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Characterization of the absorption, metabolism, and excretion of islatravir, an HIV nucleoside reverse transcriptase translocation inhibitor, in humans

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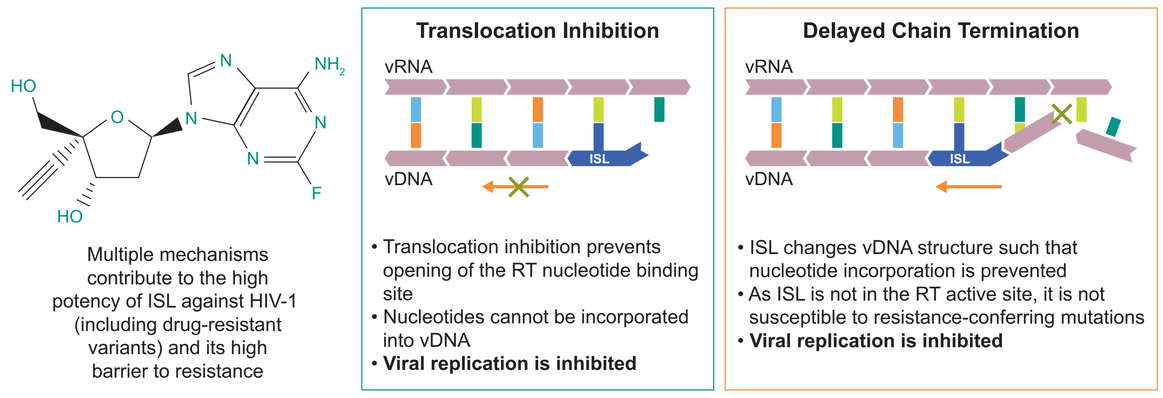
Background

- Islatravir (MK-8591) is a deoxyadenosine analog in development for the treatment of HIV-1 infection (**Figure 1**)[1,2]

Figure 1. Islatravir, a deoxyadenosine analog with multiple mechanisms of action[1,3,4]



ISL, islatravir; RT, reverse transcriptase; vDNA, viral DNA; vRNA, viral RNA.

- Following single-dose oral administration, islatravir is rapidly absorbed, with a median time of maximum plasma concentration (T_{max}) of 0.5 hours and an apparent plasma half-life ($t_{½}$) of 49-61 hours[2]
- After cellular uptake, islatravir is phosphorylated to its active form (islatravir-triphosphate), which has a long intracellular $t_{1/2}$ of 177-209 hours[5,6]
- Nonclinical data demonstrate that 4′-ethynyl-2-fluorodeoxyinosine (M4) is the major metabolite of islatravir[7]
- Previous clinical studies have demonstrated that unchanged islatravir is excreted in urine,[6,7] and M4 is also expected to be excreted renally[8]

Objective

- A human mass balance study was conducted to assess the absorption, metabolism, and excretion of islatravir, providing data on the route of elimination and metabolic profile of islatravir

Methods

- This open-label phase 1 study (MK-8591-025) was performed in healthy adult participants aged 18-55 years with a body mass index (BMI) >18 to ≤32 kg/m^2
- Participants were administered a single 10-mg dose of [^{14}C]islatravir (~62 µCi)
- Blood samples were collected at predose and at 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours postdose for quantification of plasma total radioactivity, islatravir pharmacokinetics, and metabolite profiling
- Urine was collected for total radioactivity analysis and metabolite profiling at predose (within 12 hours before dosing); at 0-4, 4-8, 8-12, 12-24, and 24-48 hours; and every 24 hours on days 3 through 14 (336 hours) postdose
- Fecal samples were obtained within 24 hours before dose administration, and full collection occurred every 24 hours through day 14 (336 hours) postdose
- Total radioactivity and metabolite profiling in excreta and plasma samples were performed via liquid chromatography–high-resolution mass spectrometry (LC-HRMS) with radiometric detection
- Safety assessments included adverse events (AEs), discontinuations, vital signs, electrocardiograms, and laboratory tests

Results

Study population

- 6 healthy male participants were included in the analyses; **Table 1** summarizes participant demographics and baseline characteristics

Table 1. Participant demographics and baseline characteristics

	N = 6
Male, n (%)	6 (100)
Age, mean (range), years	38 (29-54)
Weight, mean (SD), kg	84.0 (9.5)
BMI, mean (SD), kg/m^2	26.7 (3.6)
Race, n (%)	
Asian	1 (16.7)
Black or African American	4 (66.7)
White	1 (16.7)
Ethnicity, n (%)	
Not Hispanic or Latino	6 (100)

BMI, body mass index; SD, standard deviation.

[^{14}C]Islatravir absorption, metabolism, and excretion

- A single oral dose of [^{14}C]islatravir 10 mg (~62 µCi) administered to healthy adult male participants was absorbed, with a median plasma T_{max} of 0.50 hours for both islatravir and total radioactivity (**Table 2**)
  - Approximately 29% of the total radioactivity area under the concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24}$) in plasma was from islatravir, and approximately 35% of the total radioactivity maximum concentration (C_{max}) was from islatravir

Table 2. Summary statistics of plasma islatravir compared with radioactivity following single 10-mg dose administration of [^{14}C]islatravir in healthy male participants (N = 6)

Parameter	GM (95% CI)	Islatravir/total radioactivity GMR (95% CI)
Islatravir $AUC_{0\text{-}24}$,[a] hour·ng/mL	198 (181-217)	0.29 (0.27-0.32)
Total radioactivity $AUC_{0\text{-}24}$,[b] hour·ngEq/mL	676 (617-741)	
Islatravir C_{max},[a] ng/mL	77.2 (63.7-93.7)	0.35 (0.29-0.43)
Total radioactivity C_{max},[a] ngEq/mL	218 (180-265)	
Islatravir C_{24},[a] ng/mL	1.08 (0.969-1.21)	0.11 (0.09-0.12)
Total radioactivity C_{24},[a] ngEq/mL	10.0 (9.00-11.2)	
Islatravir T_{max},[b] hours	0.50 (0.50-0.50)	NA
Total radioactivity T_{max},[b] hours	0.50 (0.50-0.50)	NA

$AUC_{0\text{-}24}$, area under the concentration-time curve from 0 to 24 hours; C_{24}, trough concentration at 24 hours; C_{max}, maximum concentration; GM, geometric least-squares mean; GMR, geometric least-squares mean ratio; NA, not applicable; T_{max}, time to maximum concentration.

[a]Back-transformed least-squares mean and CI from linear mixed-effects model performed on natural log-transformed values.
[b]Median (minimum, maximum) is reported.

- Overall, an arithmetic mean of 98% of the radioactive dose was recovered, with 91% recovered in urine and 6% recovered in feces (**Table 3**)

Table 3. Arithmetic mean percentage of radioactive dose recovered following single 10-mg dose administration of [^{14}C]islatravir in healthy male participants (N = 6)

	Urine	Feces	Total
Fraction of radioactivity recovery, mean % (95% CI)	91.4 (87.9-95.0)	6.3 (3.7-8.9)	97.7 (96.4-99.0)

[^{14}C]Islatravir metabolite profiling

- The major metabolite in AUC-proportional pooled plasma was M4, with 31% of the radioactivity attributable to M4 and 58% attributable to parent islatravir (**Table 4; Figure 2**)

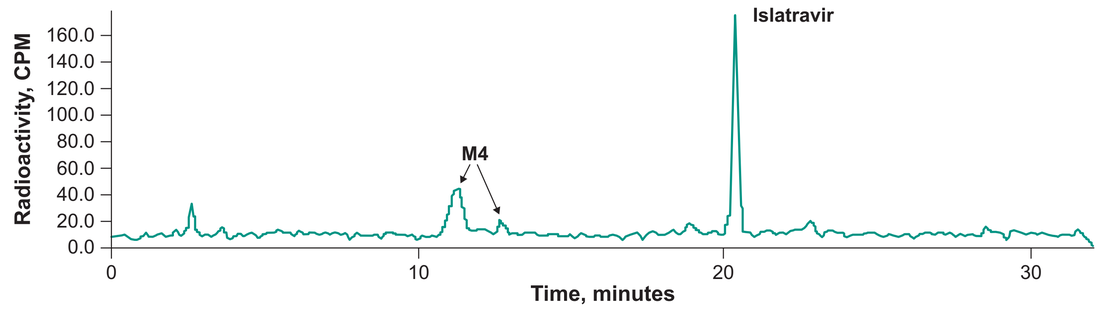
Table 4. Summary of metabolites recovered in pooled plasma, urine, and feces following single 10-mg dose administration of [^{14}C]islatravir in healthy male participants

	Percentage of total radioactivity (dose percentage)		
Component	Plasma (0-24 hours)	Urine (0-96 hours)[a]	Feces (0-144 hours)
Islatravir	58	35 (32.0)	ND
M4	31	58 (53.0)	Trace[b]
M6	ND	Trace[b]	ND
M7	ND	Trace[b]	ND
Unidentified metabolites	<7	1 (0.9)	ND

ND, not detected.

[a]Values in parentheses represent the percentage of the dose calculated using the total percentage of dose recovered in urine over 0-336 hours.
[b]Trace metabolites were detected by high-resolution mass spectrometry only.

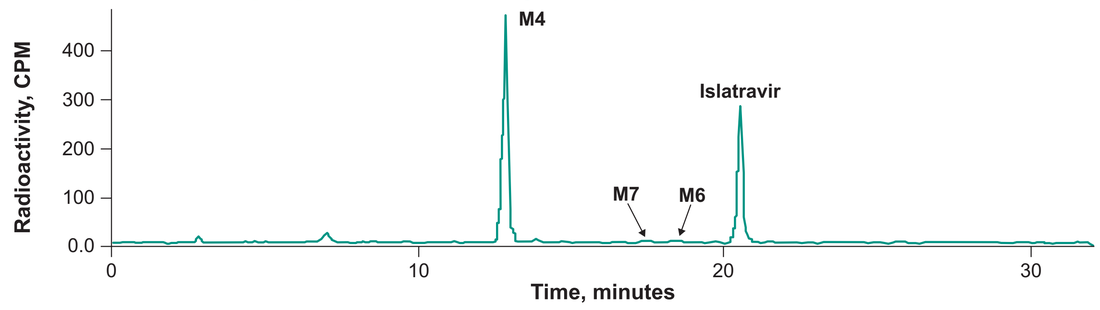
Figure 2. Representative radiochromatogram of pooled plasma (0-24 hours in proportion to $AUC_{0\text{-}24}$) following single 10-mg dose administration of [^{14}C]islatravir in healthy male participants



$AUC_{0\text{-}24}$, area under the concentration-time curve from 0 to 24 hours; CPM, counts per minute.
M4 was observed as 2 peaks; the splitting was attributed to a matrix effect that resulted from the ~16-fold concentration of the pooled plasma sample used in this radiometric analysis.

- Other metabolic products were observed in trace quantities and are thus not likely significant contributors to the overall elimination of islatravir (**Figure 3**)

Figure 3. Representative radiochromatogram of pooled urine (0-96 hours) following single 10-mg dose administration of [^{14}C]islatravir in healthy male participants



CPM, counts per minute.
Metabolites M6 and M7 were detected by high-resolution mass spectrometry analysis only.

- In urine, the majority of the radioactivity was assigned to M4, accounting for 53% of the administered dose, while unchanged islatravir accounted for 32% of the dose

Safety

- A single dose of [^{14}C]islatravir 10 mg was generally well tolerated
  - There were no AEs or discontinuations
  - There were no findings of significance with respect to vital signs, electrocardiograms, and laboratory safety results before and after [^{14}C]islatravir treatment

Conclusions

- Following oral administration of a single 10-mg dose of [^{14}C]islatravir to healthy male participants, islatravir was well absorbed, and unchanged islatravir was the major circulating species
  - The lower levels of islatravir in plasma noted in **Table 2** likely reflect an overestimation of total radioactivity in the first 24 hours due to limitations in the radioactivity assay
- M4 was the major metabolite in plasma, indicating that the major route of metabolism for islatravir is oxidative deamination[7]
  - Other metabolic products were present in trace amounts and are thus not likely significant contributors to islatravir metabolism
- M4 was the major drug-related species in urine, with a significant amount of unchanged parent islatravir also excreted in urine
- A 10-mg dose of islatravir was found to be generally well tolerated in healthy male adults

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