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No pharmacokinetic interaction between islatravir and methadone

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Background

- HIV-1 infection remains a worldwide health issue, with an estimated 38 million individuals infected globally and approximately 1.5 million new infections worldwide in 2020[1]
- According to the Centers for Disease Control and Prevention (CDC), HIV diagnoses among people who inject drugs have remained stable in recent years, but use of injectable drugs continues to be a significant risk factor for becoming infected with HIV[2]
- Islatravir (MK-8591) is a deoxyadenosine analog in development for the treatment of HIV-1 infection (**Table 1**)[3,4]
- Persons living with HIV may benefit from islatravir, and a segment of this population may also be receiving methadone maintenance therapy

Table 1. Summary of islatravir characteristics

Mechanism of action	Deoxyadenosine analog with multiple mechanisms of action (reverse transcriptase translocation inhibition and delayed viral DNA chain termination inhibition)[5,6]
	Activity against common NRTI- and NNRTI-resistant variants[7]
PK and metabolism	Apparent plasma $t_{½}$ of 49-61 hours[4]
	Phosphorylated intracellularly to its active form (islatravir-triphosphate), which has a long intracellular $t_{½}$ of 177-209 hours[7,8]
	Eliminated via urinary excretion of parent and metabolism by adenosine deaminase[8,9]
	Not expected to be victim of inhibitors/inducers, nor an inhibitor or inducer of major metabolic enzymes or transporters[9]
Safety	Single and multiple doses of oral islatravir have been generally well tolerated in phase 1 and phase 2 studies[4,10]

NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PK, pharmacokinetics; t½, apparent terminal half-life.

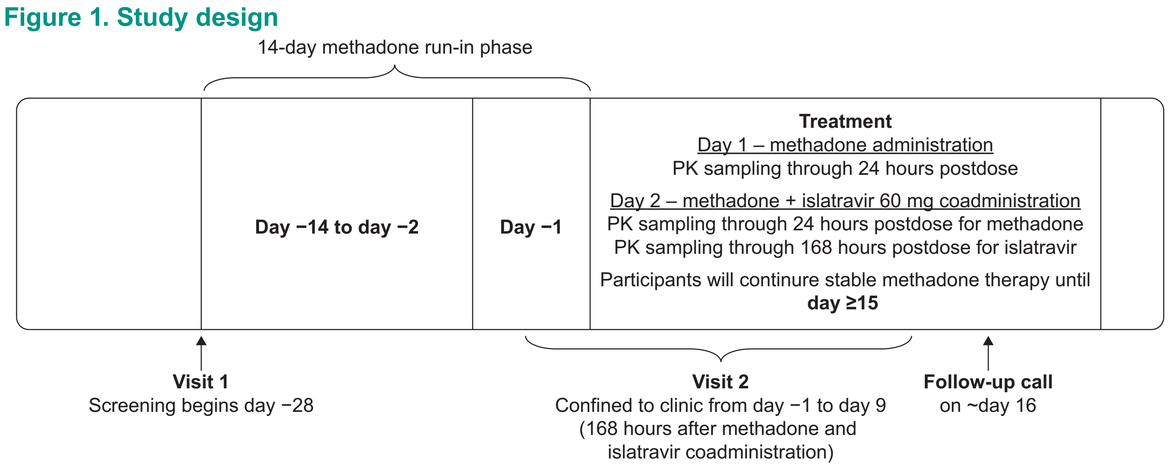
Objective

- A 2-way drug-drug interaction study was conducted to assess methadone and islatravir safety and pharmacokinetics (PK) with coadministration

Methods

- This open-label phase 1 study (MK-8591-029; NCT04568603) enrolled adults aged 18-65 years receiving stable once-daily methadone maintenance therapy (20-200 mg) to receive a single 60-mg dose of islatravir (**Figure 1**)

Figure 1. Study design



PK, pharmacokinetics.

- PK assessments included dose-normalized area under the concentration-time curve from zero to 24 hours (AUC_{0-24}), maximum concentration (C_{max}), trough concentration at 24 hours (C_{24}), and time to maximum concentration (T_{max}) of plasma methadone (R- and S-enantiomers) and plasma islatravir
- Safety assessments included adverse events (AEs), vital signs (heart rate, blood pressure, respiration rate, and oxygen saturation), electrocardiogram parameters, and laboratory tests
- The study was approved by the appropriate independent review boards, and all participants provided written informed consent

Results

Study population

- 14 participants were enrolled in the study; 13 participants (92.9%) completed the study; 1 participant discontinued on day 1 for reasons unrelated to study medications (**Table 2**)

Table 2. Participant demographics and baseline characteristics

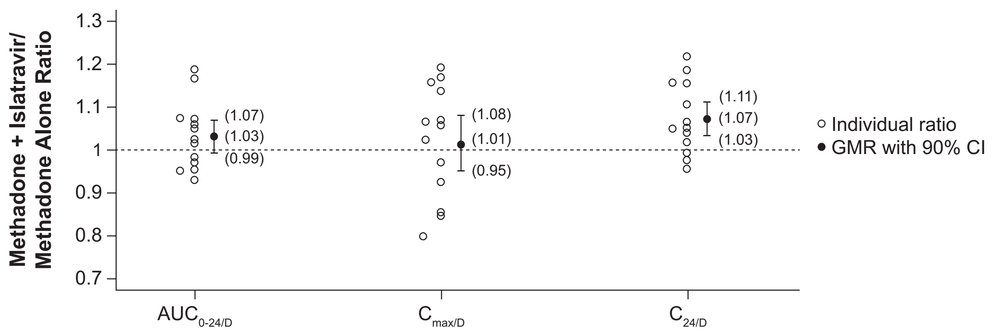
Parameter	N = 14
Male, n (%)	9 (64.3)
Age, median (range), years	42 (26-63)
BMI, median (range), kg/m²	24.3 (19.6-32.4)
Race, n (%)	
Native Hawaiian or other Pacific Islander	1 (7.1)
White/Asian	1 (7.1)
White	12 (85.7)
Ethnicity, n (%)	
Hispanic or Latino	3 (21.4)

BMI, body mass index.

Pharmacokinetics

- The statistical comparison of dose-normalized total methadone, R-methadone, and S-methadone plasma PK following the administration of an oral maintenance dose of methadone (20-200 mg) with and without a single oral dose of islatravir 60 mg in methadone maintenance participants is presented in **Figure 2** and **Tables 3 and 4**

Figure 2. Individual dose-normalized total methadone AUC_{0-24}, C_{max}, and C_{24} ratios (methadone + islatravir/methadone alone), GMRs, and 90% CIs



$AUC_{0-24/D}$, dose-normalized area under the concentration-time curve from 0 to 24 hours; $C_{24/D}$, dose-normalized trough concentration at 24 hours; $C_{max/D}$, dose-normalized maximum concentration; GMR, least-squares geometric mean ratio.
y-axis values are logarithmically spaced.

Table 3. Statistical comparison of dose-normalized plasma PK of R-methadone following the administration of an oral maintenance dose of methadone (20-200 mg) with and without a single oral dose of islatravir 60 mg in adult participants

Parameter	Methadone + islatravir N = 13 GM (95% CI)	Methadone alone N = 13 GM (95% CI)	Methadone + islatravir/ methadone alone GMR (90% CI)	%CV[a]
$AUC_{0-24/D}$,[b] ng·hour/mL/mg	63.9 (52.2, 78.1)	61.9 (49.3, 77.7)	1.03 (1.00, 1.07)	5.1
$C_{max/D}$,[b] ng/mL/mg	3.71 (3.14, 4.40)	3.64 (3.00, 4.43)	1.02 (0.96, 1.09)	9.1
$C_{24/D}$,[b] ng/mL/mg	2.23 (1.78, 2.78)	2.09 (1.63, 2.69)	1.06 (1.03, 1.10)	4.5
T_{max},[c] hours	2.00 (0.67, 4.00)	2.00 (1.47, 3.00)	NA	NA

$AUC_{0-24/D}$, dose-normalized area under the concentration-time curve from 0 to 24 hours; $C_{24/D}$, dose-normalized trough concentration at 24 hours; $C_{max/D}$, dose-normalized maximum concentration; CV, coefficient of variation; GM, geometric mean; GMR, least-squares geometric mean ratio; NA, not applicable; T_{max}, time to maximum concentration.
[a]Pseudo within-participant %CV = 100·sqrt ((σ2A + σ2B − 2σAB)/2), where σ2A and σ2B 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]Median (minimum, maximum) is reported.

Table 4. Statistical comparison of dose-normalized plasma PK of S-methadone following the administration of an oral maintenance dose of methadone (20-200 mg) with and without a single oral dose of islatravir 60 mg in adult participants

Parameter	Methadone + islatravir N = 13 GM (95% CI)	Methadone alone N = 13 GM (95% CI)	Methadone + islatravir/ methadone alone GMR (90% CI)	%CV[a]
$AUC_{0-24/D}$,[b] ng·hour/mL/mg	65.1 (51.7, 82.0)	63.1 (48.9, 81.5)	1.03 (0.99, 1.07)	5.7
$C_{max/D}$,[b] ng/mL/mg	4.31 (3.49, 5.32)	4.25 (3.45, 5.25)	1.01 (0.94, 1.09)	10.1
$C_{24/D}$,[b] ng/mL/mg	2.07 (1.60, 2.68)	1.91 (1.44, 2.54)	1.08 (1.04, 1.13)	6.4
T_{max},[c] hours	2.00 (0.67, 3.00)	1.50 (1.02, 3.00)	NA	NA

$AUC_{0-24/D}$, dose-normalized area under the concentration-time curve from 0 to 24 hours; $C_{24/D}$, dose-normalized trough concentration at 24 hours; $C_{max/D}$, dose-normalized maximum concentration; CV, coefficient of variation; GM, geometric mean; GMR, least-squares geometric mean ratio; NA, not applicable; T_{max}, time to maximum concentration.
[a]Pseudo within-participant %CV = 100·sqrt ((σ2A + σ2B − 2σAB)/2), where σ2A and σ2B 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]Median (minimum, maximum) is reported.

- The statistical comparison of islatravir plasma PK following the administration of a single oral dose in healthy participants (historical data obtained from protocol MK-8591-026 [healthy control group])[11] and following coadministration of an oral maintenance dose of methadone and islatravir 60 mg in methadone maintenance participants is presented in **Table 5**

Table 5. Statistical comparison of plasma PK of islatravir following the administration of a single oral dose of islatravir 60 mg in healthy participants and coadministration of an oral maintenance dose of methadone (20-200 mg) and islatravir 60 mg in adult methadone-maintenance participants

Parameter	Methadone + islatravir N = 13 GM (95% CI)	Islatravir alone (historical data) N = 6 GM (95% CI)	Methadone + islatravir/ islatravir alone (historical data) GMR (90% CI)
$AUC_{0-\infty}$,[a] hour·µmol/L	7.72 (6.79, 8.77)	6.54 (5.42, 7.90)	1.18 (0.98, 1.42)
C_{max},[a] µmol/L	1.02 (0.84, 1.25)	1.19 (0.89, 1.60)	0.86 (0.64, 1.15)
AUC_{0-24},[a] hour·µmol/L	4.65 (4.19, 5.17)	ND	NA
AUC_{0-168},[a] hour·µmol/L	6.78 (6.12, 7.52)	ND	NA
T_{max},[b] hours	2.00 (0.50, 2.00)	0.75 (0.50, 1.00)	NA
$T_{½}$, hours (%GCV)	86.9 (9.2)	72.0 (15.5)	NA

ANOVA, analysis of variance; $AUC_{0-\infty}$, area under the concentration-time curve from 0 to infinite time; C_{max}, maximum concentration; GCV, geometric coefficient of variation; GM, geometric mean; GMR, least-squares geometric mean ratio; NA, not applicable; ND, not determined; $T_{½}$, apparent terminal half-life; T_{max}, time to maximum concentration.
[a]Back-transformed least-squares mean and CI from ANOVA model performed on natural log-transformed values.
[b]Median (minimum, maximum) is reported.

Safety

- Islatravir and methadone were generally well tolerated when administered concomitantly
  - Six participants reported 8 AEs, all grade 1 or 2 that resolved by end of study
  - Two AEs were considered drug related by the investigator: pruritus (n = 1, 7%) and vomiting (n = 1, 7%)
- No clinically meaningful changes in electrocardiograms, vital signs, or safety laboratory values were noted

Conclusions

- Coadministration of islatravir and methadone did not meaningfully affect the PK of either compound
- Coadministration of islatravir and methadone was generally well tolerated

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