Islatravir (MK-8591) has no meaningful effect on the pharmacokinetics of atorvastatin and metformin following coadministration

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Background

- Islatravir (ISL), a nucleoside reverse transcriptase translocation inhibitor (NRTTI), inhibits reverse transcriptase by multiple actions, including translocation inhibition and delayed chain termination, and it is being studied as treatment for HIV-1[1-4]
- Because people living with HIV often have comorbidity, such as dyslipidemia and/or type 2 diabetes mellitus, we investigated the effects of ISL coadministration on atorvastatin (ATV) and metformin (MET) pharmacokinetics (PK). Results of a previous bioequivalence study showed no clinically relevant interactions between ATV and MET,[5] supporting coadministration of these compounds in the current study
- An open-label, 2-period, fixed-sequence design was chosen for this study to evaluate the potential 1-way drug-drug interaction (DDI) of ISL on ATV and MET
- An ISL dose of 60 mg was assessed because a 60-mg monthly dose was the highest dose being studied in phase 3 trials at the time of the current study, and a lack of effect at 60 mg would support a lack of effect at lower doses
- Based on several clinical ISL DDI studies, as well as preclinical drug interaction data, no interaction between ISL and ATV or MET was expected[6-10]

Objective

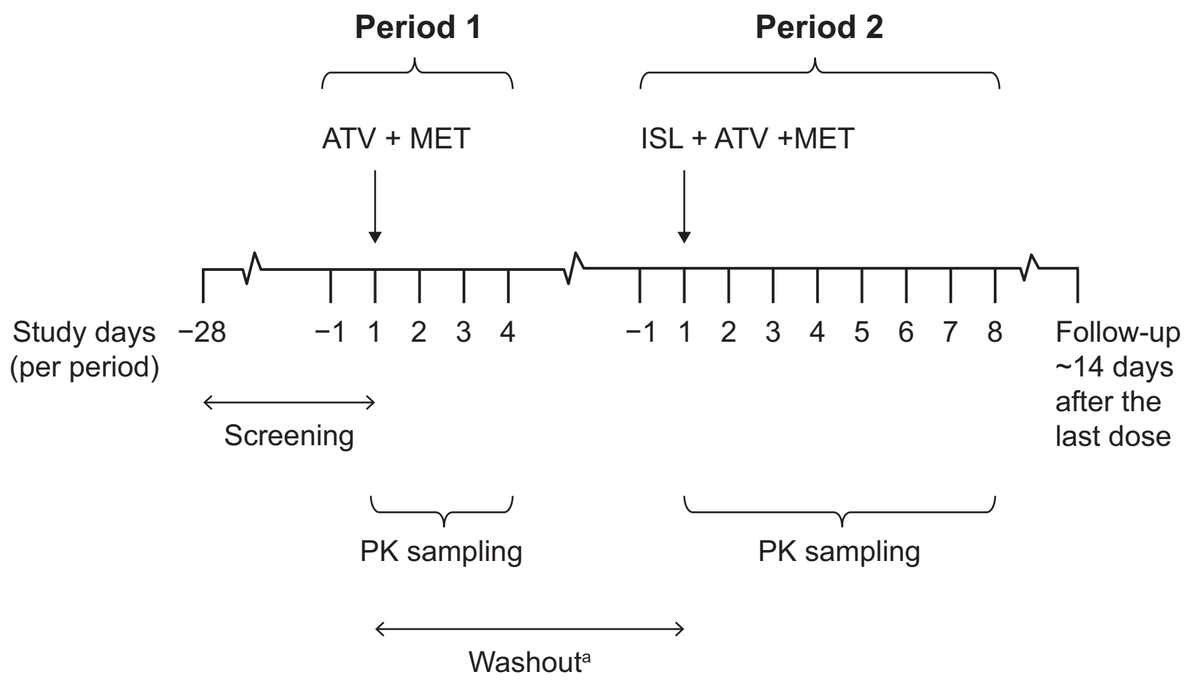
- To evaluate the effects on the plasma exposure (area under the concentration-time curve from 0 hours to infinity [$AUC_{0-\infty}$]) of ATV and MET when coadministered with a single oral dose of ISL

Methods

Study population

- Protocol MK-8591-040 was a nonrandomized, 2-period, fixed-sequence, open-label, phase 1 DDI study of the effects of ISL on ATV and MET PK in healthy adult participants (**Figure 1**)

Figure 1. Study design



[a]There will be at least 5 days of washout between dosing in each period.

- In period 1, participants were coadministered a single dose of ATV 20 mg + MET 1000 mg
- After a 5-day washout period, participants received ATV 20 mg + MET 1000 mg coadministered with a single oral dose of ISL 60 mg in period 2

Pharmacokinetics

- Blood samples were collected up to 72 hours after dosing in each period to characterize the plasma concentrations and PK of ATV and MET
- In period 2, serial blood sampling was collected up to 168 hours after dosing to characterize ISL PK
- PK parameters assessed were $AUC_{0-\infty}$, maximal concentration (C_{max}), and trough concentration at 24 hours (C_{24})
- Safety and tolerability were monitored throughout the study

Results

Study population

- 14 participants (10 males, 4 females) aged 22-55 years were enrolled and completed the study (**Table 1**)

Table 1. Participant demographics and baseline characteristics

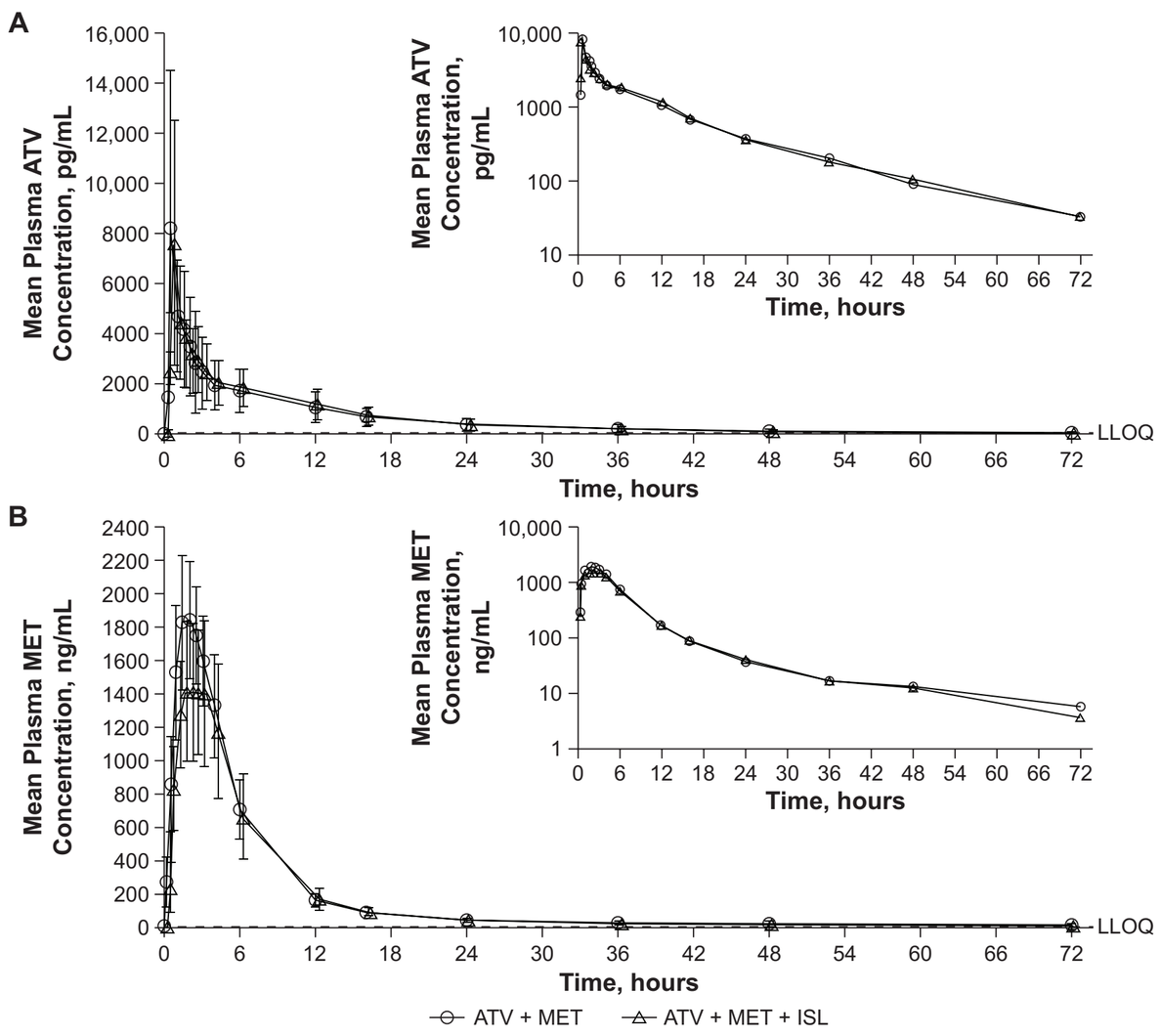
Parameter	N = 14
Male, n (%)	10 (71.4)
Female, n (%)	4 (28.6)
Age, median (range), years	33.5 (22-55)
BMI, mean (range), kg/m²	28.2 (23.0-31.0)
Race, n (%)	
Asian	1 (7.1)
Black/African American	1 (7.1)
White	12 (85.7)
Ethnicity, n (%)	
Hispanic or Latino	11 (78.6)
Not Hispanic or Latino	3 (21.4)

BMI, body mass index.

Pharmacokinetics

- The arithmetic mean plasma concentration-time profiles of ATV and MET are shown in **Figures 2A and 2B**, respectively, for healthy participants who received ATV and MET with or without ISL

Figure 2. Plasma concentration-time profiles of ATV[a] (A) and MET[b] (B) after an oral dose of ATV and MET with or without a single dose of ISL



LLOQ, lower limit of quantitation.

[a]The arithmetic mean at time 0 was presented as 0 for intervention ATV + MET + ISL because <50% of participants had a quantifiable concentration ≥ LLOQ (10.00 pg/mL). Inset = semi-log scale.

[b]The arithmetic mean at time 0 was presented as 0 for intervention ATV + MET + ISL because <50% of participants have a quantifiable concentration ≥ LLOQ (2.00 ng/mL). Inset = semi-log scale.

- Summary statistics and statistical comparisons are presented in **Tables 2 and 3** for ATV and MET plasma PK after administration of a single oral dose of ATV and MET with and without a single oral dose of ISL in healthy participants

Table 2. ATV plasma PK after an oral dose of ATV and MET with and without a single oral dose of ISL

	ATV + MET n = 14	ATV + MET + ISL n = 14	ATV + MET + ISL/ATV + MET n = 14	
	GM (95% CI)	GM (95% CI)	GMR (90% CI)	%CV[a]
ATV PK parameters				
$AUC_{0-\infty}$,[b] hour·pg/mL	35,400 (26,500-47,400)	37,000 (28,800-46,700)	1.04 (1.00-1.10)	7.1
C_{max},[b] pg/mL	8200 (5890-11,400)	7080 (5150-9740)	0.86 (0.72-1.04)	27.4
C_{24},[b] pg/mL	312 (220-443)	317 (230-437)	1.01 (0.93-1.10)	12.5

$AUC_{0-\infty}$, area under the concentration-time curve from 0 hours to infinity; C_{24}, trough concentration at 24 hours; C_{max}, maximal concentration; CV, coefficient of variation; GM, geometric least-squares mean; GMR, geometric least-squares mean ratio.

[a]Pseudo within-participant %CV = 100 × √ [(σA² + σB² − 2σAB)/2], where σA² and σB² 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.

Table 3. MET plasma PK after a single oral dose of ATV and MET with or without a single oral dose of ISL

	ATV + MET n = 14	ATV + MET + ISL n = 14	ATV + MET + ISL/ATV + MET n = 14	
	GM (95% CI)	GM (95% CI)	GMR (90% CI)	%CV[a]
MET PK parameters				
$AUC_{0-\infty}$,[b] hour·ng/mL	11,500 (10,600-12,500)	10,000 (8550-11,700)	0.87 (0.79-0.96)	15.0
C_{max},[b] ng/mL	1970 (1770-2190)	1580 (1350-1830)	0.80 (0.70-0.91)	19.6
C_{24},[b] ng/mL	33.5 (29.6-37.8)	37.7 (34.1-41.7)	1.13 (1.00-1.26)	17.2

$AUC_{0-\infty}$, area under the concentration-time curve from 0 hours to infinity; C_{24}, trough concentration at 24 hours; C_{max}, maximal concentration; CV, coefficient of variation; GM, geometric least-squares mean; GMR, geometric least squares mean ratio.

[a]Pseudo within-participant %CV = 100 × √ [(σA² + σB² − 2σAB)/2], where σA² and σB² 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.

- Coadministration of ATV and MET with a single oral dose of ISL did not have a meaningful effect on the PK profiles of the metabolites of ATV: ortho-hydroxy (2-OH) ATV and para-hydroxy (4-OH) ATV (data not shown)
- ISL PK was obtained to ensure sufficient ISL exposures were achieved after the 60-mg single dose. The ISL PK data seemed comparable with historical ISL 60-mg (data not shown)

Safety

- Coadministration of ATV and MET with a single oral dose of ISL was generally well tolerated
  - Four participants reported adverse events (AEs) during the study; 1 participant reported AEs that were mild to moderate. All AEs resolved before study completion. No clinically meaningful relationships were observed for changes in clinical laboratory values, vital signs, or safety electrocardiogram parameter values as a function of study intervention

Conclusions

- Coadministration of ATV and MET with a single oral dose of ISL did not have a clinically meaningful effect on the PK profiles of either ATV (including ATV metabolites 2-OH and 4-OH) or MET
- Coadministration of ATV and MET with a single oral dose of ISL was generally well tolerated

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