00432

Islatravir does not prolong QTc in a thorough QT study in healthy participants

Randolph P. Matthews[1]; Yang Liu[1]; Catherine Matthews[1]; Kristin Butterfield[1]; Terry O'Reilly[2]; S. Aubrey Stoch[1]; Marian Iwamoto[1]

[1]Merck & Co., Inc., Kenilworth, NJ, USA; [2]Celerion, Tempe, AZ, USA

Background

- Islatravir is a nucleoside reverse transcriptase translocation inhibitor under clinical investigation for treatment and prevention of HIV-1
  - Administered as part of an oral once-daily (QD) regimen and as part of a once-weekly (QW) regimen[1,2]
  - Used for pre-exposure prophylaxis (PrEP) with once-monthly (QM) oral administration or subdermal implantation[3,4]
- Islatravir has been generally well tolerated up to single doses of 400 mg[1]; however, in recent clinical studies,[5] decreases in total lymphocyte and CD4+ T-cell counts were observed in some participants who received islatravir
- Nonclinical data suggest that islatravir is not expected to change cardiac repolarization
  - In the human ether-à-go-go-related gene (hERG) current voltage clamp electrophysiology assay, islatravir inhibited hERG current at concentrations well above the projected maximum plasma concentration (C_{max}) levels for QD, QW, and QM dosing (data on file)
  - In preclinical toxicity studies, a slight decrease in the heart rate–corrected QT interval (QTc) was observed in anesthetized guinea pigs administered high doses of islatravir, whereas no effect of islatravir on QTc was seen in monkey telemetry studies (data on file)

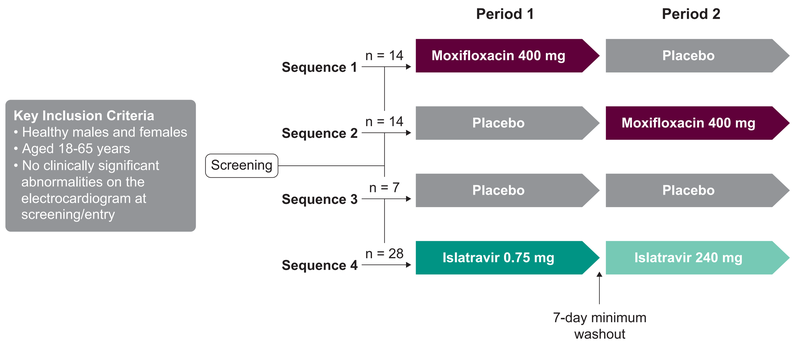
Objectives

- To assess potential QT prolongation from use of islatravir at a daily therapeutic dose of 0.75 mg and a supratherapeutic dose of 240 mg in healthy study participants
- To evaluate the pharmacokinetics of islatravir, metabolite M4, and moxifloxacin

Methods

- Protocol 032 is a double-blind, placebo-controlled, phase 1 trial evaluating the effect of single doses of islatravir 0.75 mg and 240 mg on the QTc of healthy adults (**Figure 1**)

Figure 1. Study design



Assessment and statistical analysis

- Cardiodynamics: Participants were given a Holter monitor to collect readings before dosing until 24 hours after dosing; they were then scheduled for triplicate 12-lead electrocardiogram assessments
- Pharmacokinetics: Plasma samples for islatravir, metabolite M4, and moxifloxacin concentrations were collected before dosing and at specified time points after dosing, along with electrocardiogram assessments
- An exposure-response model was used to characterize the relationship between islatravir or moxifloxacin concentrations and change in population-corrected QT interval (ΔQTcP)
  - ΔQTcP was evaluated using a linear mixed-effects model, with fixed effects for treatment and time point and continuous effects for islatravir or moxifloxacin plasma concentration and centered baseline QTcP; a double-compound symmetry covariance structure was assumed
  - An estimate of the expected mean effect, upper 1-sided 95% confidence limit of placebo-corrected change from baseline QTcP (ΔΔQTcP) for islatravir, and lower 1-sided 95% confidence limit of ΔΔQTcP for moxifloxacin were computed at the observed geometric mean C_{max}
  - A supportive model-based time point by time point analysis was conducted for islatravir and moxifloxacin using a linear mixed-effects model to estimate the mean between-treatment difference (moxifloxacin-placebo and islatravir-placebo) in QTcP change from baseline at each dose level and each time point
  - The least squares mean (LSM; 95% CI) of QTcP change from baseline and the least squares difference (90% CI) between treatment and placebo groups were obtained from the LSMEANS statement (SAS; SAS Institute)
- Safety: All participants who received 1 dose of study drug were included in safety/tolerability assessments

Results

Study disposition and baseline characteristics

Table 1. Disposition of participants

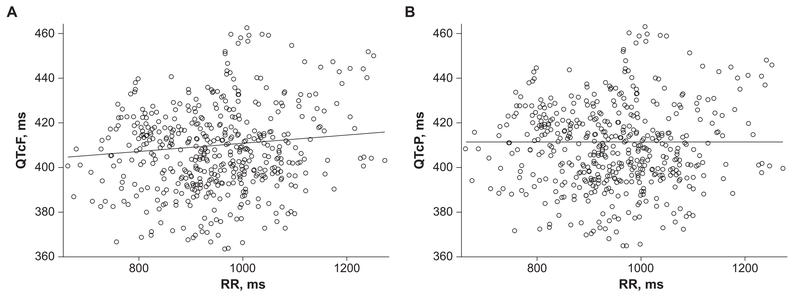
Disposition	n (%)
Randomly assigned	63 (100)
Completed study medication	59 (93.7)
Discontinued study medication	4 (6.3)
Due to an AE	4 (6.3)

AE, adverse event.

- 63 randomly assigned participants (safety population) received at least 1 dose of study drug (**Table 1**)
  - 28 received moxifloxacin 400 mg (sequences 1 and 2); 26 (92.9%) received all doses and completed the study
  - 7 received only placebo (sequence 3); 7 (100.0%) completed the study
  - 28 received islatravir (28 received 0.75 mg; 26 continued to 240 mg) (sequence 4); 26 (92.9%) received all doses and completed the study
- Most participants were female (76.2%), White (88.9%), and Hispanic or Latino (77.8%)
- Median age was 41 years (range, 19-64 years)

Cardiodynamic and pharmacokinetic outcomes

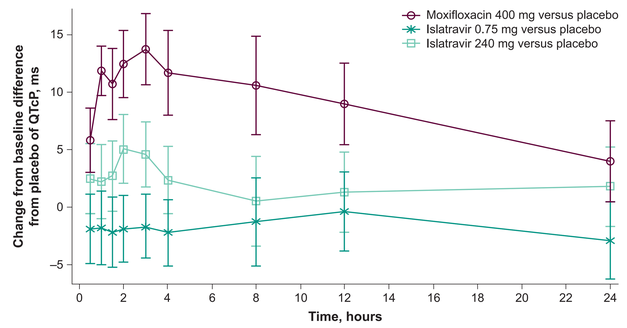
Figure 2. Individual QTcF (milliseconds) and QTcP (milliseconds) versus R wave to R wave (milliseconds) values obtained during placebo and drug-free time points with estimated linear regression line



QTcF, Fridericia's formula-corrected QT interval; QTcP, population-corrected QT interval; RR, R wave to R wave.

- QTcF (**Figure 2A**) was an inadequate correction factor because the 95% CI for the estimated slope did not contain zero
- QTcP (**Figure 2B**) correction was adequate, with a slope estimate of −0.000019 with a 95% CI of the slope containing zero

Figure 3. Islatravir and moxifloxacin QTcP change from baseline difference from placebo (LSM difference with 90% CI) by time point and treatment



LSM, least squares mean; QTcP, population-corrected QT interval.

Table 2. Predicted placebo-corrected change from baseline in QTcP at C_{max} after single-dose oral administration

Analyte	Dose mg	n	Predicted ΔΔQTcP, ms	
			LSM	90% CI[a]
Islatravir	0.75	28	−0.73	−3.19 to 1.73
	240	26	0.03	−2.89 to 2.96
Moxifloxacin	400	28	13.84	12.10 to 15.58

ΔΔQTcP, placebo-corrected change from baseline in QTcP; C_{max}, maximum plasma concentration; LSM, least squares mean; QTcP, population-corrected QT interval.
[a]The 2-sided 90% CI is equivalent to a 1-sided upper 95% CI for islatravir and 1-sided lower 95% CI for moxifloxacin.

- Administration of a single dose of islatravir 0.75 mg (n = 28) or 240 mg (n = 26) did not prolong the QTc to a clinically significant degree (**Table 2**)
- Administration of a single 400-mg dose of moxifloxacin (n = 28) was associated with an increase in the QTc
- The ΔΔQTcP associated with islatravir 0.75 mg and 240 mg was <10 ms at all time points

Table 3. Summary statistics of islatravir, metabolite M4, and moxifloxacin pharmacokinetics after single-dose oral administration

Analyte	Period	Dose mg	n	Geometric mean, %GCV				
				C_{max} μM	T_{max}[a] hours	$AUC_{0\text{-}inf}$ h·μM	$AUC_{0\text{-}24}$ h·μM	$AUC_{0\text{-}168}$ h·μM
Islatravir	1	0.75	28	0.0250 (33.8)	0.50 (0.48-1.00)	0.0989 (26.7)	0.0641 (26.3)	0.0903 (26.3)
	2	240	26	3.83 (35.5)	1.08 (0.50-8.00)	29.8 (26.6)	21.2 (27.5)	28.2 (26.9)
Metabolite M4	1	0.75	28	0.0223 (31.9)	0.52 (0.50-1.58)	NR	NR	NR
	2	240	26	2.07 (44.5)	1.15 (0.50-4.02)	8.52 (29.6)	7.18 (31.3)	8.34 (29.6)
Moxifloxacin	1	400	14	1790[b] (30.9)	NA	NA	NA	NA
	2	400	14	1870[b] (17.5)	NA	NA	NA	NA
	1/2	400	28	1830[b] (24.6)	NA	NA	NA	NA

AUC, area under the concentration-time curve; $AUC_{0\text{-}24}$, area under the concentration-time curve from 0 to 24 hours; $AUC_{0\text{-}168}$, area under the concentration-time curve from 0 to 168 hours; $AUC_{0\text{-}inf}$, area under the concentration-time curve from 0 to infinity; C_{max}, maximum plasma concentration; %GCV, percent geometric coefficient of variation; NA, not applicable; NR, not reported; T_{max}, time to reach maximum plasma concentration.
[a]Median (range).
[b]Moxifloxacin C_{max} is expressed in nanograms per milliliter.

- The area under the concentration-time curve (AUC) and C_{max} for islatravir doses of 0.75 mg and 240 mg were similar to those of previous studies at comparable doses[1] (**Figure 3, Table 3**)
- Islatravir has shown dose proportionality over a wide range (0.25-400 mg)[1]; therefore, results are likely applicable to doses ≤240 mg, although the potential effect of intrinsic and extrinsic factors leading to increases in C_{max} must be considered

Safety outcomes

- Across all groups, the most frequently reported treatment-related adverse events (AEs) were headache (n = 6), nausea (n = 5), vomiting (n = 3), dizziness (n = 2), and rash (n = 2)
  - All were toxicity grade 1 or 2
  - There were no AEs due to laboratory abnormalities, including no AEs due to decreased lymphocyte counts
- There were no deaths, drug-related serious AEs, or discontinuations due to drug-related AEs
- The 4 discontinuations noted were due to SARS-CoV-2 positivity or COVID-19

Conclusions

- At the therapeutic dose of 0.75 mg and the supratherapeutic dose of 240 mg, islatravir does not prolong QTc and does not lead to other effects on electrocardiographic parameters
- Islatravir at doses of 240 mg and 0.75 mg was generally well tolerated
- These data support the continued development of islatravir for the treatment of HIV-1 or as PrEP for the prevention of HIV-1

References

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