Original Article

A Phase 1 Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Between Islatravir and Methadone in Participants on Stable Methadone Therapy

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Randolph P. Matthews[1], Wendy Ankrom[1,†], Whitney Handy[1,†], Munjal Patel[1], Catherine Matthews[1], Zhiqing Xu[1], Kezia Gravesande[1,†], Shawn Searle[2,#], Howard Schwartz[3], S. Aubrey Stoch[1], and Marian Iwamoto[1,†]

Abstract

Islatravir is a nucleoside reverse transcriptase translocation inhibitor in development for the treatment of HIV-1. People living with HIV-1 receiving methadone maintenance therapy may benefit from islatravir. This study was designed to evaluate single-dose islatravir on steady-state methadone pharmacokinetics. A nonrandomized, open-label study (NCT04568603) was conducted and included adult participants receiving methadone therapy. Participants received their standard methadone therapy and a single oral dose of islatravir 60 mg concomitantly. Blood samples were collected to determine methadone and islatravir pharmacokinetics. Fourteen participants aged 26-63 years were enrolled; 13 completed the study. The geometric mean ratios for methadone area under the concentration-time curve from time 0 to 24 hours ($AUC_{0\text{-}24}$), maximum plasma concentration (C_{max}), and concentration at 24 hours (C_{24}) were 1.03, 1.01, and 1.07, respectively. Similar effects were seen for the R- and S-enantiomer of methadone (R-methadone: $AUC_{0\text{-}24}$, 1.03; C_{max}, 1.02; and C_{24}, 1.06; S-methadone: $AUC_{0\text{-}24}$, 1.03; C_{max}, 1.01; and C_{24}, 1.08). For islatravir, based on a comparison with historical data, the geometric mean ratios for $AUC_{0\text{-}inf}$ and C_{max} were 1.18 and 0.86, respectively. Coadministration of a single dose of islatravir and methadone was generally well tolerated. Single-dose islatravir did not affect steady-state methadone pharmacokinetics in a clinically meaningful way.

Keywords

clinical pharmacology, coadministration, human immunodeficiency virus, nucleoside reverse transcriptase translocation inhibitor, people who inject drugs

Islatravir (also known as MK-8591) is an HIV-1 nucleoside reverse transcriptase translocation inhibitor being developed for the treatment of HIV.[1] Islatravir is unique due to its multiple mechanisms of action, including reverse transcriptase translocation inhibition and delayed viral DNA chain termination.[2–5] Islatravir is phosphorylated to its active triphosphate form, which has a long intracellular terminal half-life of 177-209 hours.[6,7] Islatravir is eliminated via metabolism by adenosine deaminase[6–8] and urinary excretion.[7,8] Single and multiple doses of oral islatravir were generally well tolerated in previous studies.[3,9–12]

Many people who inject drugs seek treatment for opioid addiction and receive maintenance therapy with the opioid agonist methadone for substance dependence.[13] The success of methadone maintenance therapy can be affected by many factors and is

[1]Merck & Co., Inc., Rahway, NJ, USA
[2]ICON/PRA Health Sciences, Salt Lake City, UT, USA
[3]CenExel RCA, Hollywood, FL, USA

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Corresponding Author:
Randolph P. Matthews, MD, PhD, Merck & Co., Inc. 126 East Lincoln Avenue, PO Box 2000, Rahway, NJ 07065.
(e-mail: randolph.matthews@merck.com)

[†]An employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, at the time of the study.
[#]An employee of ICON/PRA Health Sciences, Salt Lake City, UT, USA, at the time of the study.

complicated by interindividual variability of the pharmacokinetics and pharmacodynamics of methadone.[14] Methadone is administered as a racemic mixture of R- and S-enantiomers; the R-enantiomer is mainly responsible for analgesia, sedation, and respiratory depression, whereas the S-enantiomer is responsible for QT prolongation.[15] Results of previous studies have shown that cytochrome P450 (CYP) 2B6, not CYP3A or other CYPs, plays a major role in methadone metabolism.[16–19] Morphine and hydromorphone, however, are primarily metabolized by uridine 5'-diphospho-glucuronosyltransferase (UGT).[20] Interactions between HIV antiretrovirals and methadone have been reported[13,14,21,22]; however, islatravir is not an inhibitor or inducer of CYP enzymes[8] and therefore is not expected to have a meaningful impact on methadone exposure.[13,14] Additionally, methadone and islatravir are metabolized via different pathways.[8,14] Although interactions were not expected between methadone and islatravir, a 2-way, drug-drug interaction, Phase 1 study was conducted to assess methadone and islatravir adverse events (AEs), tolerability, and pharmacokinetics with coadministration.

Methods

Study Design

In this open-label Phase 1 study conducted between October 2020 and July 2021 (MK-8591-029; ClinicalTrials.gov NCT04568603), participants aged 18-65 years who were receiving stable once-daily oral methadone maintenance therapy (20-200 mg) were assigned to receive a single dose of oral islatravir 60 mg. This study was conducted at 2 centers, including PRA Health Sciences (Salt Lake City, UT) and Research Centers of America, LLC (Hollywood, FL). At the time of the study, 60 mg was the top dose in Phase 3 clinical trials. Participants received their usual methadone therapy during a ≥14-day run-in phase (Figure S1). On Days 1 and 2, participants received their standard dose of methadone (same formulation and dose) after a ≥8-hour fast. On Day 2, participants received a single oral dose of islatravir 60 mg concomitantly with their usual dose of methadone. Participants continued to receive their usual methadone therapy from Day 3 to at least Day 15.

The objectives of the trial were to determine the effects of coadministration of islatravir and methadone on the plasma pharmacokinetics of dose-normalized methadone and the R- and S-enantiomers of methadone (R-methadone and S-methadone, respectively); the safety, AEs, and tolerability of coadministration of islatravir and methadone; and the effect of methadone on islatravir pharmacokinetics.[23]

The current trial was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice standards, applicable country and local requirements regarding ethical committee review, informed consent, and the protection of the rights and welfare of human participants in biomedical research. The institutional review boards were Midlands, LLC (Lenexa, KS) and Advarra, Inc. (Columbia, MA).

Pharmacokinetics Assessment

On Days 1 and 2, serial blood samples to determine methadone pharmacokinetics were collected before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 12, 16, and 24 hours after dosing. Additionally, on Day 2, serial blood samples to determine islatravir pharmacokinetics were collected before dosing and at 0.25, 0.5, 1, 2, 6, 12, 16, 24, 48, 72, 96, and 168 hours after dosing. For evaluation of islatravir pharmacokinetics, islatravir pharmacokinetic data were compared with prespecified historical data after administration of islatravir 60 mg in a healthy control cohort from the MK-8591-026 study (NCT04303156).

The following dose-normalized pharmacokinetic parameters were assessed for plasma methadone (R- and S-enantiomers): area under the plasma concentration-time curve (AUC) from time 0 to 24 hours ($AUC_{0\text{-}24}$), maximum plasma concentration (C_{max}), concentration at 24 hours after dosing (C_{24}), and time to maximum plasma concentration (t_{max}). AUC from time 0 to infinity ($AUC_{0\text{-}inf}$), AUC from time 0 to 168 hours, C_{max}, t_{max}, and apparent terminal half-life were assessed for plasma islatravir. All pharmacokinetic analyses were performed using the per-protocol population, which included all participants for whom data were available and considered sufficient to exhibit the effects of treatment.

Analytical Methods

The analyte islatravir and its internal standard, [^{13}C,$^{15}N_3$]-islatravir, were extracted from a 0.200-mL aliquot of human dipotassium-ethylenediaminetetraacetic acid plasma using an automated liquid–liquid extraction technique. The extracted samples were injected into a liquid chromatograph equipped with an X Select HSS T3 column (50 × 2.1 mm, 2.5 µm; Waters Corp.). The mobile phases A and B were mixtures of Milli-Q (Merck & Co., Inc.) water/methanol with propionic acid (in different proportions). The detection method was tandem mass spectrometry. Plasma samples were assayed for islatravir using a validated ultraperformance liquid chromatography-tandem mass spectrometry (LC-MS/MS) method by Syneos Health Clinique

Inc. (Québec). The analytical range of the assay was 20.00-20,000.00 pg/mL.

R-methadone and S-methadone plasma concentrations were measured using Analyst software Version 1.6.3 (AB SCIEX LLC), according to an LC-MS/MS detection method developed and validated by Pharma Medica Research Inc. The method for extraction was a liquid–liquid extraction. The standard calibration range for each enantiomer was 0.0250-15.0 ng/mL using a plasma sample volume of 0.5 mL. Samples below the limit of quantification were treated as 0. Methadone-d_9 was used as the internal standard. Plasma samples were extracted under basic conditions with a mixture of organic solvents; the organic phase was dried, reconstituted, and transferred for analysis by LC-MS/MS (Prominence-i High-Performance Liquid Chromatograph, Shimadzu, Kyoto, Japan; and API 4000, AB SCIEX LLC). Sample analysis was conducted using reversed phase chromatography. R-methadone and S-methadone were analyzed by the use of mass spectrometry using the positive ion scan mode with a parent–daughter transition of m/z 310-265 Da. Similarly, the internal standards were analyzed using a parent-daughter m/z transition of 319-268. The expected retention times for R-methadone and the internal standard are approximately 5.1 minutes and for S-methadone and the internal standard, approximately 6.2 minutes. For R-methadone, the difference between the mean concentrations of the quality control (QC) samples extracted with and without the methadone derivative metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine was 0.0% for all 3 QC samples; for S-methadone, the difference was –0.3% for QC A and 0.0% for QC B and QC C.

The extraction method had recoveries for R-methadone and S-methadone of 76.1%-89.8%. Moreover, the matrix effect had a precision of ≤2.3% for R-methadone and a precision of ≤2.9% for S-methadone. The sensitivity for R-methadone within-batch precision was within 2.7%, with an accuracy of 102.8%-105.2%; and for S-methadone 3.9%, with an accuracy of 106.4%-108.4%.

Adverse Events and Tolerability Assessments

AEs and tolerability were evaluated, including opioid withdrawal symptoms assessed before and after treatment with islatravir and methadone. Vital signs (heart rate, blood pressure, respiration rate, oxygen saturation), electrocardiogram parameters, and laboratory assessments were monitored. AEs were graded per the National Institutes of Health Division of AIDS table (Version 2.1, July 2017) for grading the severity of adult and pediatric AEs, as described in the Supplemental Information.[24]

Statistical Analysis

The $AUC_{0\text{-}24}$, C_{max}, and C_{24} for R- and S-methadone were dose-normalized by the methadone dose for each participant (parameter value/dose [D]) and natural log-transformed. Pharmacokinetic data were analyzed with a linear mixed-effects model with a fixed-effect term for treatment, and 90% confidence intervals (CIs) were constructed for the difference in least squares mean on the log scale. Exponentiating the log scale 90% CI provided a 90% CI geometric mean ratio (GMR) for the coadministration of methadone with islatravir and methadone alone. Geometric mean and corresponding 95% CI were also provided by treatment, and t_{max} was descriptively analyzed.

To assess the effect of methadone on islatravir, a cross-study comparison was conducted. Because the participants who were enrolled in this trial were receiving stable once-daily oral methadone maintenance therapy (20-200 mg) and could not be asked to stop their maintenance therapy during the trial, a comparison of islatravir pharmacokinetics after administration of islatravir 60 mg alone from a healthy control group was required.[23] Islatravir $AUC_{0\text{-}inf}$, AUC from time 0 to 168 hours, and C_{max} from the current study and islatravir historical data were natural log-transformed and analyzed using an analysis of variance model with a factor for treatment (methadone + islatravir, islatravir alone). A 90% CI was constructed for the difference in least squares mean on the log scale. Exponentiating the log-scale 90% CI provided a 90% CI for the GMR (methadone + islatravir/islatravir alone). GM and corresponding 95% CI and t_{max} were also provided by treatment.

Sample Size and Power Calculations

With a sample size of 12 participants who completed the study, if the true GMR of R-methadone $AUC_{0\text{-}24}$/D (methadone + islatravir/methadone alone) was 1.00, then there was >99% probability of observing the 90% CI for the GMR between 0.70 and 1.43 for R-methadone $AUC_{0\text{-}24}$/D; if the true GMR of S-methadone $AUC_{0\text{-}24}$/D (methadone + islatravir/methadone alone) was 1.00, then there was >99% probability of observing the 90% CI for the GMR <2.0 for S-methadone AUC_{024}/D. Overall, there was a 98% probability that the 2 primary hypotheses would be met.

Results

Subject Demographics

A total of 14 participants were enrolled, and 13 (92.9%) completed the study. One participant discontinued on Day 1 after dosing for reasons unrelated to the study drugs. Most participants were men (9 [64.3%]), White (12 [85.7%]), and not Hispanic or Latino (11 [78.6%]).

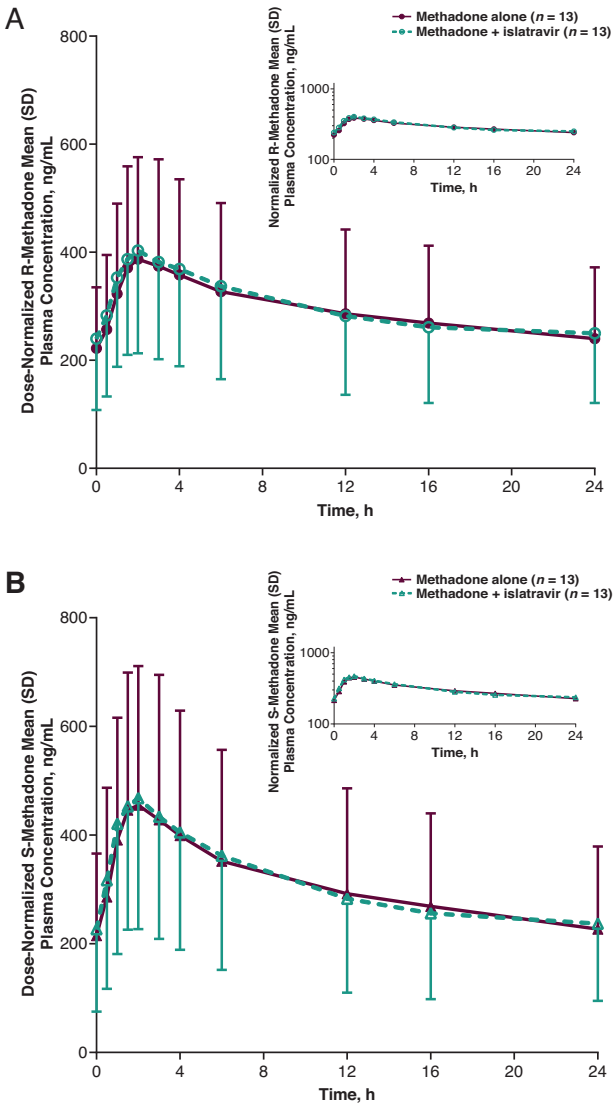

Figure 1. Arithmetic mean (±SD) plasma concentration-time profiles of (A) R-methadone and (B) S-methadone alone and after coadministration of methadone and a single oral dose of islatravir 60 mg in participants receiving methadone maintenance therapy. Main panel: linear scale; inset: semilogarithmic scale. SD, standard deviation.

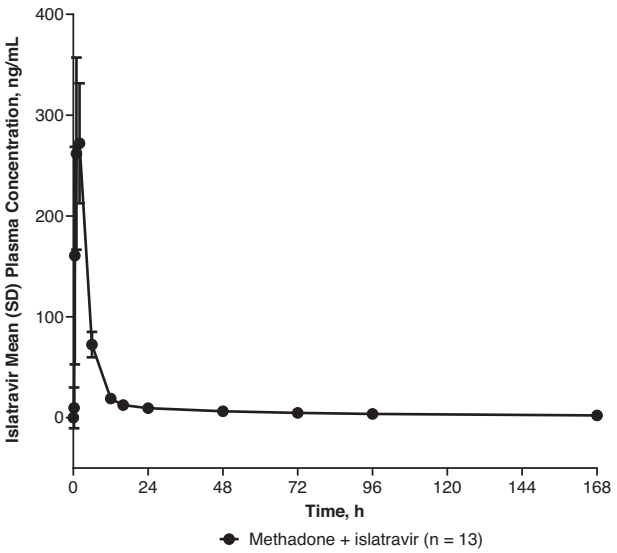

Figure 2. Arithmetic mean (±SD) plasma concentration-time profiles of islatravir after coadministration of methadone and a single oral dose of islatravir 60 mg in participants receiving methadone maintenance therapy. SD, standard deviation.

The mean age (standard deviation) of participants was 43.5 (12.0) years, and the mean body mass index (standard deviation) was 25.3 (3.6) kg/m^2.

Methadone Pharmacokinetics When Coadministered With Islatravir

The arithmetic mean plasma concentration over time profiles of R- and S-methadone were similar when administered alone or when coadministered with islatravir (Figure 1). The GMRs (90% CI) of R-methadone and S-methadone $AUC_{0\text{-}24}$/D, C_{max}/D, and C_{24}/D for methadone alone and coadministered with islatravir were all close to unity (Table 1).

Islatravir Pharmacokinetics When Coadministered With Methadone

The arithmetic mean plasma concentration over time of islatravir when coadministered with methadone is shown in Figure 2. Islatravir plasma pharmacokinetics were compared after coadministration with methadone against a single oral dose of islatravir 60 mg in a historic cohort of healthy participants from a previous study (Table 2).[23] The GMRs (90% CI) of $AUC_{0\text{-}inf}$ and C_{max} were 1.18 (0.98-1.42) and 0.86 (0.64-1.15), respectively, indicating that there is no clinically meaningful difference in islatravir exposure or peak concentrations when coadministered with methadone.

Adverse Events and Tolerability

Islatravir and methadone were well tolerated when administered concomitantly. Of the 14 participants enrolled, 6 (42.9%) experienced one or more AEs during the study; all AEs were determined by the investigator to be toxicity Grade 1 or 2 (mild or moderate, respectively), and resolved by the end of the study. Two AEs were considered drug related by the investigator: pruritus (n = 1 during methadone + islatravir treatment, 7%) and vomiting (n = 1 during methadone-alone treatment, 7%); both were Grade 1. No participants discontinued due to an AE and no serious AEs or deaths were reported. No clinically meaningful changes in electrocardiogram parameters, vital signs, or safety laboratory values were noted.

Table 1. Statistical Comparison of Dose-Normalized Plasma Pharmacokinetics of R- and S-Methadone After Administration of Methadone With and Without a Single Oral Dose of Islatravir 60 mg in Adult Participants Receiving Methadone Maintenance Therapy

	R-Methadone						S-Methadone					
	Methadone + islatravir (n = 13)		Methadone alone (n = 13)		Methadone + islatravir/ methadone alone		Methadone + islatravir (n = 13)		Methadonex alone (n = 13)		Methadone + islatravir/ methadone alone	
PK parameter	GM (95% CI)	Mean (SD)	GM (95% CI)	Mean (SD)	GMR (90% CI)	%CV[a]	GM (95% CI)	Mean (SD)	GM (95% CI)	Mean (SD)	GMR (90% CI)	% CV[a]
$AUC_{0\text{-}24}/D^b$ (ng•h/mL/mg)	63.9 (52.2-78.1)	67.1 (21.5)	61.9 (49.3-77.7)	65.9 (23.3)	1.03 (1.00-1.07)	5.1	65.1 (51.7-82.0)	70.0 (30.5)	63.1 (48.9-81.5)	69.0 (33.9)	1.03 (0.99-1.07)	5.7
C_{max}/D^b (ng/mL/mg)	3.71 (3.14-4.40)	3.85 (1.07)	3.64 (3.00-4.43)	3.82 (1.21)	1.02 (0.96-1.09)	9.1	4.31 (3.49-5.32)	4.57 (1.76)	4.25 (3.45-5.25)	4.52 (1.85)	1.01 (0.94-1.09)	10.1
C_{24}/D^b (ng/mL/mg)	2.23 (1.78-2.78)	2.36 (0.81)	2.09 (1.63-2.69)	2.25 (0.86)	1.06 (1.03-1.10)	4.5	2.07 (1.60-2.68)	2.26 (1.05)	1.91 (1.44-2.54)	2.13 (1.16)	1.08 (1.04-1.13)	6.4
$t_{max}{}^c$ (hour)	2.00 (0.67-4.00)	NA	2.00 (1.47-3.00)	NA	NA	NA	2.00 (0.67-3.00)	NA	1.50 (1.02-3.00)	NA	NA	NA

$AUC_{0\text{-}24}/D$, dose-normalized area under the plasma concentration-time curve from time 0 to 24 hours; C_{24}/D, dose-normalized concentration at 24 hours; CI, confidence interval; C_{max}/D, dose-normalized maximum plasma concentration; CV, coefficient of variation; GM, geometric mean; GMR, least squares geometric mean ratio; NA, not applicable; PK, pharmacokinetic; SD, standard deviation; t_{max}, time to maximum plasma concentration.

[a]Pseudo within-participant $\%CV = 100 \times \text{sqrt}((\sigma 2A + \sigma 2B - 2\sigma AB)/2)$, where $\sigma 2A$ and $\sigma 2B$ are the estimated variances on the log scale for the 2 treatments being compared, and σAB is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[b]Back-transformed least squares mean and CI from mixed-effects model performed on natural log-transformed values.

[c]T_{max} is represented as median (range).

Table 2. Plasma Islatravir Pharmacokinetics After Coadministration of Islatravir With Methadone in Participants Receiving Methadone Maintenance Compared With Historic Islatravir Plasma Pharmacokinetics in Healthy Participants After a Single Oral Dose of Islatravir 60 mg

	Methadone + islatravir (n = 13)		Islatravir alone (n = 6) (historical data)[23]	Methadone + islatravir/ islatravir alone
PK parameter	GM (95% CI)	Mean (SD)	GM (95% CI)	GMR (90% CI)
$AUC_{0\text{-}inf}$[a,b]	7.72 (6.79-8.77) µmol•h/L	2296 (399) ng•h/mL	6.54 (5.42-7.90) µmol/L	1.18 (0.98-1.42)
C_{max}[a]	1.02 (0.84-1.25) µmol/L	307.9 (70.4) ng/mL	1.19 (0.891-1.60) µmol/L	0.86 (0.64-1.15)
AUC_{0168}[a]	6.78 (6.12-7.52) µmol•h/L	2018 (352) ng•h/mL	ND	NA
t_{max}, (hour)[c]	2.00 (0.50-2.00)	NA	0.75 (0.50-1.00)	NA
$t_{\frac{1}{2}}$ (hour)[d]	86.9 (9.2)	87.3 (7.97)	72.0 (15.5)	NA

$AUC_{0\text{-}168}$, area under the plasma concentration-time curve from time 0 to 168 h; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GCV, geometric coefficient of variation; GM, geometric mean; GMR, least squares geometric mean ratio; NA, not applicable; ND, not determined; PK, pharmacokinetic; SD, standard deviation; $t_{\frac{1}{2}}$, apparent terminal half-life; t_{max}, time to maximum plasma concentration.

[a]Back-transformed least squares mean and CI from analysis of variance model performed on natural log-transformed values.

[b]$AUC_{0\text{-}inf}$ was estimated by extrapolation of the terminal phase of the measured profile.

[c]T_{max} is represented as median (range).

[d]$t_{\frac{1}{2}}$ is represented as GM (%GCV).

Discussion

Islatravir is an antiretroviral agent being developed for once-daily (doravirine 100 mg/islatravir 0.25 mg) and once-weekly (islatravir 2 mg/lenacapavir 300 mg) treatment of HIV-1.[11,25–27] Because islatravir could be administered to individuals with HIV receiving methadone maintenance therapy, this study was conducted to assess the potential impact of coadministration on the pharmacokinetics, AEs, and tolerability of these drugs. Single-dose administration of islatravir 60 mg did not alter methadone pharmacokinetics to a clinically relevant extent. Historically, Phase 1 drug-drug interaction trials were conducted with the anticipated maximum therapeutic dose (original high dose of islatravir, 60 mg once monthly). Given that a single high dose of islatravir did not alter methadone pharmacokinetics, it is reasonable to conclude that drug-drug interaction would not be expected at lower dose levels.

Methadone is primarily metabolized in vivo by multiple CYP enzymes, including CYP2B6, CYP3A4, and CYP2D6,[14,28] none of which is inhibited or induced by islatravir in vitro.[8] Because islatravir does not affect the activity of these CYP enzymes in vitro, islatravir was not expected to affect the metabolism of methadone in vivo, consistent with the current results that indicate a lack of interaction between the 2 agents. Because other opioids, including fentanyl and oxycodone, are also metabolized by at least some of these CYP enzymes,[20] it is likely that islatravir would not affect these compounds either. Opioids not metabolized by CYP enzymes, including morphine, are metabolized by UGT enzymes.[20] Because of a similar lack of effect of islatravir on UGT enzymes in vitro, islatravir would also be expected to have no effect on the pharmacokinetics of the compounds, although clinical data are lacking.

No stereospecific interactions between islatravir and methadone were observed because the pharmacokinetics of both methadone enantiomers were essentially unaffected by coadministration with islatravir. These results are consistent with the results of previous drug-drug interaction clinical trials in which islatravir had no meaningful effect on the pharmacokinetics of oral contraceptives[29] and specific antiretroviral agents.[1,30]

Plasma islatravir pharmacokinetics after administration alone, from historical data in healthy participants and after coadministration with methadone in methadone maintenance participants, were comparable. Although within-participant comparisons are often preferred to reduce the influence of individual factors on drug-drug interaction outcomes, the comparable methodologies and conditions used in these 2 trials supported the validity of cross-study comparisons. In both studies, islatravir pharmacokinetics were evaluated after a single dose of islatravir 60 mg using the same sampling scheme over 7 days after dosing. The assessments were made under similar, well-controlled trial conditions. The minor differences may be attributable to interstudy variation. These observations suggest that islatravir pharmacokinetics are not meaningfully affected with or in the absence of methadone coadministration, which is anticipated on the basis of the metabolic profiles of each drug.

In terms of overall AEs, coadministration of islatravir and methadone seemed to be generally well

tolerated. The incidence of AEs was generally similar between Day 1 (methadone alone) and Day 2 (coadministration of methadone with islatravir). All AEs reported in the study were toxicity Grade 1 or 2, and all reported AEs were resolved before study completion. No serious AEs were reported in the current study.

Conclusions

The AEs, tolerability, and pharmacokinetic profiles of methadone and islatravir after coadministration were comparable to that of methadone and islatravir administered alone. These results support the use of islatravir in patients receiving stable methadone maintenance therapy.

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Conflicts of Interest

Randolph P. Matthews, Wendy Ankrom, Whitney Handy, Munjal Patel, Catherine Matthews, Zhiqing Xu, S. Aubrey Stoch, Kezia Gravesande, and Marian Iwamoto are current or former employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, and may own stock and/or options in Merck & Co., Inc., Rahway, New Jersey. Shawn Searle and Howard Schwartz have no conflicts to report.

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Data Availability Statement

The data-sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to: dataaccess@merck.com.

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Supplemental Information

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