Bemnifosbuvir Does Not Alter Cardiac Repolarization in Healthy Participants: Results from a Thorough QT Study

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INTRODUCTION

- Nucleoside/nucleotide analogs with potent antiviral activity, and a high barrier to resistance, are essential for the treatment of many acute and chronic viral infections
- Drug-induced cardiotoxicity is a known potential complication of this drug class. Additionally, regulatory guidance emphasizes the need for robust data on the effect of novel compounds on electrocardiogram (ECG) parameters, especially cardiac repolarization, to evaluate the potential risk of cardiac arrhythmias[1,2]
- Bemnifosbuvir (BEM, AT-527), is an oral double prodrug of a guanosine nucleotide analog with potent activity against flaviviruses and coronaviruses. BEM in combination with ruzasvir is under clinical development for the treatment of chronic hepatitis C (Phase 2)[3–5]
- BEM is readily absorbed and metabolized to the active triphosphate metabolite AT-9010 in mammalian cells[3]
  - Dephosphorylation of AT-9010 forms the guanosine nucleoside metabolite AT-273, which is a surrogate plasma marker for intracellular concentrations of AT-9010[6,7]
  - Sequential hydrolysis of the BEM free base, AT-511, also forms the intermediate prodrug AT-551 and a nucleoside metabolite AT-229 in the plasma[7]
- Preliminary clinical studies of cardiac safety, via robust concentration-QTc analysis in healthy participants, demonstrated no clinically relevant effects of BEM on cardiac conduction and ECG morphology, confirming previous pre-clinical studies that suggested BEM has a low potential for cardiotoxicity and is unlikely to inhibit the mitochondrial DNA-directed RNA polymerase[3,7,8]
- Here we report the results of a Phase 1 thorough QT (TQT) study of bemnifosbuvir in healthy participants (NCT05905484)[9]

METHODS

Study design

- 36 eligible healthy participants 18–55 years were randomized to receive a single oral dose of BEM 550 mg (therapeutic dose), BEM 1100 mg (supratherapeutic dose), matching placebo, and open-label moxifloxacin 400 mg (positive control) in a 4-period, 12-sequence, cross-over design with 3 participants per sequence
  - Each sequence included three double-blind treatments (BEM 550 mg, BEM 1100 mg, and matching placebo) and one open-label treatment (moxifloxacin 400 mg)
  - The total number of participants receiving BEM 550 mg, BEM 1100 mg, placebo and moxifloxacin were 32, 33, 30 and 34, respectively

Cardiac safety assessment

- Continuous ECG recorders were applied pre- and post-dose (up to 48 hours during each period), and 12-lead ECGs extracted at PK-matched time points
- ECG intervals were measured by the central laboratory in a blinded manner using the Early Precision QT technique
  - Up to 10 ECG replicates were extracted at each time point for semi-automated QT measurements
  - T-wave morphology analysis and measurement of PR and QRS intervals were performed manually on 3 of the 10 ECG replicates
- Primary objective: evaluate the effect of BEM on cardiac repolarization, as measured by the QTc interval corrected for heart rate (HR) using the Fridericia method (QTcF), via C-QTc analysis (placebo-corrected change-from-baseline QTcF; ΔΔQTcF)
- Secondary objectives: evaluate the effect of BEM on heart rate (HR), PR interval, QRS duration/interval relative to moxifloxacin (positive control) and placebo, demonstrate assay sensitivity using oral moxifloxacin as a positive control, and evaluate the effect of BEM on T-wave morphology and U-wave presence

RESULTS

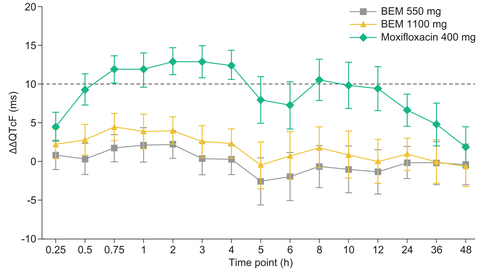
Effect on HR

- BEM at the studied doses did not have a clinically relevant effect on HR; the least-squares mean (LSM) placebo-corrected ΔHR on BEM varied from -1.2 bpm to +2.6 bpm across post-dose time points, and there were no outliers in terms of HR changes

Effect on cardiac repolarization: the QT interval

- In by-time-point analysis, the LS mean change from baseline QTcF (ΔQTcF) on BEM generally followed the pattern observed in participants receiving placebo
  - LSM ΔΔQTcF on BEM varied from -2.5 ms to 4.5 ms and did not indicate a dose-dependent effect; the upper bound of the 90% CI was below 10 ms across all post-dose timepoints for both BEM doses
- In contrast, the LSM ΔΔQTcF for moxifloxacin (positive control) peaked at 13.0 ms (at 2 and 3 h post-dose), with the lower bound of the 2-side 90% CI well above 5 ms at several time points, demonstrating the sensitivity of the assay (**Figure 1**)

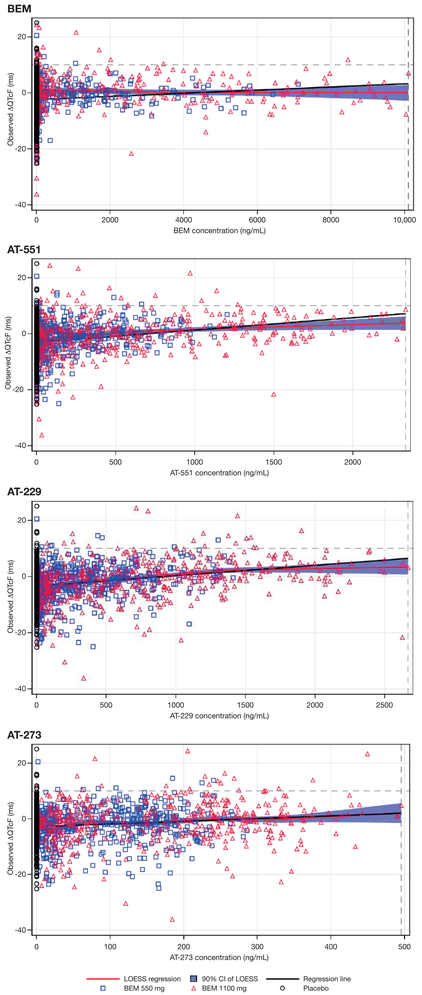
Figure 1. Placebo-corrected change-from-baseline QTcF (ΔΔQTcF) at each time point with statistical modeling (By-time point analysis set)



LS mean and 90% CI based on a linear mixed-effects model: ΔQTcF = treatment + time + treatment × time + period + sequence + baseline QTcF. An unstructured covariance structure was used to specify the repeated measures (post-dose time points for participant within treatment period). The dashed line denotes the theoretical limit of a ΔQTcF of 10 ms.

- A linear mixed-effects model, including BEM and its metabolites AT-551, AT-229 and AT-273 as explanatory variables, was initially fitted and model selection was performed according to pre-specified criteria (**Figure 2**)
- A full model including all analytes was individually fitted and revealed minimal between-model variation in Akaike Information Criterion (AIC) values and shallow slopes in all models. The model with AT-229 alone (Model F) had the lowest AIC value and was selected as the primary model (**Table 1**)
- The estimated population slope of the plasma AT-229 C-QTc relationship was shallow (0.0028 ms/ng/mL) and statistically significant (90% CI: 0.00179, 0.00378; P<0.0001), with a small treatment effect-specific intercept of -0.51 ms that was not statistically significant (90% CI: -1.129, 0.112; P=0.1779) (**Figure 3**)

Figure 2. Scatter plots of ΔQTcF vs plasma concentrations of BEM and metabolites with simple linear regression and LOESS regression



The red line with the blue shaded area denotes the LOESS regression and 90% confidence limits. The black solid line denotes the simple linear regression line. The plotted points denote the pairs of observed BEM/AT-551/AT-229/AT-273 plasma concentrations and ΔQTcF. The dashed line is a refence line at 10 ms. The maximum observed concentrations of BEM, AT-551, AT-229 and AT-273 were 10,104 ng/mL, 2117 ng/mL, 2666 ng/mL, and 496 ng/mL, respectively. CI, confidence interval; LOESS, locally estimated scatter plot smoothing; ΔQTcF, change from baseline in corrected QT interval using Fridericia's formula.

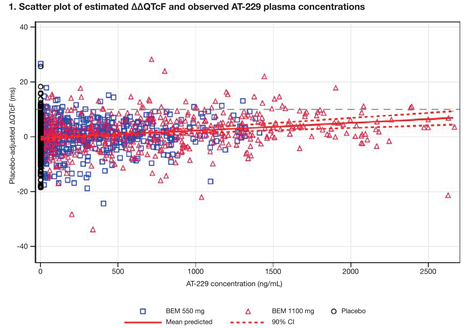
Table 1. AIC values for all models from C-QTc analysis

Model	Analytes included in model	AIC value	Treatment effect, ms (t-value)	Estimated slope of analyte concentration, ms/ng/mL (P-value)			
				BEM	AT-551	AT-229	AT-273
A	BEM, AT-551, AT-229, AT-273	8820.7	-0.69 (-1.54)	0.00032 (0.0382)	-0.000085 (0.9217)	0.0027 (0.0004)	0.00038 (0.8944)
B	BEM, AT-229, AT-273	8808.4	-0.69 (-1.54)	0.00031 (0.0134)		0.0026 (<0.0001)	0.00043 (0.8792)
C	BEM, AT-229	8798.6	-0.65 (-1.73)	0.00030 (0.0087)		0.0026 (<0.0001)	
D	BEM	8816.5	0.65 (2.03)	0.00048 (0.0033)			
E	AT-551	8763.5	0.03 (0.09)		0.0033 (0.0006)		
F	**AT-229**	**8760.0**	**-0.51 (-1.35)**			**0.0028 (<0.0001)**	
G	AT-273	8800.2	0.026 (0.06)				0.0071 (0.0357)

AIC, Akaike information criterion.

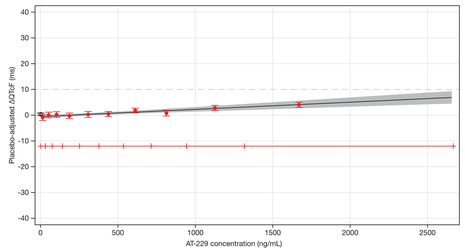
Figure 3. Primary C-QTc model (Model F: AT-229)

1. Scatter plot of estimated ΔΔQTcF and observed AT-229 plasma concentrations



The solid red line with dashed red lines denotes the model-predicted mean ΔΔQTcF with 90% CI, which is calculated from the equation ΔΔQTcF (ms) = -0.51 (ms) + 0.0028 (ms per ng/mL) × AT-229 plasma concentration (ng/mL). The plotted points denote the pairs of observed drug plasma concentrations and estimated ΔΔQTcF by participants for each active dose group and placebo group. The individually estimated placebo-adjusted ΔQTcF$_{i,k}$ (ΔΔQTcF$_{i,k}$) equals the individual ΔQTcF$_{i,k}$ for participant i administered with active drug or placebo at time point k minus the estimation of the time effect at time point k.

2. Model predicted ΔΔQTcF (mean and 90% CI) and estimated ΔΔQTcF (mean and 90% CI) across deciles of AT-229 plasma concentrations



The solid black line with gray shaded area denotes the model-predicted mean ΔΔQTcF with 90% CI, which is calculated from the equation ΔΔQTcF (ms) = -0.51 (ms) + 0.0028 (ms per ng/mL) × AT-229 plasma concentration (ng/mL). The red filled circles with vertical bars denote the estimated mean ΔΔQTcF with 90% CI displayed at the associated median plasma concentration within each decile for AT-229, among which the individually estimated placebo-adjusted ΔQTcF$_{i,k}$ (ΔΔQTcF$_{i,k}$) equals the individual ΔQTcF$_{i,k}$ for participant i administered with AT-229 at time point k minus the estimation of time effect at time point k. The black circle with vertical bars denotes the mean ΔΔQTcF with 90% CI for placebo at a concentration of 0. The horizontal red line with notches shows the range of concentrations divided into deciles for AT-229. The area between each decile represents the point at which 10% of the data are present; the first notch to second notch denotes the first 10% of the data, the second notch to third notch denotes the 10–20% of the data and so on.

- At the geometric mean C_{max} of AT-229 after single BEM doses of 550 mg and 1100 mg, the model-predicted effects on ΔΔQTcF were 1.86 ms (90% CI: 1.06, 2.66) and 4.29 ms (90% CI: 2.74, 5.83), respectively. All upper bounds of the 2-sided 90% CI were far below the established 10 ms threshold of concern (**Table 2**)

Table 2. Predicted ΔΔQTcF interval at geometric mean peak concentrations for AT-229

Treatment	Geometric mean C_{max} of AT-229, ng/mL	ΔΔQTcF estimate, ms [90% CI]
BEM 550 mg	849.2	1.86 [1.06, 2.66]
BEM 1100 mg	1721.5	4.29 [2.74, 5.83]

Based on a linear mixed-effects model with ΔQTcF as the dependent variable, time-matched AT-229 plasma concentration as an explanatory variate, centered baseline as an additional covariate, treatment (active = 1 or placebo = 0) and time as fixed effects, and a random intercept and slope per participant. C_{max}, maximum plasma concentration.

- The predicted effect on ΔΔQTcF with C-QTc models for BEM and other metabolites alone were similar to those from the primary model
- Thus, a ΔΔQTcF effect exceeding 10 ms can be excluded across the full observed plasma concentration ranges for BEM and its metabolites AT-551, AT-229 and AT-273 (up to ~10,104 ng/mL, ~2117 ng/mL, ~2666 ng/mL and ~496 ng/mL, respectively)

Effect on cardiac repolarization: the PR and QRS intervals

- BEM at the studied doses did not have a clinically relevant effect on PR and QRS intervals; changes from baseline in these intervals were not significantly different vs placebo

Categorical outlier and morphology analyses

- Categorical treatment-emergent ΔQTcF outliers and morphology findings are summarized in **Table 3**
- There were no treatment-emergent outliers in HR, or PR or QRS intervals

Table 3. Categorical outliers and treatment-emergent ECG morphology findings occurring in ≥1 participant

ECG finding, n (%)	Treatment period			
	550 mg (n=32)	1100 mg (n=33)	MOX (n=34)	Placebo (n=30)
QTcF >450 and ≤480 ms	2 (6.3)	1 (3.0)	3 (8.8)	1 (3.3)
QTcF >480 and ≤500 ms	0	0	1 (2.9)	0
ΔQTcF >30 and ≤60 ms	0	0	3 (8.8)	0
T wave: inversion	1 (3.1)	0	1 (2.9)	0
T wave: biphasic	1 (3.1)	0	0	0
T wave: flat	1 (3.1)	0	3 (8.8)	1 (3.3)

MOX, moxifloxacin

CONCLUSIONS

- BEM had no clinically relevant effects on cardiac repolarization, heart rate, PR interval, or QRS duration
- A QTc effect exceeding 10 ms, the established threshold of concern, can be excluded across the observed plasma concentrations of BEM and its metabolites at the therapeutic and supratherapeutic doses

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Disclosures

XJZ, MM, KP, BB, SL, DJ, AH, and JH are employees of and may own stock in Atea Pharmaceuticals. BD and HX are employees of Clario (USA), and GM is an employee of Altasciences (Canada), which were contracted to perform this analysis.

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