Official Protocol Title:	A Clinical Trial to Study the Effect of a Single Dose of Islatravir (MK-8591) on the Pharmacokinetics of Methadone
NCT number:	NCT04568603
Document Date:	28-Aug-2020

Title Page

THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., NJ, U.S.A. (MSD).

Protocol Title: A Clinical Trial to Study the Effect of a Single Dose of Islatravir (MK-8591) on the Pharmacokinetics of Methadone

Protocol Number: 029-00

Compound Number: MK-8591

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	128,595

Approval Date: 28 August 2020

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Original Protocol	28-AUG-2020	Not applicable

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Clinical Trial to Study the Effect of a Single Dose of Islatravir (MK-8591) on the Pharmacokinetics of Methadone

Short Title: Islatravir and Methadone Drug Drug Interaction

Acronym:

Hypotheses, Objectives, and Endpoints:

Primary Objectives	Primary Endpoints
- To determine the effect of ISL on the plasma pharmacokinetics of methadone (eg, AUC0-24 for S- and R-enantiomers of methadone) following co-administration of a single dose of methadone. Primary Hypothesis: The methadone (R-enantiomer) plasma AUC0-24 obtained after single dose co-administration of methadone with ISL is similar to the methadone (R-enantiomer) plasma AUC0-24 obtained after single dose administration of methadone alone. That is, the true GMR (methadone and ISL/methadone alone) for the dose-normalized AUC0-24 (AUC0-24/D) of methadone (R-enantiomer) is contained within (0.7, 1.43). Primary Hypothesis: The methadone (S-enantiomer) plasma AUC0-24 obtained after single dose co-administration of methadone with ISL is similar to the methadone (S-enantiomer) plasma AUC0-24 obtained after single dose administration of methadone alone. That is, the true GMR (methadone and ISL/methadone alone) for the dose-normalized AUC0-24 (AUC0-24/D) of methadone (S-enantiomer) is less than 2.0.	- Dose-normalized AUC0-24 (AUC0-24/D) of plasma methadone (R-, and S-methadone).

Secondary Objectives	Secondary Endpoints
- To determine the effect of ISL on the plasma pharmacokinetics of methadone (eg, Cmax, C24, and Tmax for the S- and R-enantiomers and AUC0-24, Cmax, C24, and Tmax for total methadone) following co-administration of methadone. Secondary Hypothesis: The methadone (R-enantiomer) plasma Cmax obtained after single dose co-administration of methadone with ISL is similar to the methadone (R-enantiomer) plasma Cmax obtained after single dose administration of methadone alone. That is, the true GMR (methadone and ISL/methadone alone) for the dose-normalized Cmax (Cmax/D) of methadone (R-enantiomer) is less than 1.43. Secondary Hypothesis: The methadone (S-enantiomer) plasma Cmax obtained after single dose co-administration of methadone with ISL is similar to the methadone (S-enantiomer) plasma Cmax obtained after single dose administration of methadone alone. That is, the true GMR (methadone and ISL/methadone alone) for the dose-normalized Cmax (Cmax/D) of methadone (S-enantiomer) is less than 2.0. Estimation: The true GMR (methadone and ISL/ methadone alone) for the dose normalized C24 (C24/D) of methadone (R-enantiomer and S-enantiomer) will be estimated. Estimation: The true GMR (methadone and ISL/methadone alone) for the dose normalized AUC0-24 (AUC0-24/D), Cmax (Cmax/D) and C24 (C24/D) of methadone (total) will be estimated.	- Dose-normalized Cmax (Cmax/D), C24 (C24/D), and Tmax of plasma methadone (R-, and S- enantiomer). - Dose-normalized AUC0-24 (AUC0-24/D), Cmax (Cmax/D), C24 (C24/D), and Tmax of plasma methadone (total).
- To evaluate the safety and tolerability of ISL co-administered with methadone.	- Adverse experiences, laboratory safety tests, ECGs, VSs (HR, BP, RR, oxygen saturation).

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
- To determine the effect of methadone on the PK of coadministered ISL	- AUC0-24, AUC0-168, AUC0-672, AUC0-inf, Cmax, Tmax, t1/2 of plasma ISL
- To explore the relationship between genetic variation and response to the treatment(s) administered and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.	- Germline genetic variation and association to clinical data collected in this study

Overall Design:

Study Phase	Phase 1
Primary Purpose	Other
Indication	Treatment of HIV infection
Population	Participants on oral methadone maintenance therapy Insert text here
Study Type	Interventional
Intervention Model	Single Group This is a single-site study.
Type of Control	Internal control
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 14 participants will be allocated/randomized.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Adminis-tration	Regimen/ Treatment Period/ Regimen	Use
Methadone Maintenance	Methadone	20 – 200 mg	QD	Oral	20 to 200 mg from Day -14 to Day -1 and Day 10 to Day 15	Back-ground Therapy
Study Intervention (Islatravir 60 mg, Individualized methadone)	ISL	30 mg	Once	Oral	2 x 30 mg capsules on Day 2	Experim ental
	Methadone	20 – 200 mg	QD	Oral	20 to 200 mg from Day 1 to Day 9	Experim ental

Abbreviations: QD=Once Daily

Other current or former name(s) or alias(es) for study intervention(s) are as follows: ISL, MK-8591, EFdA

Total Number of Intervention Groups/ Arms	1
Duration of Participation	Each participant will participate in the study for approximately 6 weeks from the time the participant signs the Informed Consent Form through the final contact.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

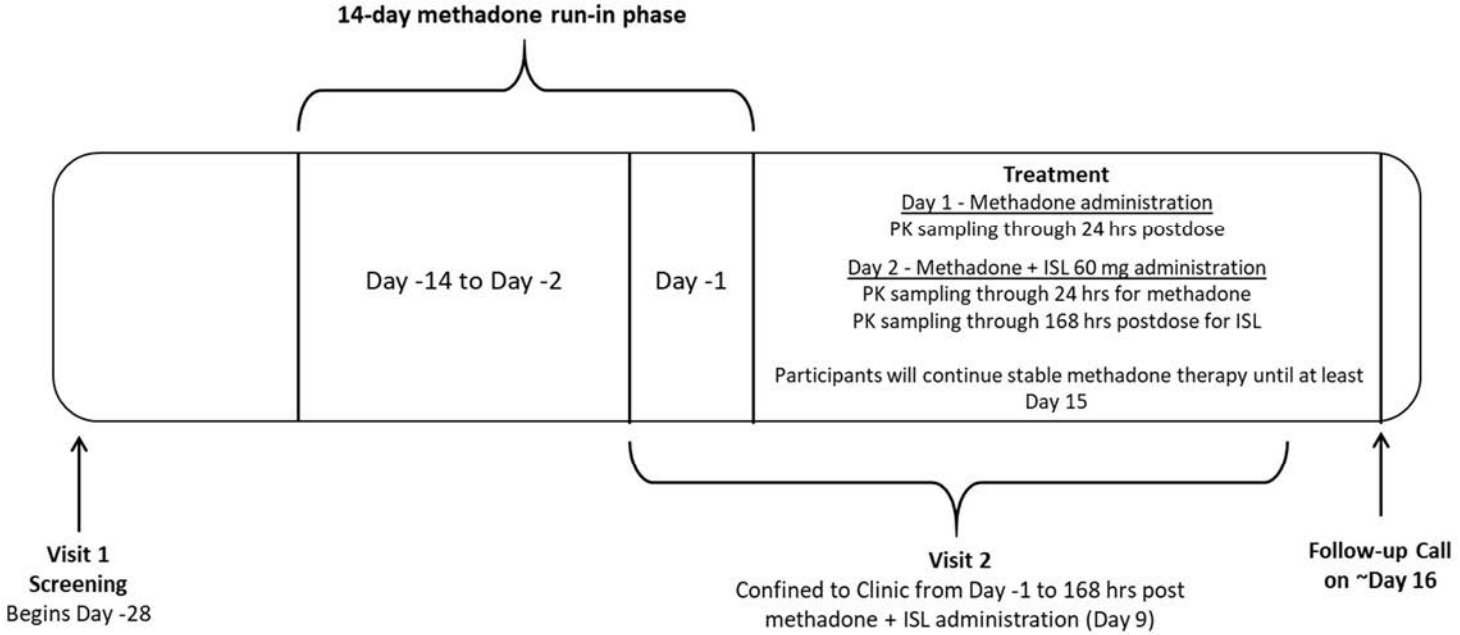
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Trial Diagram



1.3 Schedule of Activities

Screening – Day 1																
	Screening	Run-In			Intervention											Notes
Scheduled Day	Screening	Day -14 to Day -2	Day-1		Day 1											
Scheduled Hour				Pre-dose	0	0.5	1	1.5	2	3	4	6	12	16	24	
Administrative/Study Procedures																
Informed Consent	X															The informed consent form must be signed prior to any protocol procedures being performed.
Informed Consent for Future Biomedical Research	X															
Participant Identification Card	X															
Inclusion/Exclusion Criteria	X			X												Inclusion/Exclusion criteria review may begin on Day-1. Eligibility to be confirmed after completion of all predose assessments.
Medical History	X															
Prior/Concomitant Medication Review	X----------X															
Assignment of Treatment/Randomization Number				X												
Methadone Maintenance Phase		X----------X														Participants will receive their standard methadone therapy from their usual clinic during a minimum 14-day run-in phase ending on Day -1.

Screening – Day 1																
	Screening	Run-In			Intervention											Notes
Scheduled Day	Screening	Day -14 to Day -2	Day-1	Day 1												
Scheduled Hour				Pre-dose	0	0.5	1	1.5	2	3	4	6	12	16	24	
Methadone Administration					X											Participants will receive a maintenance dose of methadone with approximately 240 mL of water after an overnight fast of at least 8 hours. Participants will continue to fast for 4 hours postdose.
Standard Meals			X								X----------X					A meal will be served on the evening of Day -1 and consumed at least 8 hrs before dosing. Standard meals will be served per site processes beginning ~4 hrs post-dose until 8 hrs prior to Day 2 dosing.
Domiciling			X----------X													Participants will check-in on Day -1.
Safety Procedures																
Full physical examination	X															
Height	X															
Weight	X															Note: BMI to be calculated only at screening

Screening – Day 1																
	Screening	Run-In			Intervention											Notes
Scheduled Day	Screening	Day -14 to Day -2	Day-1	Day 1												
Scheduled Hour				Pre-dose	0	0.5	1	1.5	2	3	4	6	12	16	24	
Vital Signs (heart rate, blood pressure, respiratory rate, oxygen saturation)	X			X			X					X				Participants should be resting in a semi-recumbent position for at least 10 mins prior to measurement. Respiratory rate and oxygen saturation will be measured as per SOPs. Predose VS should be measured within 3 hours of methadone dosing.
Vital Signs (temperature)	X			X												Predose VS should be measured within 3 hours of methadone dosing.
12-lead ECG	X			X			X				X					Participants should be resting in a semi-recumbent position for at least 10 mins prior to measurement. Screening and pre-dose ECGs should be performed in triplicate, 1 to 2 minutes apart. Predose ECGs should be measured within 3 hours of methadone dosing.
Serum hCG	X		X													Performed for women of childbearing potential.
Serum FSH	X															Performed for postmenopausal women.
Hepatitis B and C screen (per site SOP)	X															

Screening – Day 1															
	Screening	Run-In			Intervention										Notes
Scheduled Day	Screening	Day -14 to Day -2	Day-1	Day 1											
Scheduled Hour				Pre-dose	0	0.5	1	1.5	2	3	4	6	12	16	24	
HIV antigen/antibody screen	X															Participants must have negative HIV antigen/antibody test at screening.
STI Urine screen	X															Includes testing for gonorrhea, chlamydia, and trichomoniasis at minimum.
Syphilis serologic screening	X															
UDS (per site SOP)	X		X													Screening and Day-1 UDS is mandatory, any additional UDS are conducted per site SOP.
Hematology, Urinalysis, Chemistry	X		X													Collected after at least an 8 hour fast at screening and predose.
AE/SAE review	X----------X															

Screening – Day 1																
	Screening	Run-In			Intervention											Notes
Scheduled Day	Screening	Day -14 to Day -2	Day-1	Day 1												
Scheduled Hour				Pre-dose	0	0.5	1	1.5	2	3	4	6	12	16	24	
Clinical Opiate Withdrawal Scale	X			X												To be administered at screening and within 1 hr predose to establish a baseline. May be administered if clinically indicated at other timepoints. Each participant should be assessed by the same clinic personnel throughout the study, if possible. Not all participants need to be assessed by the same individual.
Pharmacokinetics																
Blood for Methadone PK				X		X	X	X	X	X	X	X	X	X	X	24 hr sample to be collected just prior to Day 2 methadone administration.
Biomarkers																
Blood for Genetic Analysis				X												Collect at any time up to 24hrs post-dose on Day 1 in enrolled participants only. See Section 8.8.

Day 2 – Post-study																			
	Intervention																	Follow-Up Call	Notes
Scheduled Day	Day 2											Day 3	Day 4	Day 5	Day 6	Day 9	Day 10 to Day 15	Day 16[a]	
Scheduled Hour	0	0.25	0.5	1	1.5	2	3	4	6	12	16	24	48	72	96	168			
Administrative/Study Procedures																			
Prior/Concomitant Medication Review	X----------X																		
Methadone Maintenance Therapy																	X		After the follow-up call on ~Day 16, methadone maintenance therapy will continue as per the participant's standard schedule.
Methadone Administration	X											X	X----------X						On Day 2, participants will receive a maintenance dose of methadone after an overnight fast of at least 8 hours with ~240 mL of water.[b] Participants will continue to fast for 4 hours postdose. From Day 3 (ie, Day 2, 24 hrs) to Day 9 (ie, Day 2, 168hrs), participants will receive methadone once daily at the clinic.
Islatravir Administration	X																		On Day 2, participants will receive a dose of ISL within 5 minutes of the methadone dose with ~240 mL of water.[b]

Day 2 – Post-study																			
	Intervention																	Follow-Up Call	Notes
Scheduled Day	Day 2											Day 3	Day 4	Day 5	Day 6	Day 9	Day 10 to Day 15	Day 16[a]	
Scheduled Hour	0	0.25	0.5	1	1.5	2	3	4	6	12	16	24	48	72	96	168			
Standard Meals								X----------								----------X			Standard meals will be served per site processes beginning approximately 4 hrs post-dose until discharge from the clinic on Day 9.
Domiciling	X----------															----------X			
Safety Procedures																			
Full physical examination																X			
Weight																X			
Vital Signs (heart rate, respiratory rate, oxygen saturation)	X			X					X			X				X			Participants should be resting in a semi-recumbent position for at least 10 mins prior to measurement. Respiratory rate and oxygen saturation will be measured as per site standard operating procedures. Predose VS on Day 2 should be measured within 3 hours of methadone dosing.
Vital Signs (temperature)																X			

Day 2 – Post-study																			
	Intervention																	Follow-Up Call	Notes
Scheduled Day	Day 2											Day 3	Day 4	Day 5	Day 6	Day 9	Day 10 to Day 15	Day 16[a]	
Scheduled Hour	0	0.25	0.5	1	1.5	2	3	4	6	12	16	24	48	72	96	168			
12-lead ECG	X			X				X				X				X			Participants should be resting in a semi-recumbent position for at least 10 mins prior to measurement. Predose ECGs should be performed in triplicate, 1 to 2 minutes apart. Predose ECGs on Day 2 should be measured within 3 hours of methadone dosing.
Serum hCG																X			Performed in women of child-bearing potential.
Hematology, Urinalysis, Chemistry												X				X			Collected after at least an 8 hour fast. Collected prior to methadone dosing.
AE/SAE review	X----------X																		
Pharmacokinetics																			
Blood for Plasma ISL	X	X	X	X		X			X	X	X	X	X	X	X	X			0 h sample to be collected just prior to ISL administration.
Blood for Methadone			X	X	X	X	X	X	X	X	X	X							

[a] Follow-up call will occur 14 days (+3 days) after the ISL dose.

[b] A total of 240 mL of water will be taken with the methadone AND ISL dose. Additional water may be provided in 50 mL increments as needed.

2 INTRODUCTION

Islatravir (MK-8591, ISL) is a novel, potent NRTTI being developed both for treatment of HIV-1 infection and for prevention of HIV-1 infection in uninfected individuals at high risk of becoming infected. Currently, ISL is being evaluated in a Phase 2 trial at a dose of 0.75 mg QD (in combination with 100 mg doravirine, DOR; NCT03272347) and in a Phase 2 trial at doses of 60 mg and 120 mg QM (NCT04003103). Additional programs with other doses and administration frequencies within the range of 0.75-120 mg are being considered as well.

2.1 Study Rationale

According to the CDC, HIV infections due to IDU have declined, but injecting drugs remains a significant risk factor in becoming infected with HIV. In 2018, 7% (2,652) of the estimated 37,881 new HIV infections in the United States were attributed to IDU[Centers for Disease Control and Prevention 2020]. Many PWID seek treatment for opioid addiction and receive maintenance therapy with the opioid agonist methadone for substance dependence. Consequently, individuals on MMT may benefit from ISL either for treatment of existing HIV infection or prophylactically to prevent new infection. Success of MMT is sensitive to many factors and complicated by inter-subject variability in both methadone PK and PD. Titration of methadone dosing is necessary to balance the reduction of craving for opiates, the medical necessity of avoiding opiate withdrawal, and the effects associated with methadone toxicity.

Methadone has been shown to be metabolized by multiple members of the cytochrome P450 family including CYP3A4, 2B6, 2C19, 2D6, 2C9 and 2C8, with CYP3A4 usually cited as the most active member when using human microsomes in vitro[Volpe, D. A., et al 2018][Eap, C. B., et al 2002]. Interactions between HIV antiretrovirals and methadone have been widely reported, with methadone being affected by both induction and inhibition of metabolic enzymes by antiretrovirals. Generally, the interactions found to be clinically meaningful were due to decreases in methadone exposure[Volpe, D. A., et al 2018][Eap, C. B., et al 2002]. ISL is not anticipated to be a perpetrator of meaningful drug interactions. ISL is not an inhibitor of major CYP enzymes (eg, CYP2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) or inducer of CYP2B6 or CYP3A4.

There are reports of methadone affecting the pharmacokinetics of coadministered HIV antiretrovirals. Methadone decreases exposure of didanosine and stavudine (older HIV antiretrovirals), possibly due to delayed gastric emptying[Rainey, P. M., et al 2000]. In addition, there are reports of increased zidovudine exposure mediated through inhibition of glucuronidation or altered renal clearance[McCance-Katz, E. F., et al 1998][Schwartz, E. L., et al 1992][Volpe, D. A., et al 2018]. Methadone is also an inhibitor of P-glycoprotein (P-gp). ISL is highly soluble and rapidly absorbed, is not metabolized via glucuronidation and is not a substrate of P-gp. Therefore, it is unlikely that methadone will affect the PK of ISL.

The concomitant use of ART to treat or prevent HIV-1 with MMT may interfere with the efficacy/safety of ART and/or with the ability to maintain stable methadone concentrations leading to symptoms of either opiate intoxication or withdrawal with serious or even life-threatening consequences. While no interaction is expected, given the importance of ensuring

appropriate exposures of both ISL and methadone, this study will evaluate the effect of ISL administration on methadone PK. Additionally, ISL PK in the presence of methadone will be evaluated.

2.2 Background

Refer to the IB/approved labeling for detailed background information on islatravir (ISL or MK-8591).

HIV-1 infection remains a global health challenge, with 38 million people living with HIV/AIDS worldwide and nearly 2 million people becoming newly infected[Joint United Nations Programme on HIV/AIDS 2020]. The use of ever-improving highly effective ART has reformed the natural history of HIV infection, such that HIV infection has become a chronic illness, provided patients remain adherent in taking ART therapy. Furthermore, use of ART as pre-exposure prophylaxis to prevent new HIV infection (eg, PrEP) has been shown to reduce sexual transmission by up to 99% and transmission in intravenous drug users by up to 74%[Centers for Disease Control and Prevention 2020]. Islatravir is an NRTTI in development as a part of a complete ART regimen for the treatment of HIV-1 or as a stand-alone therapy for the prevention of new HIV-1 infection. Islatravir is differentiated from other ARTs because of its high potency, long half-life, favorable drug resistance profile and broad pharmacological distribution. Because of these properties, not only does ISL have the potential to be an effective treatment and prevention therapy, ISL is also well-suited to be delivered in less frequent dosing regimens.

Understanding the effect of DDIs with ISL and medications used to manage common comorbidities is an important aspect of clinical development of the compound. One such medication which will be evaluated in this study is methadone, an opioid agonist indicated for treatment of moderate to severe pain and/or opioid addiction.

2.2.1 Pharmaceutical and Therapeutic Background

Islatravir is a highly potent HIV-1 NRTTI. Unlike conventional NRTIs, ISL acts via multiple mechanisms, leading to both immediate and delayed chain termination. The inactive parent is phosphorylated to the active ISL-TP in PBMCs and other cells. In in vitro studies in PBMCs, ISL-TP demonstrated antiviral activity, with an IC_{50} of 0.21 nM, while other NRTIs demonstrated IC_{50}s ranging from 10.1 to 144 nM. ISL demonstrates a favorable mutant selection profile compared to other NRTIs, selecting only for the M184V/I mutant, against which ISL is active but with a decrease in sensitivity of 7.3-to 9.5-fold.

ISL is not anticipated to be a victim or a perpetrator of meaningful drug interactions. Elimination of ISL is anticipated to be balanced between renal excretion and ADA-mediated metabolism. Metabolism via ADA is a non-CYP mediated pathway. ISL is not a substrate of P-gp. ISL is not an inhibitor of major drug transporters, inhibitor of CYP enzymes (eg, CYP2B6, 2C8, 2C9, 2C19, 2D6, and 3A4), inducer of CYP2B6 or CYP3A4, or an inhibitor of UGT1A1.

2.2.2 Clinical Studies

Across Phase 1 studies, as of 30-Jun-2020, 218 adult participants (including 30 participants with HIV-1 infection) received an ISL single dose (up to 400 mg orally) or multiple doses (up to 100 mg QW for 3 weeks and up to 5 mg QD for 6 weeks orally). In the Phase 1 studies, single and multiple doses of ISL have been generally well tolerated, with no drug-related SAEs and no discontinuations due to a drug-related AE. For all Phase 1 studies with oral administration, the most frequently reported drug-related AE (≥2% of participants in any protocol) was headache.

Following oral administration, plasma PK data indicate that ISL was rapidly absorbed with a median Tmax of 0.5 hr, and an apparent terminal t½ of 47 to 64 hr after single doses. Intracellular ISL-TP levels reached C_{max} between 6 to 24 hr and declined with an apparent terminal t½ of 79 to 214 hr. Over the entire Phase 1 clinical program, ISL plasma exposure and ISL-TP levels appeared to increase in an approximately dose-proportional manner between ISL doses of 0.25 and 400 mg. Following administration of 30 mg ISL with a high-fat meal, PK of ISL and ISL-TP in PBMCs were largely unaffected. Examinations of DDIs between ISL and DTG/TDF, ISL and LNG/EE, ISL and DOR, and ISL and pantoprazole demonstrated no clinically meaningful interactions.

After ISL administration to treatment-naïve participants with HIV-1 infection at doses of 0.5 mg, 1 mg, 2 mg, 10 mg, and 30 mg, viral load reduction data show greater than 1.0 log drop on average at all doses tested. Pharmacokinetic data in participants infected with HIV-1 generally were consistent with the data in healthy participants.

2.2.3 Ongoing Clinical Studies

There are ten ongoing studies of oral ISL, including 4 Phase 1 trials, 2 Phase 2 trials and 4 Phase 3 trials. To date, the ISL remains generally well tolerated.

Protocol 011 (NCT03272347) is an ongoing Phase 2 trial in treatment-naive persons living with HIV-1, examining efficacy of daily ISL (0.25 mg, 0.75 mg, or 2.25 mg) in combination with DOR. As of 31-Mar-2020, ISL has been administered to ~90 HIV-1 positive individuals for at least 96 weeks. Protocol 016 (P016) is a double-blind, placebo-controlled Phase 2 PrEP trial (NCT04003103), examining doses of 60 mg and 120 mg. As of 30-June-2020, 156 of a planned 250 participants (62%) have been randomized and 78 participants have received all 6 planned once-monthly doses of study drug and 53 have received between 3-5 doses; the remaining 25 participants have received fewer than 3 doses.

The 4 Phase 3 trials initiated in early 2020; information on general tolerability is limited.

2.2.4 Information on Other Study-related Therapy

Methadone is an opioid agonist indicated for the management of pain for which alternative treatment options are inadequate and for the detoxification treatment of opioid addiction. Together with appropriate social and medical services, methadone is also used as MMT for the treatment of opioid addiction [U.S. Prescribing Information 2019].

Methadone is a synthetic narcotic analgesic that acts as an opioid μ-receptor agonist with multiple actions quantitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle [U.S. Prescribing Information 2019]. Methadone is supplied and administered clinically as a racemate of R- and S- enantiomers, though the R- enantiomer accounts for the majority of its pharmacological activity. Due to high intersubject variability both in PK and pharmacological response, methadone dose must be individually titrated[Volpe, D. A., et al 2018][Eap, C. B., et al 2002].

Following oral administration, the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 to 7.5 hours. While dose proportionality of methadone PK has not been definitively established, after administration of daily oral doses ranging from 10 to 225 mg, the steady-state plasma concentrations ranged from 65 to 630 ng/mL and the peak concentrations ranged between 124 to 1255 ng/mL. These data suggest that generally, PK of methadone increases dose proportionally [U.S. Prescribing Information 2019]. Published reports indicate that after multiple dose administration the apparent plasma clearance of methadone ranged between 1.4 and 126 L/h, and the terminal half-life was highly variable and ranged between 8 to 59 hours in different studies [U.S. Prescribing Information 2019].

2.3 Benefit/Risk Assessment

Participants in clinical studies will not receive direct benefit from treatment during participation as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

The data generated will be used to support coadministration of ISL and methadone. Patients taking methadone have a high rate of HIV-infection or are at elevated risk for acquiring new HIV infection. Therefore, ISL may be an important therapy for HIV treatment or prevention in this population.

Additional details regarding specific benefits and risks for participants taking part in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

The study population includes male and female participants from 18 years to 65 years of age, inclusive.

Objectives	Endpoints
Primary	
• To determine the effect of ISL on the plasma pharmacokinetics of methadone (eg, AUC0-24 for R- and S-enantiomers of methadone) following co-administration of a single dose of methadone. Primary Hypothesis: The methadone (R-enantiomer) plasma AUC0-24 obtained after single dose co-administration of methadone with ISL is similar to the methadone (R-enantiomer) plasma AUC0-24 obtained after single dose administration of methadone alone. That is, the true GMR (methadone and ISL/methadone alone) for the dose-normalized AUC0-24 (AUC0-24/D) of methadone (R-enantiomer) is contained within (0.7, 1.43). Primary Hypothesis: The methadone (S-enantiomer) plasma AUC0-24 obtained after single dose co-administration of methadone with ISL is similar to the methadone (S-enantiomer) plasma AUC0-24 obtained after single dose administration of methadone alone. That is, the true GMR (methadone and ISL/methadone alone) for the dose-normalized AUC0-24 (AUC0-24/D) of methadone (S-enantiomer) is less than 2.0.	• Dose-normalized AUC0-24 (AUC0-24/D) of plasma methadone (R- and S-methadone).

Objectives	Endpoints
Secondary	
• To determine the effect of ISL on the plasma pharmacokinetics of methadone (eg, Cmax, C24, and Tmax for the R- and S-enantiomers and AUC0-24, Cmax, C24, and Tmax for total methadone) following co-administration of methadone. Secondary Hypothesis: The methadone (R-enantiomer) plasma Cmax obtained after single dose co-administration of methadone with ISL is similar to the methadone (R-enantiomer) plasma Cmax obtained after single dose administration of methadone alone. That is, the true GMR (methadone and ISL/methadone alone) for the dose-normalized Cmax (Cmax/D) of methadone (R-enantiomer) is less than 1.43. Secondary Hypothesis: The methadone (S-enantiomer) plasma Cmax obtained after single dose co-administration of methadone with ISL is similar to the methadone (S-enantiomer) plasma Cmax obtained after single dose administration of methadone alone. That is, the true GMR (methadone and ISL/methadone alone) for the dose-normalized Cmax (Cmax/D) of methadone (S-enantiomer) is less than 2.0. Estimation: The true GMR (methadone and ISL/ methadone alone) for the dose normalized C24 (C24/D) of methadone (R-enantiomer and S-enantiomer) will be estimated. Estimation: The true GMR (methadone and ISL/methadone alone) for the dose normalized AUC0-24 (AUC0-24/D), Cmax (Cmax/D) and C24 (C24/D) of methadone (total) will be estimated.	• Dose-normalized Cmax (Cmax/D), C24 (C24/D), and Tmax of plasma methadone (R- and S- enantiomer). • Dose-normalized AUC0-24 (AUC0-24/D), Cmax (Cmax/D), C24 (C24/D), and Tmax of plasma methadone (total).

Objectives	Endpoints
• To evaluate the safety and tolerability of ISL co-administered with methadone.	• Adverse experiences, laboratory safety tests, ECGs, VSs (HR, BP, RR, oxygen saturation).
Tertiary/Exploratory	
• To determine the effect of methadone on the PK of coadministered ISL.	• AUC0-24, AUC0-168, AUC0-672, AUC0-inf, Cmax, Tmax, t1/2 of plasma ISL
• To explore the relationship between genetic variation and response to the treatment(s) administered and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.	• Germline genetic variation and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is a nonrandomized, single-site, open-label study of ISL in adult male and female participants on stable methadone therapy.

Participants will receive their standard methadone therapy from their usual clinic during a minimum 14-day run-in phase. Dosing at the CRU will commence on Day 1, continuing on the same formulation and dose of methadone as from the run-in phase. On Day 1 and 2, participants will receive their usual dose of methadone in the morning following an at least 8 hr fast. Serial blood samples for methadone PK will be collected through 24 hours post dose. On Day 2, participants will also receive a single dose of ISL 60 mg concomitantly with their usual dose of methadone. Blood samples for methadone PK will be collected through 24 hours post dose and for ISL PK through 168hrs post dose. Participants will remain domiciled in the CRU through 168 hrs post ISL dose. While domiciled, the site staff will administer participants their individualized methadone dose daily. After discharge from the CRU, participants will continue their standard MMT at their usual clinic. A follow-up call will be conducted at 14 days post ISL dose to assess for AEs.

Safety and tolerability will be evaluated until the follow-up call. Opioid withdrawal symptoms will also be assessed prior to and following treatment with ISL and methadone.

Approximately 14 participants will be enrolled.

Because this is a Phase 1 assessment of ISL in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

This study will evaluate the potential drug-drug interaction between methadone and ISL. The study design was chosen to optimally assess the objectives of the study.

A fixed-sequence design was selected for operational efficiency given the half-life of plasma ISL and intracellular ISL-TP.

Population: Steady state methadone disposition cannot be evaluated safely in participants not on methadone for the duration specified in this trial without a substantial risk of causing methadone addiction. Participants without HIV infection will be enrolled to avoid interactions between ISL and other ART or to avoid exposing HIV infected individuals not on ART to HIV monotherapy. Participants will be screened for illicit drug use (except cannabis) and STIs as use of injection drugs and presence of STIs may indicate increased risk of contracting HIV during the study[Centers for Disease Control and Prevention 2020][Centers for Disease Control and Prevention 2015].

Run-in Period: Methadone dose must be individually titrated and periodically adjusted to maintain optimal therapeutic effect. In addition, methadone has the potential to be both an inducer and autoinducer. To ensure that evaluation of a DDI on Day 1 and 2 in this study is done at steady-state concentrations of methadone and at steady-state levels of metabolic enzymes, a 14-day run-in period at a stable methadone dose will proceed the active treatment period in this study.

Doses: Methadone doses are individually titrated. Participants will remain on their stable methadone dose. A wide range of doses will be evaluated in this study (20 to 200 mg). Lower doses may not be clinically relevant, while increases in QTc prolongation were observed at doses >200 mg [U.S. Prescribing Information 2019].

A dose of 60 mg ISL has been selected to be administered as a one-time oral dose in this trial. This dose of ISL is the anticipated highest clinical dose being considered for development, and ISL has demonstrated dose-proportional PK over the entire range studied to date (0.25 mg – 400 mg). While no drug interaction between ISL and methadone is anticipated, it is desirable to test this hypothesis at the upper end of the clinically relevant dose range as a lack of effect at this dose could be extrapolated to lower doses. As plasma accumulation of ISL is low and no induction or time dependent inhibitory effect is

anticipated, a single dose paradigm is considered adequate to assess the DDI with methadone.

Food: The effect of food on the bioavailability of methadone has not been evaluated [U.S. Prescribing Information 2019]. There is no clinically relevant effect of food on ISL pharmacokinetics. However, dosing on Days 1 & 2 will be conducted under fasting conditions to decrease variability and because historical comparator data for ISL PK were also obtained under fasted conditions. Participants will be domiciled in the clinic from the night prior to dosing which will ensure that the protocol-specified overnight fast is completed.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

There are no efficacy endpoints.

4.2.1.2 Safety Endpoints

Participants will be observed at the clinical trial site where they are housed. Symptoms of CNS or respiratory depression that would be associated with enhanced effects of opiates will be observed by staff trained in the management of opiate overdose and/or critical care. Respiratory rate and oxygen saturation via pulse oximetry will be measured at select timepoints including near Tmax. A baseline COWS assessment will be done at screening and prior to dosing on Day 1; in the event that overt signs of opiate withdrawal are observed during the study, additional COWS assessments may be conducted as clinically indicated [Wesson, D. R. 2003].

In addition, safety laboratory evaluations (hematology and chemistry), ECGs and vital signs will be conducted to monitor subject safety throughout the study. Particular attention will be paid to the QTc interval of participants as methadone is known to cause QTc prolongation. No effects of ISL on QTc is predicted based on the electrophysiologic studies of ISL in vitro and in vivo animal models or clinical trials.

4.2.1.3 Pharmacokinetic Endpoints

To characterize the pharmacokinetics of methadone (R- and S-enantiomers and total) and determine if there is a clinically meaningful change in methadone pharmacokinetics when co-administered with ISL, AUC0-24, Cmax, C24 and Tmax will be evaluated on Day 1 (without ISL administration) and on Day 2 (following co-administration with ISL). AUC0-24 will be evaluated since the PK evaluations are under steady-state conditions.

Methadone is supplied and administered clinically as a racemic mixture, although only one enantiomer (R-) accounts for the majority of its pharmacological activity. Therefore, lower clinical significance bounds are set around PK of the R-enantiomer. The level to which methadone concentrations may safely change in any given patient is complicated by high interindividual variability in both PK and PD. Literature surveys have shown that mean

reductions in methadone exposure on the order of ~30% to ~50% are associated with withdrawal symptoms in at least some individuals (eg, due to interaction with efavirenz or nevirapine). Therefore, the lower bound in this study for the R-enantiomer is being set at 0.7.

While methadone intoxication/toxicity related to on-target pharmacological activity has been less widely reported with inhibition, increases in drug levels are associated with QT prolongation. An increase of 47% of the R-enantiomer and 103% of the S-enantiomer in the presence of voriconazole are accompanied by cautionary QT label language [U.S. Prescribing Information 2019][Maremmani, I., et al 2005][Eap, C. B., et al 2002]. Based on this, the upper bound of clinical significance for AUC is set symmetrically at 1.43 for R-methadone and an upper bound of 2.0 is set for S-methadone. Upper bounds of 1.43 for R-methadone Cmax and 2.0 for S-methadone Cmax will be tested as a secondary hypothesis.

As participants will remain on their stable dose of methadone during the study, each participant may be taking a different dose of methadone. As such, dose normalized PK will be reported. Within participant comparisons are not impacted by dose as individuals will be on a stable dose.

For ISL, AUC0-24, AUC0-168, AUC0-672, AUC0-inf, Cmax, and Tmax will be evaluated. Both AUC0-672 and AUC0-inf will be estimated by extrapolation of the terminal phase of the measured profile. Efficacy is most closely associated with intracellular ISL-TP concentrations at trough (C168). Because ISL-TP has been shown to correlate closely with plasma ISL AUC which can be more readily measured, plasma ISL AUC is being assessed as a surrogate associated with efficacy. It is also considered the most relevant parameter for toxicity. Given the range of dosing frequencies being evaluated in ISL development, AUC0-24 (daily), AUC0-168 (weekly), and AUC0-672 (monthly) will all be estimated. It is not possible to remove MMT patients from their established dosing regimen without substantial risk of inducing withdrawal symptoms and their attendant psychological sequelae. As a consequence, it is not possible to include an ISL alone treatment period for comparison to the methadone + ISL coadministration. Therefore, ISL plasma PK will be evaluated in this study with methadone coadministration and compared in an exploratory way to historical ISL PK data.

4.2.1.4 Pharmacodynamic Endpoints

No pharmacodynamic endpoints will be evaluated.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

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

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

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

4.2.1.6 Future Biomedical Research

The Sponsor will conduct FBR on DNA specimens for which consent was provided during this clinical study.

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

4.3 Justification for Dose

The rationale for dose is detailed in Section 4.2.

As this is a Phase 1 assessment of ISL in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the

study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Males and females meeting the criteria outlined below will be enrolled.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Has a BMI > 18 and ≤ 35 kg/m2. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI=weight (kg)/height $(m)^2$.

2. Is in good health based on laboratory safety tests obtained at the screening visit and prior to administration of study drug. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out of range laboratory values.

   Note: participants infected with Hepatitis C or Hepatitis B may be included if Screening and Baseline ALT is <2-fold the upper limit of normal and direct bilirubin is <2-fold the upper limit of normal. Participants slightly exceeding these limits may be retested and enrolled upon consultation with Sponsor.

3. Is in good health based on medical history, physical examination, VS measurements and ECGs performed prior to randomization. Appendix 9 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria.

4. Has a negative HIV antigen/antibody test at screening.

Demographics

5. Is male or female, from 18 years to 65 years of age, inclusive, at the time of signing the informed consent.

Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP

  OR

- Is a WOCBP and using an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix [5] during the intervention period and for at least 21 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (serum) as required by local regulations within 24 hours before the first dose of study intervention.

- Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

6. The participant provides written informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the main study without participating in FBR.

Additional Categories

7. Is reliably participating in a methadone maintenance program for at least two (2) months prior to Day 1. Subjects are required to be on a documented stable dose of methadone for at least 14 days prior to Day 1.

8. Agrees to not change their current maintenance methadone dose of 20-200 mg administered as a single daily dose (unless for safety reasons) from screening until

collection of the last PK sample. Subjects must agree to have their daily methadone dose administration observed and documented during the period of the study during which they are domiciled.

9. Agrees to take the following precautions to reduce the risk of acquiring HIV infection from the time of signing the informed consent until 3 months after the last dose of study medication:

    a. Use a male or female condom (but not both together) during all occurrences of penetrative vaginal or anal intercourse.

    b. Avoid coming into contact with another individual's blood (eg, by sharing a hypodermic needle).

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.

   Exception: Subjects infected with hepatitis B or hepatitis C virus may participate if they meet Inclusion Criteria 2 and 3.

2. Is mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.

3. Has a history of cancer (malignancy).

   Exceptions: (1) Adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies which have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (eg, malignancies which have been successfully treated ≥10 years prior to the prestudy [screening] visit).

4. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or non-prescription drugs or food.

5. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the screening visit.

6. Tests positive for a sexually transmitted infection at screening. Participants with a past history of syphilis may be enrolled if, in the opinion of the investigator, clinical evidence do not indicate presence of a new infection.

Prior/Concomitant Therapy

7. With the exception of methadone, is unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to the first dose of the 14 day methadone maintenance run-in phase prior to Day 1, throughout the trial, until the AE follow-up call (Day 16). Upon discussion with the Sponsor, concomitant use of benzodiazepines may be permitted during the study provided that the subject has been receiving a stable benzodiazepine dose prescribed by a physician for at least 2 months prior to administration of the first dose of study drug in this trial. In addition, there may be certain prescription and non-prescription drugs that are permitted, see Section 6.5.

Prior/Concurrent Clinical Study Experience

8. Has participated in another investigational study within 4 weeks (or 5 half-lives) prior to the prestudy (screening) visit. The window will be derived from the date of the last visit in the previous study.

Diagnostic Assessments

9. Has a QTc interval >450 msec (males) or >470 msec (females), has a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome), has uncorrected hypokalemia or hypomagnesemia, is taking concomitant medications that prolong the QT/QTc interval other than methadone.

Other Exclusions

10. Is under the age of legal consent.

11. Does not limit smoking to no more than 10 cigarettes per day while in the CRU. No smoking will be permitted from 2 hours predose to 2 hours postdose on Days 1 and 2. In addition, participant must agree to follow the smoking restrictions defined by the CRU.

12. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator. Participants must have a negative alcohol breath test at check-in.

13. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.

14. With the exception of THC, has a positive screen for drugs with a high potential for abuse such as cocaine, amphetamines, MDMA, barbiturates, benzodiazepines (with the exception noted in exclusion criteria 7), or opiates/opioids on Day -1 that cannot be explained by concomitant medications, unless at the discretion of the principal investigator and the sponsor.

    Subjects must have a negative UDS prior to randomization, with the exception of THC and prescription benzodiazepines.

15. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

16. Has a COWS score of ≥ 5 at screening or prior to randomization.

17. Is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).

18. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Fasting requirements for study procedures, such as but not limited to laboratory safety evaluations are specified in Appendix 2.

On full pharmacokinetic sampling days, ie, Days 1 and 2, participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration until the first scheduled meal at approximately 4 hours postdose. Otherwise, meals and snack(s) will be provided by the investigator per site standards during domiciling in the clinic. Participants will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals will be the same on Day 1 and Day 2. After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

Water will be provided during study drug administration. With the exception of water provided with treatments, water will be restricted 1 hour prior to and 1 hour after study drug administration on Days 1 and 2.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks prior to administration of the first dose of the 14day methadone maintenance run-in phase prior to Day 1 until discharge from the clinic on Day 9.

On full pharmacokinetic sampling days, ie, Days 1 and 2, participants will refrain from the consumption of all fruits and fruit juices 24 hours prior to and 4 hours following trial drug administration. On all other days during the study, consumption of fruits and fruit juices (except for grapefruit, grapefruit juices, and grapefruit products) is allowed.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours prior to the prestudy visit until after the visit, from 12 hours prior to and after study drug administration on Days 1 and 2, and from 12 hours prior to the Day 9 (ie, 168hr post ISL dose) procedures. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day (1 unit = 120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours prior to the prestudy visit until after the visit, and from 24 hrs prior to Day -1 until the completion of Day 9 (ie, 168hr post ISL dose) procedures. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.2.3 Tobacco Restrictions

Smoking will be limited to no more than 10 cigarettes per day while in the CRU. No smoking will be permitted from 2 hours predose to 2 hours post dose on Days 1 and 2. In addition, participants will follow the smoking restrictions defined by the CRU.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weightlifting, running, bicycling, etc.) from the prestudy (screening) visit until discharge from the clinic on Day 9.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information may be included, as outlined in the eCRF entry guidelines. Minimal information may include

demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant withdraws from the study a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number. The study site should contact the Sponsor for the replacement participant's treatment/randomization number.

The replacement participant may begin dosing at the subsequent dose level for that panel, based on investigator and Sponsor review and discussion.

6 STUDY INTERVENTION

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

Clinical supplies of ISL will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Run-in	Experi mental	Methadone	Drug	Per Local Guidelines	Varies	20-200 mg	Oral	Once daily for 14 days prior to Day 1	Experi mental	NIMP	Provided Locally by Outpatient Clinic
Maintenance Therapy	Experi mental	Methadone	Drug	Per Local Guidelines	Varies	20-200 mg	Oral	Once daily Days 2-9	Experi mental	IMP	Provided Locally by Site
Maintenance Therapy	Experi mental	Methadone	Drug	Per Local Guidelines	Varies	20-200mg	Oral	Once daily Days 10-15	Experi mental	NIMP	Provided Locally by Outpatient Clinic
ISL	Experi mental	ISL	Drug	Capsule	30 mg	60 mg	Oral	Single Dose Day 2	Experi mental	IMP	Provided Centrally by Sponsor
The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible.

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.2.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this trial will be allocated by non-random assignment as shown in Table 2.

Table 2 Sample Allocation Schedule

Subjects	Day 1	Day 2
N=14	Single oral dose of methadone 20 – 200 mg	Single oral dose of methadone 20 – 200 mg + ISL 60 mg

6.3.2 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

6.3.3 Blinding

This is a single treatment arm open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

If a participant does not discontinue all prior medications within 14 days or 5 half-lives of the first dose of methadone run-in therapy, they may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the study.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, after run-in maintenance phase begins) until the follow-up call must first be discussed between the investigator and Sponsor prior to administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree.

Paracetamol/acetaminophen at ≤2000 mg total daily dose may be used for minor ailments without prior consultation with the Sponsor.

In addition, the following concomitant medications are permitted:

1. The participants' prescribed methadone treatment.

2. The concomitant use of benzodiazepines may be permitted during the study provided the participant has been receiving a stable benzodiazepine dose (as prescribed by a physician) for at least 2 months prior to the first dose of study drug administered in this trial. Use must be discussed with Sponsor prior to enrollment.

3. Truvada® or Descovy® for the prevention of HIV-infection, provided the participant initiates use of these products no later than the start of the 14-day run-in period or after the Day 9 clinic discharge.

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification

Not applicable.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

For studies using controlled substances, all Federal, State, Province, Country, etc., regulations must be adhered to in regard to their shipping, storage, handling, and dispensing of controlled substances. Additionally, the investigator should have the appropriate controlled drug license(s) as mandated by Federal, State, Province, Country, etc., laws in which the study is being conducted.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a protocol clarification letter.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Sections 8.1.9.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant requires a dose adjustment to their methadone treatment which, in the opinion of the investigator and/or Sponsor, would interfere with the scientific integrity of the trial.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last

known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

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

The maximum amount of blood collected from each participant over the duration of the study will not exceed 241 mL [Appendix 8].

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

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

If the investigator recommends continuation of study intervention beyond disease progression, the participant or his/her legally acceptable representative will be asked to sign consent.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before the start of the methadone run-in phase.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to intervention allocation on Day 1. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. Once a

treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Study Intervention Administration

During the methadone run-in phase, participants will retrieve the stable daily dose of methadone from their usual local methadone clinic and self-administer as directed for 14 days.

On Days 1-9, administration of study medication will be witnessed by the investigator and/or study staff. Approximately 240 mL of water will be provided during trial drug administration. Additional water may be provided in ~50 mL increments if necessary. Water will be restricted 1 hour prior to and 1 hour after study drug administration. Details on water and dietary restrictions are outlined in Section 5.3.1.

Once discharged from the CRU, participants will continue to retrieve their methadone therapy from their usual local methadone clinic and self-administer at least until the follow-up call.

8.1.8.1 Timing of Dose Administration

Methadone will be administered in the morning of Day 1 after an overnight fast with approximately 240 mL of water (regardless of formulation). Participants should continue to fast until at least 4 hours postdose.

On Day 2, participants will receive an oral dose of ISL 60 mg once within 5 minutes of their dose of methadone after an overnight fast (methadone to be administered first at approximately the same time as on Day 1). A total of 240 mL of water will be used for ISL and methadone dosing. Additional water may be provided if needed. Participants should continue to fast until at least 4 hours postdose.

The time of methadone administration will be deemed Time “0” and study assessments will be relative to this.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.4.1 after the last dose of study intervention to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period

(Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.11 Domiciling

Participants will report to the CRU on Day -1 and remain in the unit until 168 hrs postdose of concomitant methadone and ISL administration (ie, Day 9). At the discretion of the investigator, participants may be requested to remain in the CRU longer.

8.1.12 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

There are no direct efficacy assessments in this study.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in Section 8.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded.

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

BMI

BMI equals a person's weight in kilograms divided by height in meters squared ($BMI=kg/m^2$). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

Body weight and height will be obtained with the participant’s shoes off and jacket or coat removed.

8.3.2 Vital Signs

Temperature, HR, BP, RR and oxygen saturation (via pulse oximeter) will be assessed.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate, Blood Pressure, Respiratory Rate, Oxygen Saturation)

Participants should be resting in a quiet setting without distractions in a semirecumbent position for at least 10 minutes prior to having VS measurements obtained with a completely automated device. Manual techniques will be used only if an automated device is not available. Semirecumbent VS will include HR, systolic and diastolic BP, oxygen saturation, and RR at timepoints indicated in the SoA. The correct size of the BP cuff and the correct positioning on the participant’s arm is essential to increase the accuracy of BP measurements.

The predose (baseline) HR and BP will be a single measurement obtained within 2 hours of dosing methadone on Day 1. These measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Postdose VS measurements will also be single measurements.

Respiratory rate and oxygen saturation (via pulse oximeter) will be measured per the site standard operating procedures. Participants should be resting in a semi-recumbent position for at least 10 minutes prior to having RR and oxygen saturation measurements obtained.

Body Temperature

Body temperature will be measured. The same method must be used for all measurements for each individual participant and should be the same for all participants.

8.3.3 Electrocardiograms

- 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Appendix 10.9 for evaluation and withdrawal criteria and additional QTc readings that may be necessary.

- At each time point when triplicate ECGs are required (ie, screening and Day 1 and 2 predose), 3 individual ECG tracings should be obtained as close as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Participants may need to be shaved to ensure proper lead placement. Participants may need to remove interfering garments.

Participants should be resting in the semi-recumbent position for at least 10 minutes prior to each ECG measurement.

The correction formula to be used for QTc is Fridericia.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each participant with an ECG skin marker pen to ensure reproducible electrode placement.

Predose ECGs will be obtained in triplicate at least 1-2 minutes apart within 2 hours prior to dosing on Days 1 and 2. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

If a participant demonstrates an increase in QTc interval ≥60 msec compared with mean predose baseline measurement, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc interval increase from baseline for any postdose time point is ≥60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc

interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If the QRS duration from any postdose ECG is 20% greater than the mean baseline QRS duration and is >120 msec (and change is not considered rate-related or pacing-induced) or there appears to be new onset intermittent bundle branch block, then the ECG will be immediately repeated twice within 5 minutes. The mean value of the QRS interval from the 3 ECGs will represent the value at that time point. If the mean QRS interval increase from baseline for any postdose time point is >20%, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QRS is within 20% of baseline. If a >20% prolongation of the QRS interval persists, a consultation with a cardiologist may be appropriate and the Sponsor should be notified.

If the QTc interval is ≥500 msec on any postdose ECG, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry-monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a cardiac or intensive care unit) is available.

If the QRS duration is prolonged by more than 20% compared to the mean baseline, and is ≥200 msec (and change is not considered rate-related or pacing-induced), then the Sponsor should be notified. The ECGs should be reviewed by a cardiologist and the participant should be considered for transfer to a location where closer monitoring and definitive care (eg, a cardiac or intensive care unit) is available.

If the participant has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the participant should be immediately transferred to an acute care setting for definitive therapy.

If prolongation of the QTc is noted, concomitant medications that prolong QTc should be held until the QTc is within 60 msec of baseline and the QTc is <500 msec.

A cardiologist will be consulted by the investigator as needed to review ECG tracings with significant abnormalities.

8.3.4 Clinical Opiate Withdrawal Scale (COWS)

The COWS will be administered at screening and at predose on Day 1 to establish a baseline. COWS will only be administered at other timepoints if overt signs of withdrawal are observed and it is determined clinically appropriate to administer COWS assessment. To minimize variability, it is preferred (but not required) that a participant be assessed by the same clinic personnel throughout the trial. Instructions on administering the COWS assessment can be found in the operations/laboratory manual.

8.3.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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

AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation, must be reported by the investigator for randomized participants only if the event is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of intervention allocation through 14 days following cessation of intervention, all AEs, SAEs and other reportable safety events must be reported by the investigator.

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation (Randomized participants only)	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

Information in this section is not applicable since participants are males and non-pregnant, non-breastfeeding females.

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

Not applicable.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger an additional evaluation for an underlying etiology. The study site guidance for

assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the study exceeding the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

8.6 Pharmacokinetics

The decision as to which plasma samples collected will be assayed for evaluation of PK/pharmacodynamics will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.6.1 Blood Collection for Plasma ISL and Plasma Methadone

Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Blood for Genetic Analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected,

leftover extracted DNA will be stored for future biomedical research. If the planned genetic analysis is not approved, but future biomedical research is approved, this sample will be collected for the purpose of future biomedical research.

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

8.9 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover DNA for future research

8.10 Visit Requirements

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

8.10.1 Screening

Approximately 4 weeks prior to intervention allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention allocation if there are Day -1 procedures planned per protocol.

8.10.2 Treatment Period

Refer to Schedule of Activities (Section 1.3).

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, a subset of study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.10.4 Poststudy

Participants will receive a follow-up call 14 days (+3 days) after receiving the dose of ISL for assessment of AEs and reporting of concomitant medications.

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, blood samples for methadone and ISL pharmacokinetics are the critical procedures.

The blood collection for ISL pharmacokinetics should be based upon the time of ISL administration. The blood collection for methadone should be based upon the time of methadone administration.

At any postdose timepoint, the blood samples for methadone and ISL need to be collected as close to the exact timepoint as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible.

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The following variance in procedure collection times will be permitted.

- PK Collection as outlined in Table 4.

Table 4 Pharmacokinetic Blood Collection Windows

PK Collection	PK Collection Window
0 - <1 hr	± 5 min
1 - <24 hr	± 15 min
24 - <48 hr	± 1 hr
48 - 168 hr	± 2 hr

- Predose standard safety evaluations: vital signs and ECG within 3 hrs prior to dosing on Days 1 and 2; COWS within 1 hr predose on Days 1 and 2; laboratory safety tests and physical exam within 24 hrs prior to dosing on Day 1

- Postdose standard safety evaluations: vital signs, ECG, laboratory safety tests <24 hr postdose (Day 1 and Day 2) may be obtained within ±15 min of the theoretical sampling time

  - 24 hr - <48 hr postdose (Day 2) may be obtained within ± 1 hr of the theoretical sampling time

  - 48 hr – 168 hr postdose (Day 2) may be obtained within ± 2 hr of the theoretical sampling time

- >168 hr postdose (Day 2) may be obtained within ± 24 hr of the theoretical sampling time

8.10.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a Phase 1 assessment of ISL in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol.

- Decrease in the dose of the study intervention administered
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data

The PK/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK or pharmacodynamic data (eg, to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to an additional 50 mL of blood may be drawn for safety, PK, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 8).

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc.) may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of study procedures for a given participant during his/her participation in the entire study.

It is understood that the current study may employ some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section contains a summary of the statistical analyses for this trial. Full detail is in the Statistical Methods (Section 9.6).

Effect of ISL on Methadone

Primary Hypotheses

AUC0-24 for methadone R-enantiomer will be dose-normalized by each subject's methadone dose before the statistical analyses. A natural log transformation will be applied to the R-methadone AUC0-24/D prior to the analysis. A linear mixed-effects model will be used to evaluate the primary hypothesis. The model includes a fixed effect term for treatment. An unstructured covariance matrix will be used to allow for unequal treatment variances and to model the correlation between the two treatment measurements within each subject via the REPEATED statement in SAS PROC MIXED. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). A ninety percent (90%) confidence interval (CI) will be constructed for the difference in LS means on the log scale R-methadone AUC0-24/D. Exponentiating the log-scale 90% CI will provide a 90% CI for the AUC0-24/D geometric mean ratio (GMR) (methadone+ISL/methadone alone). The hypothesis that the methadone (R-enantiomer) AUC0-24 obtained after single dose co-administration of methadone with ISL is similar to the methadone (R-enantiomer) AUC0-24 obtained after single dose administration of methadone alone will be supported if the 90% CI for the AUC0-24/D GMR of R-methadone is contained within the interval (0.70, 1.43).

AUC0-24 for methadone S-enantiomer will be analyzed based on the same model. The GMR (methadone+ISL/methadone alone) and 90% CI for methadone S-enantiomer will be estimated. The hypothesis that the methadone (S-enantiomer) AUC0-24 obtained after single dose co-administration of methadone with ISL is similar to the methadone (S-enantiomer) AUC0-24 obtained after single dose administration of methadone alone will be supported if the 90% CI for the AUC0-24/D GMR of S-methadone is below 2.0.

Secondary Hypotheses

Dose normalized Cmax of R- and S- enantiomer will also be analyzed based on the same model. The GMRs (methadone+ISL/methadone alone) and 90% CIs for each parameter will be estimated. The hypothesis that the methadone (R-enantiomer) Cmax obtained after single dose co-administration of methadone with ISL is similar to the methadone (R-enantiomer) Cmax obtained after single dose administration of methadone alone will be supported if the 90% CI for the Cmax/D GMR of R-methadone is below 1.43. The hypothesis that the methadone (S-enantiomer) Cmax obtained after single dose co-administration of methadone with ISL is similar to the methadone (S-enantiomer) Cmax obtained after single dose administration of methadone alone will be supported if the 90% CI for the Cmax/D GMR of S-methadone is below 2.0.

Estimations

Dose normalized C24 of R-methadone and S-methadone, and dose normalized AUC0-24, Cmax and C24 of methadone total will be analyzed similarly using the above model. The GMR (methadone+ISL/methadone alone) and 90% CI for every afore-mentioned parameter will be estimated. Geometric means (GMs) and corresponding 95% CIs will also be provided for AUC0-24/D, Cmax/D and C24/D of methadone (R-, S-, and total methadone) by treatment. Plots with the individual ratios, GMR and 90% confidence interval will be provided for AUC0-24/D, Cmax/D and C24/D of methadone (R-, S-, and total methadone).

Exploratory - Effect of Methadone on ISL

ISL AUC0-24 will be compared with the most appropriate available historical data following administration of MK-8591 60 mg alone. Potential historical data to be used include MK-8591 P026 and P030. ISL AUC0-24 following co-administration of methadone and ISL and the historical data will be natural log transformed and analyzed using an ANOVA model with a factor for treatment (methadone+ISL, ISL alone). A ninety percent (90%) CI will be constructed for the difference in LS means on the log scale ISL AUC0-24. Exponentiating the log-scale 90% CI will provide a 90% CI for the AUC0-24 GMR (methadone+ISL/ISL alone). Similarly, ISL AUC0-168, AUC0-672, AUC0-inf, and Cmax will be analyzed and compared with historical data. GMs and corresponding 95% CIs will also be provided by treatment.

Safety

Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or VS as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). AEs will be listed and tabulated.

Sample Size and Power Calculations

The following power estimates are based on within-subject SD obtained from MK-1439 Protocol 045. With a sample size of 12 completers, if the true GMR of R-methadone AUC0-24hr/D (methadone+ISL/methadone alone) is 1.00, then there is a greater than 99% probability of observing the 90% CI for the GMR within (0.70, 1.43) for R-methadone AUC0-24hr/D; if the true GMR of S-methadone AUC0-24hr/D (methadone+ISL/methadone alone) is 1.00, then there is a greater than 99% probability of observing the 90% CI for the GMR below 2.0 for S-methadone AUC0-24hr/D. Overall, there is a 98% probability to meet the two primary hypotheses. With a sample size of 12 completers, if the true GMR of R-methadone AUC0-24hr is between 0.77 to 1.30 then there is at least 80% probability that the 90% CI for R-methadone AUC0-24hr/D is between (0.70, 1.43); if the true GMR of S-methadone AUC0-24hr is less than 1.76 then there is at least 80% probability that the 90% CI for S-methadone AUC0-24hr/D is less than 2.0. A total of 14 participants will be recruited for enrollment in case of discontinuations.

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics Department and Translational Pharmacology Department of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

9.3 Hypotheses/Estimation

Primary Hypotheses:

The methadone (R-enantiomer) plasma AUC0-24 obtained after single dose co-administration of methadone with ISL is similar to the methadone (R-enantiomer) plasma AUC0-24 obtained after single dose administration of methadone alone. That is, the true GMR (methadone and ISL/methadone alone) for the dose-normalized AUC0-24 (AUC0-24/D) of methadone (R-enantiomer) is contained within (0.7, 1.43).

The methadone (S-enantiomer) plasma AUC0-24 obtained after single dose co-administration of methadone with ISL is similar to the methadone (S-enantiomer) plasma AUC0-24 obtained after single dose administration of methadone alone. That is, the true GMR (methadone and ISL/methadone alone) for the dose-normalized AUC0-24 (AUC0-24/D) of methadone (S-enantiomer) is less than 2.0.

Secondary Hypotheses:

The methadone (R-enantiomer) plasma Cmax obtained after single dose co-administration of methadone with ISL is similar to the methadone (R-enantiomer) plasma Cmax obtained after single dose administration of methadone alone. That is, the true GMR (methadone and ISL/methadone alone) for the dose-normalized Cmax (Cmax/D) of methadone (R-enantiomer) is less than 1.43.

The methadone (S-enantiomer) plasma Cmax obtained after single dose co-administration of methadone with ISL is similar to the methadone (S-enantiomer) plasma Cmax obtained after single dose administration of methadone alone. That is, the true GMR (methadone and ISL/methadone alone) for the dose-normalized Cmax (Cmax/D) of methadone (S-enantiomer) is less than 2.0.

Estimations:

The true GMR (methadone and ISL/ methadone alone) for the dose normalized C24 (C24/D) of methadone (R-enantiomer and S-enantiomer) will be estimated.

The true GMR (methadone and ISL/methadone alone) for the dose normalized AUC0-24 (AUC0-24/D), Cmax (Cmax/D) and C24 (C24/D) of methadone (total) will be estimated.

9.4 Analysis Endpoints

Primary Endpoints

The primary PK endpoints include dose-normalized AUC0-24 (AUC0-24/D) of plasma methadone (R- and S-methadone).

Secondary Endpoints

The secondary PK endpoints include dose-normalized Cmax (Cmax/D), C24 (C24/D), and Tmax of plasma methadone (R-, and S- enantiomer), and dose-normalized AUC0-24 (AUC0-24/D), Cmax (Cmax/D), C24 (C24/D), and Tmax of plasma methadone (total).

The secondary safety endpoints include adverse experiences, laboratory safety tests, ECGs, and VSs (HR, BP, RR, oxygen saturation).

Exploratory Endpoints

The exploratory PK endpoints include AUC0-24, AUC0-168, AUC0-672, AUC0-inf, Cmax, Tmax and t1/2 of plasma ISL.

9.5 Analysis Populations

The following populations are defined for the analysis and reporting of data. All participants will be reported, and their data analyzed, according to the treatment(s) they actually received.

All Subjects as Treated (ASaT): The All Subjects as Treated Population consists of all participants who receive at least one dose of treatment. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP): The Per-Protocol Population consists of the subset of participants who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data considered sufficient to exhibit the effect of treatment will be included in the Per-Protocol dataset. This population will be used for the PK analyses.

9.6 Statistical Methods

Pharmacokinetics

Effect of ISL on Methadone

Primary Hypotheses

AUC0-24 for methadone R-enantiomer will be dose-normalized by each subject's methadone dose before the statistical analyses. A natural log transformation will be applied to the R-methadone AUC0-24/D prior to the analysis. A linear mixed-effects model will be used to evaluate the primary hypothesis. The model includes a fixed effect term for treatment. An unstructured covariance matrix will be used to allow for unequal treatment variances and to model the correlation between the two treatment measurements within each subject via the REPEATED statement in SAS PROC MIXED. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). A ninety percent (90%) confidence interval (CI) will be constructed for the difference in LS means on the log scale R-methadone AUC0-24/D. Exponentiating the log-scale 90% CI will provide a 90% CI for the AUC0-24/D geometric mean ratio (GMR) (methadone+ISL/methadone alone). The hypothesis that the methadone (R-enantiomer) AUC0-24 obtained after single dose co-administration of methadone with ISL is similar to the methadone (R-enantiomer) AUC0-24 obtained after single dose administration of methadone alone will be supported if the 90% CI for the AUC0-24/D GMR of R-methadone is contained within the interval (0.70, 1.43).

Sample SAS code is given below:

```
proc mixed data=dataset;
  class treatment subject;
  model y = treatment/ddfm=kr;
  repeated treatment / subject=subject type=un;
run;
```

AUC0-24 for methadone S-enantiomer will be analyzed based on the same model. The GMR (methadone+ISL/methadone alone) and 90% CI for methadone S-enantiomer will be estimated. The hypothesis that the methadone (S-enantiomer) AUC0-24 obtained after single dose co-administration of methadone with ISL is similar to the methadone (S-enantiomer) AUC0-24 obtained after single dose administration of methadone alone will be supported if the 90% CI for the AUC0-24/D GMR of S-methadone is below 2.0.

Secondary Hypotheses

Dose normalized Cmax of R- and S- enantiomer will also be analyzed based on the same model. The GMRs (methadone+ISL/methadone alone) and 90% CIs for each parameter will be estimated. The hypothesis that the methadone (R-enantiomer) Cmax obtained after single dose co-administration of methadone with ISL is similar to the methadone (R-enantiomer) Cmax obtained after single dose administration of methadone alone will be supported if the

90% CI for the Cmax/D GMR of R-methadone is below 1.43. The hypothesis that the methadone (S-enantiomer) Cmax obtained after single dose co-administration of methadone with ISL is similar to the methadone (S-enantiomer) Cmax obtained after single dose administration of methadone alone will be supported if the 90% CI for the Cmax/D GMR of S-methadone is below 2.0.

Estimations

Dose normalized C24 of R-methadone and S-methadone, and dose normalized AUC0-24, Cmax and C24 of methadone total will be analyzed similarly using the above model. The GMR (methadone+ISL/methadone alone) and 90% CI for every aforementioned parameter will be estimated. Geometric means (GMs) and corresponding 95% CIs will also be provided for AUC0-24/D, Cmax/D and C24/D of methadone (R-, S-, and total methadone) by treatment. Plots with the individual ratios, GMR and 90% confidence interval will be provided for AUC0-24/D, Cmax/D and C24/D of methadone (R-, S-, and total methadone).

Exploratory - Effect of Methadone on ISL

ISL AUC0-24 will be compared with the most appropriate available historical data following administration of MK-8591 60 mg alone. Potential historical data to be used include MK-8591 P026 and P030. ISL AUC0-24 following co-administration of methadone and ISL and the historical data will be natural log transformed and analyzed using an ANOVA model with a factor for treatment (methadone+ISL, ISL alone). A ninety percent (90%) CI will be constructed for the difference in LS means on the log scale ISL AUC0-24. Exponentiating the log-scale 90% CI will provide a 90% CI for the AUC0-24 GMR (methadone+ISL/ISL alone). Similarly, ISL AUC0-168, AUC0-672, AUC0-inf, and Cmax will be analyzed and compared with historical data. GMs and corresponding 95% CIs will also be provided by treatment.

Individual values will be listed for each PK parameter by treatment and analyte including dose-normalized AUC0-24 (AUC0-24/D), Cmax (Cmax/D), C24 (C24/D), and Tmax of plasma methadone (total, R-, and S-methadone), and AUC0-24, AUC0-168, AUC0-672, AUC0-inf, Cmax, Tmax and t1/2 of plasma ISL, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale.

Safety:

Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or VS as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). AEs will be listed and tabulated.

9.7 Interim Analyses

Not applicable.

9.8 Multiplicity

Since both primary hypotheses (R- and S-methadone plasma AUC0-24) must be supported in order for the overall clinical hypothesis to be supported, there is no need for a multiplicity adjustment.

9.9 Sample Size and Power Calculations

The following power estimates are based on within-subject SD obtained from MK-1439 Protocol 045.

With a sample size of 12 completers, if the true GMR of R-methadone AUC0-24hr/D (methadone+ISL/methadone alone) is 1.00, then there is a greater than 99% probability of observing the 90% CI for the GMR within (0.70, 1.43) for R-methadone AUC0-24hr/D; if the true GMR of S-methadone AUC0-24hr/D (methadone+ISL/methadone alone) is 1.00, then there is a greater than 99% probability of observing the 90% CI for the GMR below 2.0 for S-methadone AUC0-24hr/D. Overall, there is a 98% probability to meet the two primary hypotheses.

With a sample size of 12 completers, if the true GMR of R-methadone AUC0-24hr is between 0.77 to 1.30 then there is at least 80% probability that the 90% CI for R-methadone AUC0-24hr/D is between (0.70, 1.43); if the true GMR of S-methadone AUC0-24hr is less than 1.76 then there is at least 80% probability that the 90% CI for S-methadone AUC0-24hr/D is less than 2.0.

Similar power calculations for R-, S-methadone Cmax/D and the precision estimations for R-, S-methadone C24/D and total-methadone AUC0-24/D, Cmax/D, and C24/D are provided in Table 5.

A total of 14 participants will be recruited for enrollment in case of discontinuations.

Table 5 Power and Precision Estimates

Hypotheses					
Parameter		Within subject SD estimate (log scale)	Bounds	Power if the True GMR is 1.00	Lowest and/or Highest True GMR to Maintain 80% Power
Primary Hypotheses					
R-methadone	AUC0-24/D	0.088	(0.7, 1.43)	99%	(0.77, 1.30)
S-methadone	AUC0-24/D	0.116	<2.0	99%	<1.76
Secondary Hypotheses					
R-methadone	Cmax/D	0.076	<1.43	99%	<1.32
S-methadone	Cmax/D	0.106	<2.0	99%	<1.78
Estimations					
Parameter		Within subject SD estimate (log scale)	Half-width of 90% CI (log scale)		90% CI if the Estimated GMR is 1.00
R-methadone	C24/D	0.119	0.087		(0.92, 1.09)
S-methadone	C24/D	0.183	0.134		(0.87, 1.14)
Total-methadone	AUC0-24/D	0.095	0.070		(0.93, 1.07)
	Cmax/D	0.087	0.064		(0.94, 1.07)
	C24/D	0.140	0.103		(0.90, 1.11)

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus

source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)	Total and direct bilirubin
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Highly sensitive serum pregnancy test (for WOCBP) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • Syphilis testing per standard of care (eg, treponemal and/or nontreponemal testing) • Urine STI screen (to include at minimum: gonorrhea, chlamydia, trichomoniasis)			
NOTES: Laboratory safety assessments will be performed after an 8- hour fast; however, in case of discontinuation or rechecks, a non-fasting assessment may be performed at the discretion of the Investigator.				

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant

number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) by recording the grade according to the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1. Any AE which changes DAIDS grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

  - Grade 1 Mild event: Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.

  - Grade 2 Moderate event: Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.

  - Grade 3 Severe event: Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.

  - Grade 4 Potentially life-threatening event: Potentially life-threatening symptoms causing inability to perform basic self-care funtions with intervention indicated to prevent permanent impairment, persistent disability, or death.

  - Grade 5 Death: Deaths related to an AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and

their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

· The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[c,d] • IUS[c,e] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[f]
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Blood Volume Table

Participants	Pre-study	Treatment Periods	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests					
Chemistry[a]	1	2	3	8.5	25.5
Hematology	1	2	3	4	12
Blood for Planned Genetic Analysis		1	1	8.5	8.5
HIV Antigen/Antibody & /Hepatitis Screen	1[b]		1	8.5	8.5
Blood for syphilis screen	1		1	5	5
Blood for methadone		21	21	6	126
Blood for ISL		13	13	4	52
	Total Blood Volume per Participant:				237.5 mL[c]

[a] Includes serum FSH (WONCBP only) and serum β-hCG (WOCBP only).
[b] Hepatitis screen conducted at pre-study visit only.
[c] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With Left Anterior Hemiblock (LAHB)	New Onset LAHB
Right Axis Deviation	RBBB With Left Posterior Hemiblock (LPHB)	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
Incomplete Right BBB (ICRBBB) (QRS <120 ms)	No Exclusion	Nothing
Short PR/ Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥450 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All
Baseline is defined as Predose Day 1; ms=milliseconds, mm=millimeter		

10.10 Appendix 10: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

    1. The participant may be excluded from the study;

    2. The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

    3. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

    OR

    4. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

        a. If the repeat test value is within the normal range, the participant may enter the study.

        b. If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADA	Adenosine deaminase
AE	adverse event
APaT	All-Participants-as-Treated
AR	adverse reaction
ART	anti-retroviral therapy
BDS	blood drug screen
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
CG	Cockcroft-Gault
CNS	central nervous system
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CrCl	creatinine clearance
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
DAIDS	Division of AIDS
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	doravarine
DTG	dolutegravir
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISL	Islatravir
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LNG/EE	Levonorgestrel/ethinyl estradiol

Abbreviation	Expanded Term
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMT	Methadone maintenance therapy
NCS	not clinically significant
NRTI	Nucleoside reverse transcriptase inhibitor
NRTTI	Nucleoside reverse transcriptase translocation inhibitor
NOAEL	no observed adverse effect level
OTC	over-the-counter
PBMC	Peripheral mononuclear blood cells
PK	pharmacokinetic
PP	per-protocol
PrEP	Pre-exposure prophylaxis
PWID	People who inject drugs
QM	Once monthly
QW	Once a week
QP2	department of quantitative pharmacology and pharmacometrics
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TDF	Tenofovir disoproxil fumarate
TP	triphosphate
UDS	urine drug screen
V	volume of distribution
VS	vital sign
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	Woman/women of nonchildbearing potential

11 REFERENCES

[Centers for Disease Control and Prevention 2015]	Centers for Disease Control and Prevention. Factors increasing the risk of acquiring or transmitting HIV. Washington (DC): Department of Health and Human Services (HHS); 2015 Dec. 4 p.	[05KS5C]
[Centers for Disease Control and Prevention 2020]	Centers for Disease Control and Prevention [Internet]. Washington (DC): Department of Health and Human Services (HHS). Diagnoses of HIV infection in the United States and dependent areas, 2018: diagnoses: diagnoses of HIV infection; [cited 2020 Aug 24]; [about 19 screens]. Available from: https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-31/content/diagnoses.html.	[05KS5B]
[Centers for Disease Control and Prevention 2020]	Centers for Disease Control and Prevention [Internet]. Washington (DC): Department of Health and Human Services (HHS). PrEP; [cited 2020 Aug 24]; [about 11 screens]. Available from: https://www.cdc.gov/hiv/basics/prep.html.	[05KS97]
[Centers for Disease Control and Prevention 2020]	Centers for Disease Control and Prevention [Internet]. Washington (DC): Department of Health and Human Services (HHS). Injection drug use and HIV risk; [cited 2020 Aug 24]; [about 5 screens]. Available from: https://www.cdc.gov/hiv/risk/idu.html.	[05KS5D]
[Eap, C. B., et al 2002]	Eap CB, Buclin T, Baumann P. Interindividual Variability of the Clinical Pharmacokinetics of Methadone: Implications for the Treatment of Opioid Dependence. Clin Pharmacokinet 2002;41(14):1153-93.	[03RRK3]
[Joint United Nations Programme on HIV/AIDS 2020]	Joint United Nations Programme on HIV/AIDS. Fact sheet: global HIV statistics. Geneva (Switzerland): Joint United Nations Programme on HIV/AIDS (UNAIDS); 2020. 7 p.	[05KS98]

[Maremmani, I., et al 2005]	Maremmani I, Pacini M, Cesaroni C, Lovrecic M, Perugi G, Tagliamonte A. QTc interval prolongation in patients on long-term methadone maintenance therapy. Eur Addict Res. 2005;11:44-9.	[05KS80]
[McCance-Katz, E. F., et al 1998]	McCance-Katz EF, Rainey PM, Jatlow P, Friedland G. Methadone effects on zidovudine disposition (AIDS Clinical Trials Group 262). J Acquir Immune Defic Syndr Hum Retrovirol. 1998 Aug 15;18(5):435-43.	[04625Z]
[Rainey, P. M., et al 2000]	Rainey PM, Friedland G, McCance-Katz F, Andrews L, Mitchell SM, Charles C, et al. Interaction of methadone with didanosine and stavudine. JAIDS 2000;24(3):241-8.	[03QQTP]
[Schwartz, E. L., et al 1992]	Schwartz EL, Brechbuhl AB, Kahl P, Miller MA, Selwyn PA, Friedland GH. Pharmacokinetic interactions of zidovudine and methadone in intravenous drug-using patients with HIV infection. J Acquir Immune Defic Syndr. 1992;5(6):619-26.	[046274]
[U.S. Prescribing Information 2019]	U.S. Prescribing Information: DOLOPHINE (methadone hydrochloride) tablets, for oral use: Oct 2019.	[05KV5B]
[Volpe, D. A., et al 2018]	Volpe DA, Xu Y, Sahajwalla CG, Younis IR, Patel V. Methadone metabolism and drug-drug interactions: in vitro and in vivo literature review. J Pharm Sci. 2018;107:2983-91.	[05KS82]
[Wesson, D. R. 2003]	Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003 Apr-Jun;35(2):253-9.	[04628F]