. Adverse Events of Special Interest Reporting Process

Not applicable.

7.4.3. Special Situations Reporting Process

7.4.3.1. Paper Special Situations Reporting Process for Study Drug

All SSRs will be recorded on the SSR form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead Patient Safety (contact information provided in Section 7.4.1.1) from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

7.4.3.2. Reporting Process for Gilead Concomitant Medications

Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead Patient Safety (contact information provided in Section 7.4.1.1) utilizing the paper SSR form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs because of a non-Gilead concomitant medication, must be reported on the AE eCRF.

7.4.3.3. Pregnancy Reporting Process

The investigator should report pregnancies in female study participants who are identified after initiation of study drug and throughout the study, including the protocol-required posttreatment follow-up period, to Gilead Patient Safety (contact information provided in Section 7.4.1.1) within 24 hours of becoming aware of the pregnancy using the pregnancy report form.

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after the study must be reported to Gilead Patient Safety.

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead Patient Safety using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead Patient Safety (contact information provided in Section 7.4.1.1).

Refer to Appendix 3 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs which may be in the form of line listings, serious adverse drug reactions, or suspected unexpected serious adverse reactions. In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant independent ethics committee in concerned Member States of applicable suspected unexpected serious adverse reactions as outlined in current regulations.

In the intended study population, Gilead anticipates the occurrence of SAEs that are manifestations of the underlying disease, commonly occur in the study population independent of drug exposure, or are components of the study endpoints. The anticipated SAEs, unless life-threatening/fatal, will not be reported to FDA.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant suspected unexpected serious adverse reaction reports associated with any study drug. The investigator should notify the IRB or independent ethics committee of suspected unexpected serious adverse reaction reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

Details for the role of the DMC are provided in Section 8.10.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity of either AEs or laboratory abnormalities should be recorded and graded according to the DAIDS Toxicity Grading Scale, Version 2.1 dated July 2017, available as follows:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

All clinical and clinically significant laboratory toxicities – except for CD4+ T-cells and absolute lymphocyte counts delineated later in this section – will be managed according to uniform guidelines detailed in Appendix 4 and the timing described below.

Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product discontinuation, unless such a delay is not consistent with good medical practice. If repeat testing is not possible within 3 calendar days of receipt of results, it may be completed within 14 calendar days of receipt of results per the investigator's discretion.

For Treatment Group 3 participants in the Randomized Phase or any Cohort 2 participants in the Extension Phase meeting either the CD4+ T-cell or absolute lymphocyte count criteria below, the Gilead medical monitor should be consulted to discuss study drug discontinuation when medically feasible:

- For those with an average baseline CD4+ T-cell count ≥ 500 cells/mm^3, a decline to < 350 cells/mm^3 that is confirmed by a repeat measure at least 10 weeks apart and in the absence of a plausible alternative cause (eg, concurrent illness, immunosuppressive medications, radiation therapy, HIV viral rebound). Average baseline is defined as the mean CD4+ T-cell count between screening and Day 1.

- For those with an average baseline CD4+ T-cell count ≥ 350 and ≤ 499 cells/mm^3 (inclusive), a decline to < 200 cells/mm^3 that is confirmed by a repeat measure at least 10 weeks apart and in the absence of a plausible alternative cause (eg, concurrent illness, immunosuppressive medications, radiation therapy, HIV viral rebound). Average baseline is defined as the mean CD4+ T-cell count between screening and Day 1.

  OR

- A Grade 2 or above (per DAIDS toxicity grading scale) absolute lymphocyte count that is confirmed by a repeat measure at least 10 weeks apart and in the absence of a plausible alternative cause for the decline (eg, concurrent illness, immunosuppressive medications, radiation therapy, HIV viral rebound).

If an alternative etiology is suspected for either CD4+ T-cell or absolute lymphocyte count declines, a participant may continue study drug with ongoing monitoring. However, at any time, if a participant receiving ISL+LEN or ISL/LEN CCI experiences CD4+ T-cell or absolute lymphocyte count declines that are clinically meaningful (eg, infections occurring as a result of such declines), out of proportion to normal clinical practice intraparticipant variability (eg, confirmed 30% decline), and/or do not have a plausible alternative cause as determined by the investigator, study drug discontinuation may be considered regardless of the above criteria.

The Gilead medical monitor should be consulted prior to study drug discontinuation when medically feasible. After study drug discontinuation, participants should be switched to an appropriate alternative ARV regimen.

Refer to Section 6.4.1 for monitoring procedures after study drug discontinuation due to CD4+ T-cell or absolute lymphocyte count decline.

See Section 7.6 for AE reporting requirements for laboratory abnormalities.

8. STATISTICAL CONSIDERATIONS

Additional details for the planned analyses will be provided in the statistical analysis plan (SAP).

8.1. Analysis Objectives and Endpoints

Objectives and endpoints are listed in Section 2.

8.2. Planned Analyses

8.2.1. Interim Analysis

Before the final analysis, interim analyses, including analyses supporting DMC evaluation, may be conducted and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program and to support regulatory filings.

8.2.1.1. Planned Interim Analyses

In addition to the primary analysis, there will be 2 planned interim analyses:

- Week 48 analysis after all participants have completed their Week 48 visits or prematurely discontinued study drug
- Week 96 (Extension Phase Week 48) analysis after all participants who entered the Extension Phase have completed their Week 96 visits or prematurely discontinued study drug

8.2.1.2. Data Monitoring Committee Analysis

Planned DMC analyses are to be conducted after all participants have completed their Week 12, 24, and 48 visits, or prematurely discontinued study drugs during the Randomized Phase.

Additionally, if 5 or more participants receiving ISL+LEN experience virologic rebound (as defined in Section 6.3.8.2.1) unrelated to poor adherence before Week 12, a DMC meeting will be convened to assess the data. If 3 or more participants receiving ISL+LEN discontinue study drug due to meeting the stopping criteria for ISL-associated CD4+ T-cell and/or absolute lymphocyte count decline (Section 7.7) at any time, a DMC meeting will be convened to assess the data.

A DMC meeting may be convened, and the supporting analyses may be conducted at other times during the study as deemed necessary. Clinical assessments will be made to determine if the nature, frequency, and severity of AEs associated with a study regimen warrant the early termination of the study in the best interest of the participants. No formal stopping rules will be used by the DMC for safety or efficacy outcomes. No alpha penalty will be applied for the primary analysis of the primary efficacy endpoint given that the study is not adequately powered for a formal efficacy evaluation. Data from these analyses may be used to support the planning of other studies.

8.2.2. Primary Analysis

The primary analysis of the primary endpoint will be conducted after all participants within each cohort have completed the Week 24 visit or have prematurely discontinued study drugs, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis. This analysis of the primary endpoint will serve as the final analysis for this endpoint and will be used to evaluate the efficacy of ISL+LEN.

8.2.3. Final Analysis

The final analysis will be performed after all participants within each cohort have completed or prematurely discontinued from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

8.3.1. Analysis Sets

The following analysis sets are defined for each cohort respectively.

8.3.1.1. Efficacy

The primary analysis set for efficacy analyses is defined as the full analysis set (FAS), which will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of study drugs. Participants will be grouped according to the treatment to which they were randomized.

8.3.1.2. Safety

The primary analysis set for safety analyses is defined as the safety analysis set, which will include all participants who have received at least 1 dose of study drugs. Participants will be grouped according to the treatment they actually received.

8.3.1.3. Pharmacokinetics

8.3.1.3.1. Pharmacokinetic Analysis Set

The primary analysis set for general PK analyses is defined as the PK analysis set, which will include all participants who (1) are randomized into the study, (2) have received at least 1 dose of study drugs, and (3) have at least 1 nonmissing PK concentration value for the analyte under evaluation reported by the PK laboratory. The PK analysis set will be used for analyses of general PK.

8.3.1.3.2. Pharmacokinetic Substudy Analysis Set

The primary analysis set for intensive PK analyses is defined as the PK substudy analysis set, which will include all participants who (1) are randomized into the study, (2) enrolled into the PK substudy, (3) have received at least 1 dose of study drugs, and (4) have at least 1 nonmissing intensive PK concentration value for the analyte under evaluation reported by the PK laboratory. The PK substudy analysis set will be used for detailed PK analyses.

8.3.1.4. All ISL+LEN Analysis Set

This analysis set is defined for All ISL+LEN analysis and will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of ISL+LEN or ISL/LEN CCI . Participants who received ISL+LEN or ISL/LEN CCI by error as partial treatment during the Randomized Phase will be excluded from the All ISL+LEN analysis set.

8.3.2. Data Handling Conventions

HIV-1 RNA reported results of 'No HIV-1 RNA detected' and '< 20 copies/mL HIV-1 RNA Detected' will be imputed as 19 copies/mL for analysis purposes. Logarithm (base 10) transformation will be applied to HIV-1 RNA levels for analysis of change from baseline in HIV-1 RNA. The HIV-1 RNA reported results will be used for listing purposes.

Laboratory data (other than HIV-1 RNA) that are continuous in nature but are above the upper limit of quantitation or less than the lower limit of quantitation (LLOQ) will be imputed to the value of the upper or lower limit plus or minus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 5.4, a value of 5.3 will be assigned).

Pharmacokinetic plasma concentration values below the limit of quantification (BLQ) will be treated as zero at predose and one-half of LLOQ for postdose time points, where LLOQ is corrected for the dilution factor (ie, reported dilution/dilution factor), for analysis purposes. The PK plasma concentrations will be transformed using natural logarithm for PK analysis. The report values that are BLQ will be presented as "BLQ" in the concentration data listing.

Missing data can have an impact upon the interpretation of the study data. In general, values for missing data will not be imputed. However, a missing pretreatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods including sample size, mean, SD, median, Q1, Q3, minimum, and maximum for continuous variables and frequency and percentages for categorical variables.

Demographic summaries will include sex at birth, sexual orientation, gender identity, race, ethnicity, and age.

Baseline data will include a summary of body weight, height, BMI, and HIV-1 infection (eg, CD4+ T-cell count).

For categorical demographic and baseline characteristics, a Fisher exact test will be used to compare the ISL+LEN group and B/F/TAF group within each cohort. For continuous demographic and baseline characteristics, a Wilcoxon rank sum test will be used to compare the ISL+LEN group and B/F/TAF group within each cohort.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy endpoint is the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}. The primary analysis of the efficacy will be based on the FAS.

The 95% CI of the difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 between the ISL+LEN group and B/F/TAF group within each cohort will be constructed based on an unconditional exact method using 2 inverted 1-sided tests {Chan 1999}.

8.5.2. Secondary Analyses

The same methods used to analyze the primary efficacy endpoint, as determined by the US FDA-defined snapshot algorithm, will be used to assess the proportion of participants with HIV1 RNA ≥ 50 copies/mL at Weeks 12 and 48 and the proportion of participants with HIV-1 RNA <50 copies/mL at Weeks 12, 24, and 48.

Changes from baseline in CD4+ T-cell count at Weeks 12, 24, and 48 will be summarized by treatment group within each cohort using descriptive statistics. The differences in changes from baseline in CD4+ T-cell count between the ISL+LEN group and B/F/TAF group within each cohort and the associated 95% CIs will be constructed using analysis of covariance (ANCOVA) models, including baseline CD4+ T-cell count as a covariate and treatment (ISL+LEN vs B/F/TAF) as a fixed-effect in the models.

8.5.3. All ISL+LEN Analysis

The following efficacy endpoints will be summarized for All ISL+LEN analysis using All ISL+LEN analysis set: (1) the proportion of participants with HIV-1 RNA categories (< 50, 50 to < 200 copies/mL, etc) by missing = excluded and missing = failure approaches by visit, (2) the change from baseline in CD4+ T-cell count by visits, and (3) the percentage change from baseline in CD4+ T-cells by visits. No statistical comparison will be conducted.

8.6. Safety Analysis

All safety analyses will be performed using the safety analysis set for the Randomized Phase analysis and using the All ISL+LEN analysis set for the All ISL+LEN analysis, unless specified otherwise.

For the Randomized Phase analysis, all safety data collected on or after the date that study drugs are first dispensed up to the date of last dose of study drugs plus 60 days for the ISL+LEN group and 30 days for the B/F/TAF group (before switching to ISL+LEN) will be summarized by treatment group (according to the study drugs received) within each cohort.

For the All ISL+LEN analysis, all safety data collected on or after the first dose date of ISL or LEN, up to the last dose date of ISL, LEN, or ISL/LEN CCI plus 60 days, will be summarized by treatment group.

All collected data will be included in data listings for all enrolled participants.

8.6.1. Extent of Exposure

A participant's extent of exposure to study drug will be generated from the study drug administration data in the eCRF. Exposure data will be summarized by treatment group within each cohort.

Dosing information for individual participants will be listed.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). System organ class, high-level group term, high-level term, preferred term, and lower-level term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drugs up to the date of last dose of study drugs plus 60 days (for ISL+LEN or ISL/LEN CCI or 30 days (for B/F/TAF), or any AE leading to study drug discontinuation.

Summaries (number and percentage of participants) of treatment-emergent AEs (by system organ class, high-level term [if applicable], and preferred term) will be provided by treatment group within each cohort. Additional summaries will include summaries for AEs by grade, investigator's assessment of relationship to study drugs, and effect on study drug dosing.

8.6.3. Laboratory Evaluations

Selected laboratory test data (using conventional units) will be summarized using only observed data. Absolute values and changes from baseline at all scheduled visits will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017, available as follows:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drugs plus 60 days (for ISL+LEN or ISL/LEN[redacted] or 30 days (for B/F/TAF), will be summarized by treatment group within each cohort. If baseline data are missing, then any postbaseline graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent. The maximum postbaseline toxicity grade will be summarized by laboratory parameter.

8.6.4. Other Safety Evaluations

Vital signs and safety ECG data will be summarized by treatment group within each cohort as appropriate.

8.7. Adjustments for Multiplicity

No adjustments will be made for multiplicity. Nominal 95% CIs and tests performed at the nominal 0.05 alpha level will be provided.

8.8. Pharmacokinetic Analysis

For the general PK analyses, the PK of ISL and LEN may be evaluated using descriptive statistics or population analysis approaches. For the intensive PK substudy, plasma concentrations of ISL and LEN will be summarized by nominal sampling time. Pharmacokinetic parameters (C_{max}, T_{max}, C_{tau}, AUC_{tau}, and $t_{1/2}$, as appropriate) will be listed and summarized using descriptive statistics.

8.9. Sample Size

A sample size of 50 participants in the ISL+LEN treatment group was chosen to estimate the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US FDA-defined snapshot algorithm to allow for the planning of Phase 3 studies. This study is not formally powered.

Cohort 1

Assuming no failure (0%) in Treatment Group 2 (B/F/TAF) at Week 24, the number of failures in Treatment Group 1 (ISL+LEN) at Week 24 would need to be ≥ 8 (16%) for the 95% CI for the between-treatment difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL to exclude 0. Similarly, assuming 1 failure (4%) in Treatment Group 2 at Week 24, the number of failures in Treatment Group 1 at Week 24 would need to be ≥ 12 (24%) for the 95% CI for the between-treatment difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL to exclude 0. The 95% CI is calculated based on an exact unconditional method {Chan 1999}.

If the underlying incidence of a specific AE is 5%, there is a 92.3% chance of observing at least 1 AE among 50 participants in Treatment Group 1 and a 72.3% chance of observing at least 1 AE among 25 participants in Treatment Group 2.

Cohort 2

Assuming no failure (0%) in Treatment Group 4 (B/F/TAF) at Week 24, the number of failures in Treatment Group 3 (ISL+LEN) at Week 24 would need to be ≥ 4 (8%) for the 95% CI for the between-treatment difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL to exclude 0. Similarly, assuming 1 failure (2%) in Treatment Group 4 at Week 24, the number of failures in Treatment Group 3 at Week 24 would need to be ≥ 7 (14%) for the 95% CI for the between-treatment difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL to exclude 0. The 95% CI is calculated based on an exact unconditional method {Chan 1999}.

If the underlying incidence of a specific AE is 5%, there is a 92.3% chance of observing at least 1 AE among 50 participants in Treatment Groups 3 and 4.

8.10. Data Monitoring Committee

A multidisciplinary DMC consisting of non-Gilead personnel will review the progress of the study, perform interim reviews of safety and efficacy data at a minimum at Weeks 12, 24, and 48, and provide recommendations to Gilead whether the nature, frequency, and severity of AEs associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or whether the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design. The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study. If the DMC determines that discontinuation of one or both treatment groups is warranted, it will recommend to do so.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with the sponsor or MSD, or of any proprietary interests in the study drugs. This documentation must be provided before the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last participant completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB. The investigator will not begin any study participant activities until approval from the IRB has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB any modifications made to the protocol or any accompanying material to be provided to the participant after initial institution review board approval, with the exception of those necessary to reduce immediate risk to study participants.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB-approved ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the participant or the participant's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB or local requirements).

The ICF will inform participants about laboratory testing and/or planned sample retention. CCI [redacted] The results of the tests performed on the stored biological samples will not be given to the participant or the investigator unless requested. The stored biological samples will be destroyed no later than 15 years after the end of study or per country requirements, but participants may at any time request that their stored samples be destroyed.

9.1.5. Confidentiality

The investigator must ensure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB, or the laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all participants screened and enrolled in the study, in accordance with the site procedures and regulations. Participant data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the investigational site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRFs, IRB, and governmental approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each participant:

- Participant identification
- Documentation that participant meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria])
- Documentation of the reason(s) a consented participant is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drugs, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, the US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the participant, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the EDC system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The inclusion/exclusion criteria and enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the CRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRB, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB in accordance with local requirements and receive documented IRB approval before modifications can be implemented.

9.2.2. Study Reports and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study personnel may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal and/or travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation and any participant records in order to verify the adherence to the protocol and the accuracy of the data recorded in the electronic case report form. The study monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The investigator agrees to cooperate with the study monitor to ensure that any problems detected through any type of monitoring (central, off site, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the Gilead study monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the participants, appropriate regulatory authority(ies), and IRB. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

9.3.5. Data Protection

The sponsor has developed enterprise level technical and organizational controls for the purpose of data protection. This includes user authentication and identification, fine grained access controls, end-to-end data encryption, security monitoring, network segregation, and physical security controls. Users of the sponsor's systems are provided training for security awareness and privacy.

To prepare for the possibility of a data security breach, the sponsor maintains a business continuity and disaster recovery plan and conducts regular disaster recovery testing to ensure that the sponsor's systems are recoverable if a cyber or data security incident is experienced. The sponsor's detailed incident response plan for any cyber or data security incident is based on the following 5 steps: detection, analysis, containment, eradication, and recovery. The sponsor's standard clinical trial agreements with study sites and vendors also obligate each party to comply with applicable data protection laws and to promptly notify the other in the event of a personal data breach.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404
USA

STUDY ACKNOWLEDGMENT

A Phase 2 Randomized, Open-Label, Active-Controlled Study Evaluating the Safety and Efficacy of an Oral Weekly Regimen of Islatravir in Combination with Lenacapavir in Virologically Suppressed People with HIV

GS-US-563-6041, Amendment 6, 02 December 2025

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD	*[See appended electronic signature]*
Name (Printed)	Signature

[See appended electronic signature]

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number

Appendix 2. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with participants being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to participants and sites:

    a) Participants may be unable to return to the site for a number of visits to get the study drugs, or the site may be unable to accept any participant visits. Without study drugs, the participant would not be able to continue receiving the study drugs as planned per protocol.

    Mitigation plan: Study drug supplies may be provided to the participant from the site without a clinic visit, once it is confirmed that the participant may safely continue on study drugs as determined by the principal investigator. A remote study visit, via phone or video conferencing, must be performed before remote study drug resupply. At the earliest opportunity, the site will schedule in-person participant visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drugs from sites to study participants if permitted by the local ethics committee/IRB/regulatory authority as applicable and with sponsor's approval.

    b) Shipments of study drugs could be delayed because of transportation issues. Without study drugs, the participant would not be able to continue receiving the study drugs as planned per protocol.

    Mitigation plan: The site's study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and investigational sites. Manual shipments will be triggered as necessary.

2) Participant safety monitoring and follow-up:

    a) Participants may be unable or unwilling to come to the investigational site for their scheduled study visits as required per protocol.

Mitigation plan: For participants who may be unable or unwilling to visit the investigational site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a remote study visit, via phone or video conferencing, to assess the participant within the target visit window date whenever possible. During the remote study visit, the following information at minimum will be reviewed:

i) Confirm if participant has experienced any AEs/SAEs/special situations (including pregnancy) and follow-up on any unresolved AEs/SAEs.

ii) Review the current list of concomitant medications and document any new concomitant medications.

iii) If applicable, confirm electronic diary questionnaires and PROs have been completed and transmitted.

iv) If applicable, confirm the participant's study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed, it will be provided as described above in (1).

v) If applicable, remind the participant to maintain current dosing and to keep all dispensed study drug kits for return at the next onsite visit.

b) Participants may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence, samples may not be sent for central laboratory analyses.

Mitigation plan: Local laboratories or other vendors may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular follow-up per protocol. Any changes in the party conducting laboratory assessments for the study due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

c) Participants may be unable or unwilling to attend the study visit to sign an updated ICF version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with the local ethics committee/IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local ethics committee/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

   a) Protocol deviations may occur in case scheduled visits cannot be conducted as planned per protocol.

      Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed participant visits or deviation to the protocol due to the pandemic must be reported in the electronic case report form and described in the CSR. Any remote study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

   b) Study monitors may be unable to carry out source data review or source data verification, or study drug accountability or assess protocol and GCP compliance. This may lead to delays in source data verification, an increase in protocol deviations, or under reporting of AEs.

      Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote source data verification may be arranged if allowed by local regulation and the Study Monitoring Plan. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct an off-site monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or participants on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

   a) There may be an increased amount of missing data due to participants missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

      Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (eg, modification of the SAP) and in compliance with regulatory authorities' guidance. Overall, the CSR will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of ISL, LEN, and B/F/TAF in study participants remains unchanged.

Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female-born participant is considered of childbearing potential until becoming postmenopausal unless the participant is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women < 54 years of age with amenorrhea of ≥ 12 months also may be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female participant of any age.

b. Definition of Male Fertility

For the purposes of this study, a male-born participant is considered fertile after the initiation of puberty unless the participant is permanently sterile by bilateral orchidectomy or with medical documentation.

2) Contraception Requirements for Female Participants

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Islatravir data on pregnant women are limited or not available. Data from nonclinical toxicity studies of ISL have demonstrated no adverse effect on fertility or embryo-fetal development. Available data indicate that ISL has demonstrated there is no reduction in the clinical efficacy of hormonal contraception. Please refer to the latest version of the ISL IB for additional information.

Lenacapavir data on pregnant women are not available. Data from nonclinical toxicity studies of LEN have demonstrated no adverse effect on fertility or embryo-fetal development. Available data indicate that LEN has demonstrated there is no reduction in the clinical efficacy of hormonal contraception. Please refer to the latest version of the LEN IB for additional information.

ISL/LEN CCI data on pregnant women are limited. Data from nonclinical toxicity studies of ISL have demonstrated no adverse effect on fertility or embryo-fetal development. Available data indicate that ISL has demonstrated there is no reduction in the clinical efficacy of hormonal contraception. Please refer to the latest version of the ISL/LEN CCI IB for additional information.

b. Contraception Requirements for Female Participants of Childbearing Potential

The inclusion of female participants of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at screening and a negative urine pregnancy test on the admission (Day 1) visit before randomization. In the event of a delayed menstrual period (over 1 month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is applicable also for female participants of childbearing potential with infrequent or irregular periods.

Duration of required contraception for female participants enrolled in this clinical study should start from the screening visit until 60 days following the last dose of ISL+LEN or ISL/LEN CCI

Female participants must agree to 1 of the following contraceptive methods:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below:
- Hormonal and nonhormonal intrauterine device (IUD)
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)
- Or

Female participants who initiate use of a hormonal contraceptive > 7 days after onset of menses as one of their birth control methods should use additional back-up contraception (eg, condoms) or avoid sexual intercourse for 7 days. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Subdermal contraceptive implant
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

- Barrier methods
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female participants must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

3) Contraception Requirements for Male Participants

No contraception measures are needed.

4) Unacceptable Birth Control Methods

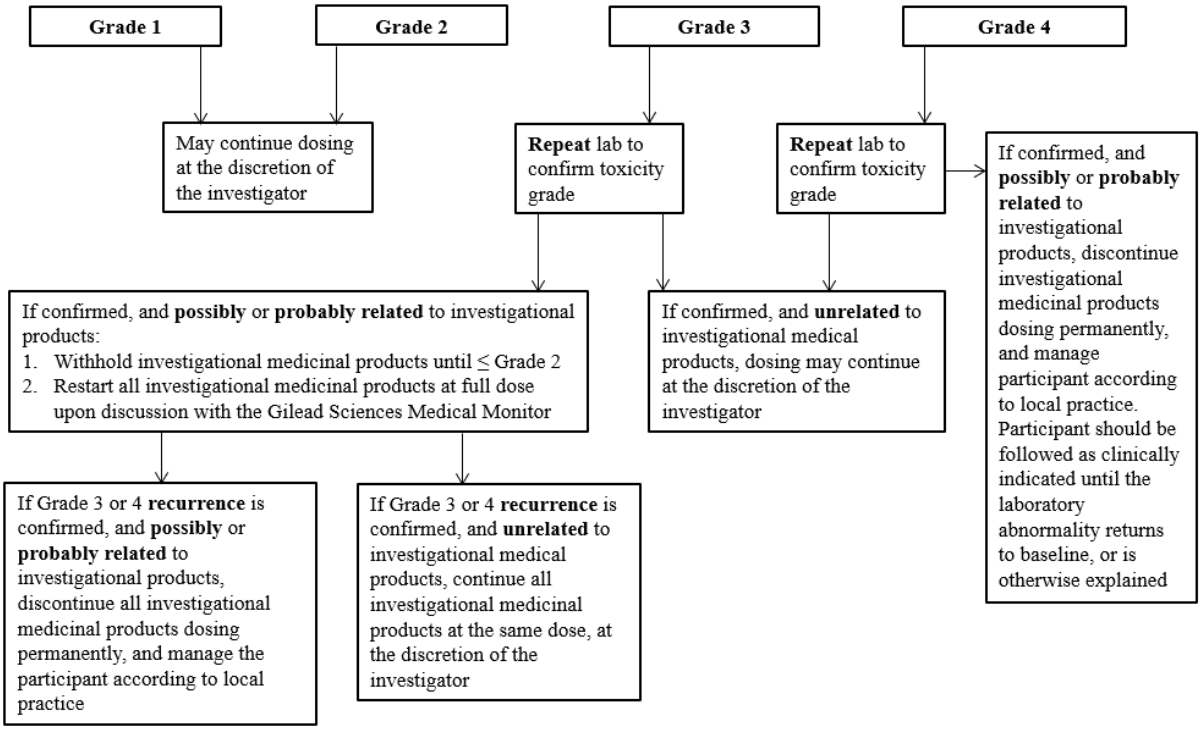
Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Female participants will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 60 days following the last dose of ISL+LEN or ISL/LEN CCI . Study drugs must be discontinued immediately.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.3.3.

Appendix 4. Management of Clinical and Laboratory Adverse Events



Appendix 5. Country-Specific Requirements

Not applicable.

Appendix 6. Amendment History

A high-level summary of this amendment history is provided in tabular form below. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

Separate summary of change documents for earlier amendments are available upon request.

A separate tracked change (red-lined) document comparing the previous version of the protocol to this amendment will be made available upon the publication of this protocol.

Appendix Table 1. Amendment 6 ( )

Rationale for Key Changes Included in Amendment 6	Affected Sections
Frequency of visits in Extension Phase changed to every 24 weeks after Week 144 to ease participant burden.	Synopsis, Study Schema, Table 2, Section 3.1
Text was added to indicate that islatravir (ISL)/lenacapavir is being developed for the treatment of HIV-1 in collaboration with Merck Sharp & Dohme LLC (MSD) and that investigators and subinvestigators will provide documentation of any financial interest or arrangements with the sponsor or MSD. Merck Sharp & Dohme LLC's name was updated to be referred to "MSD" throughout the document.	Sections 1.2, 6.3.9, and 9.1.2
Information was added relative to drug-drug interactions between lamivudine or emtricitabine and ISL-triphosphate; drug-drug interactions between deoxycytidine kinase substrates and islatravir triphosphate.	Section 5.8
Added text regarding the responsibilities of the investigator in confirming participant eligibility.	Section 6.2
New sections for Adverse Events of Special Interest were added as per new updates in the Gilead protocol template and mentioned as not applicable.	Section 7
Language regarding reporting of any sequelae from a special situation event was added for clarity.	Section 7.1.4
Clarified text related to death as a serious adverse event.	Section 7.3.3
Added section regarding data protection as per Gilead protocol template.	Section 9.3.5
Minor grammatical and typographical changes.	Throughout as needed.

Appendix Table 2. Amendment 5 (19 November 2024)

Rationale for Key Changes Included in Amendment 5	Affected Sections
Dosing instructions for ISL/LEN fixed-dose combination (CCI) 2/300 mg added in Cohort 2.	Throughout as needed
Added new section providing reference to clinical studies of coadministered ISL and LEN, as well as ISL/LEN CCI .	Section 1.4
Additional rationale language inserted to clarify the switch to ISL/LEN CCI	Section 1.6
Updated study schematic to better reflect treatment regimen of Cohort 2 transitioning from ISL+LEN to ISL/LEN CCI during Extension Phase.	Figure 1
ISL/LEN CCI dispensation row added in Study Procedure Table of Cohort 2.	Table 2

Rationale for Key Changes Included in Amendment 5	Affected Sections
Footnote x was updated and footnote y was added to Study Procedure Table of Cohort 2.	Table 2
CCI	
Section pertaining to Description and Handling of ISL/LEN CCI added.	Section 5.5
Language regarding Planned Interim Analysis was updated to include Week 48 analysis for Extension Phase (Study Week 96) instead of Week 24.	Section 8.2.1.1
Added new section for an analysis set with consideration to the addition of ISL/LEN CCI.	Section 8.3.1.3.4
Added new efficacy analysis section for All ISL+LEN analysis.	Section 8.5.3
Updated safety analysis section for the Randomized Phase analysis regarding All ISL+LEN analyses.	Section 8.6
CCI, rBA, and NNRTI added to List of Abbreviations and Definition of Terms.	List of Abbreviations and Definition of Terms
Included mention of ISL/LEN CCI where appropriate.	Throughout as needed
Added new table for ISL/LEN CCI missed dose recommendations for Cohort 2 and introduced the use of an ISL/LEN CCI CCI dose under special circumstances.	Figure 1, Table 23
Added language to clarify the process for reporting SAE information using electronic forms.	Section 7.4.1.1
Added language specific to contraception requirements for female participants administered ISL/LEN CCI.	Appendix 3

Appendix Table 3. Amendment 4 (21 February 2024)

Rationale for Key Changes Included in Amendment 4	Affected Sections
Study Procedures Table for Cohort 2 updated for accuracy to include urine pregnancy test at early study drug discontinuation (ESDD) visit, to remove time point Week 48 for B/F/TAF dispensation, and to remove HCV Ab from the screening assessments. In addition, footnotes 'j' and 'k' were updated to clarify the time points for the PP-R and PP-RC PROs.	Study Procedures for Cohort 2 (Table 2)
Clarified that participants assigned female at birth of childbearing potential must have a negative urine pregnancy test at Day 1.	Appendix 3
Language regarding the number of planned interim analyses was updated to remove the Week 12 planned interim analysis as the key summary tables including the Week 12 snapshot (secondary endpoint) are provided in the Week 12 DMC analysis (Section 8.10).	Section 8.2.1.1
Language regarding an internal Safety Assessment Committee was deleted due to a template update and is not applicable to this open-label study.	Section 7.8
Minor grammatical and typographical changes.	Throughout as needed.

Appendix Table 4. Amendment 3 (26 October 2022)

Rationale for Key Changes Included in Amendment 3	Affected Sections
An ISL dose of CCI capsules) was implemented for Cohort 2 in the Randomized Phase. • Treatment groups in Cohort 2 were changed to CCI ISL CCI) + LEN group (current Treatment Group 3; previously 1 mg ISL+LEN) or B/F/TAF group (current Treatment Group 4; previously treatment Group 5). • The 3 mg ISL+LEN dose (previously Treatment Group 3) was removed from Cohort 2.	Synopsis; Study Schema (Figure 1); Study Procedures for Cohort 2 (Table 2); Sections 3.1, 5.1.1, and 5.5
An ISL dose of CCI CCI) + LEN was implemented for participants in the Extension Phase.	Synopsis; Section 3.1; Table 21
The Cohort 2 ISL dose selection rationale was revised, including the predicted ISL exposures and predicted changes in mean lymphocytes and CD4+ T cells, based on an ISL dosage of CCI) QW.	Section 1.6
The General Information section was revised to update the location of additional information regarding changes in absolute lymphocyte and lymphocyte subset counts (ie, information is available in the IB for ISL). A cross-reference to Section 1.8 Risk/Benefit Assessment) was also added.	Section 1.2.1
The Risk/Benefit Assessment section was revised to include information related to the scope of the observed lymphocyte and lymphocyte subset decreases across the ISL program.	Section 1.8
The frequency of HBV/HCV screening was expanded into the Extension Phase to repeat every 48 weeks after the Week 48 visit of the Randomized Phase.	Study Procedures for Cohort 2 (Table 2); Section 6.3.6
HCV Ab was added to the list of HBV/HCV tests for Cohort 2.	Study Procedures for Cohort 2 (Table 2); Table 24
The description of ISL drug product and labeling were revised to accommodate the CCI) dose. The description and labeling of ISL 3 mg drug product were removed.	Synopsis; Sections 5.2.1, 5.2.2, and 5.2.3
The missed dose recommendations were revised in order to specify the number of ISL 1 mg capsules and LEN 300 mg tablets to be taken for each missed dose.	Table 22
The End of Randomized Treatment Visit was removed since the dose of ISL in the Extension Phase will be the same as in the Randomized Phase (ie, CCI	Synopsis; Study Schema (Figure 1); Study Procedures for Cohort 2 (Table 2); Section 5.5
The number of participants planned in Cohort 2 was revised from 150 (50 participants randomized in a 1:1:1 ratio to Treatment Groups 3, 4, and 5) to 100 participants in a 1:1 ratio (50 participants in Treatment Group 3 [CCI	Synopsis; Sections 4.1 and 5.1.1

Rationale for Key Changes Included in Amendment 3	Affected Sections
ISL+LEN] and 50 participants in Treatment Group 4 [B/F/TAF]).	
The study procedures/frequency section of the Synopsis for Cohort 2 was updated to clarify occurrence of onsite and telephone visits in the Randomized and Extension Phases.	Synopsis
Exclusion criterion no. 6 was revised to add active ***or occult*** HBV coinfection as exclusionary.	Section 4.3
Minor grammatical and typographical changes.	Throughout as needed.

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eSignature Approval Task Verdict: Approved (eSigned)	PPD

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