# Sisunatovir Inhibition of Multiple Ion Channel Subtypes Prevents the Risk for QT Prolongation Due to hERG Channel Inhibition

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## Introduction

- Sisunatovir (PF-07923568) is a Respiratory Syncytial Virus (RSV) F-protein inhibitor with high *in vitro* potency against RSV A & B strains.
- A Viral Challenge study (NCT03258502) demonstrated that sisunatovir 200 mg Q12h for 5 days significantly reduced viral load and symptoms with a favorable safety and tolerability profile.
- Sisunatovir inhibits the hERG channel in vitro ($IC_{50}$: 1.8 µM), potentially producing clinical QTc prolongation. However, sisunatovir inhibits additional cardiac ion channel subtypes (Cav1.2 [$IC_{50}$ 19.8 µM] and Nav1.5 [$IC_{50}$ 12.1 µM]), potentially offsetting delayed repolarization of the cardiac action potential via hERG inhibition.
- A thorough QT (TQT) study was conducted with a positive control to assess assay sensitivity and a supratherapeutic dose to cover high clinical exposures (288 ng/mL; ~118 nM).
- The objective of this study was to evaluate the impact of sisunatovir on QTc prolongation, at high clinical exposures, utilizing preclinical and clinical data.

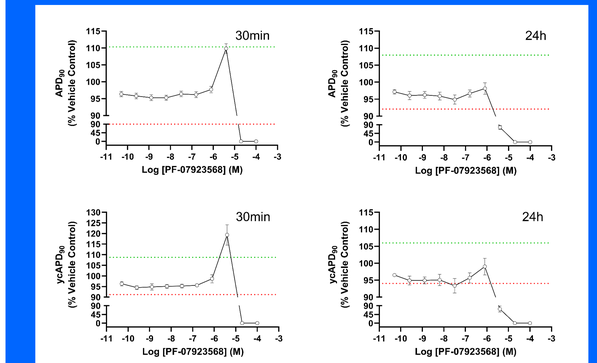
## Methods

- Human induced pluripotent stem cell (hiPSC) derived cardiomyocyte model used nominal and rate-corrected action potential duration changes to predict the concentration associated with a clinical 10 ms QTc prolongation following acute (30-minute) or chronic (24-hour) exposure.
- An *In silico* model, trained on a library of clinical compounds with known proarrhythmic risk (CredibleMeds), was developed to define the potential for Torsade de Pointes (TdP) relative to effective free therapeutic plasma concentrations (EFTPCs).
- A Phase 1, double-blind, sponsor-open, randomized, 3-period, placebo and positive-controlled crossover, TQT study was conducted in 43 healthy participants at Pfizer Clinical Research Unit (PCRU) at New Haven, CT. (NCT05878522).
  - Sisunatovir 300 mg Q12h x 5 doses (n=13) did not achieve high clinical exposure; dose increased to 350 mg Q12h x 5 doses (n=29),
  - QTc prolongation evaluated at steady-state,
  - Administration in fed state to decrease exposure variability and improve GI tolerability,
  - Moxifloxacin 400 mg administered as positive control
- Pre-specified linear mixed effects (LME) model to characterize relationship between sisunatovir concentration and QTc change (C-QTc). The LME model was used to derive predictions of placebo-corrected change from baseline in QTcF (ΔΔQTcF) and corresponding 2-sided 90% CIs for the concentration range.

## Results (hiPSC)

- Acute sisunatovir exposure (30 min) in hiPSC was predicted to cause a 10 ms increase in clinical QTc duration at 1.8 µM (>15-fold above high clinical exposure).
- Chronic sisunatovir exposure (24 h) was predicted to cause no prolongation in clinical QTc up to 76 µM (>640-fold high clinical exposure).
- In the hiPSC model, it is predicted that 200 mg sisunatovir Q12h for 5 days is unlikely to result in QTc prolongation (Figure 1).

**Figure 1: Effect of sisunatovir on action potential duration at 90% repolarization (APD90) and Yamamoto rate corrected APD90 (ycAPD90)**

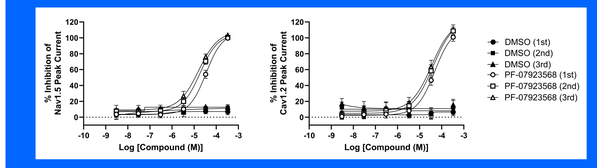



Data represent mean ± standard deviation (N = 4).
Green dashed lines represent the threshold levels for an **increase** in response
Red dashed lines represent the threshold level for a **decrease** in response

## Results (Cardiac Ion Channels)

- Fluorescent polarization binding assay used to evaluate hERG (Ki = 6.0 µM; margin = 51x) inhibition.
- Planar patch clamp technique used to record currents from Nav1.5 ($IC_{50}$ = 12.1 µM; margin = 103x) and Cav1.2 ($IC_{50}$ = 19.8 µM; margin = 168x) channels expressed in mammalian cell (Figure 2).

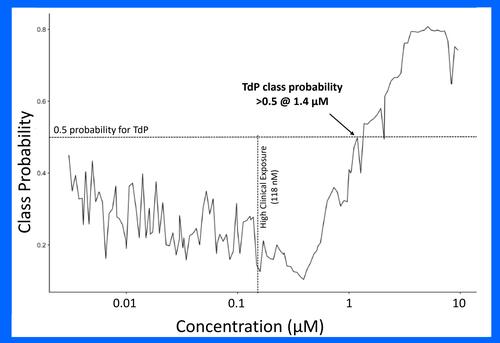
**Figure 2: *In vitro* inhibition of sisunatovir at Nav1.5 and Cav1.2 ion channels**




## Results (*In Silico* Model)

- Over the test range of free plasma sisunatovir concentrations from 3 nM to 10 µM, the in silico model predicted ≥1.4 µM (>11-fold high clinical exposure) would be associated with a TdP class probability risk (Figure 3).
- These data support the prediction that there is a low risk of significant clinical QTc prolongation with sisunatovir.

**Figure 3: The model Tdp class probability as a function of the clinical EFTPC**




## Results (Clinical Study)

- Participants: Male (65%), Mean (Range) Age: 43.3 (23-64) Years.
- All treatments were safe and well-tolerated.
- The lower limits of the two-sided Bonferroni-adjusted 90% CI (96.7% CI) for mean differences in QTcF between moxifloxacin and placebo were significant at 3- and 4-hours post-dose (8.03 and 7.65 msec, respectively). Thus, the study was deemed to have adequate sensitivity to detect QTc prolongation.

**Table 1: Randomization sequence**

| Sequence | Period 1 | Period 2 | Period 3 |
|---|---|---|---|
| 1 (n=7) | A | B | C |
| 2 (n=7) | A | C | B |
| 3 (n=7) | B | A | C |
| 4 (n=7) | B | C | A |
| 5 (n=7) | C | A | B |
| 6 (n=7) | C | B | A |

Treatment A = Sisunatovir capsules Q12h x 5 doses (fed)
Treatment B = Placebo capsules Q12h x 5 doses (fed)
Treatment C = Moxifloxacin (positive control) (fed)

## Results (Clinical Exposure)

- Steady-state exposure of 350 mg Q12h sufficient to cover High Clinical Exposure (Figure 4 and Table 2).

**Figure 4: Plasma PK Profile of 300 and 350 mg Q12h Sisunatovir**

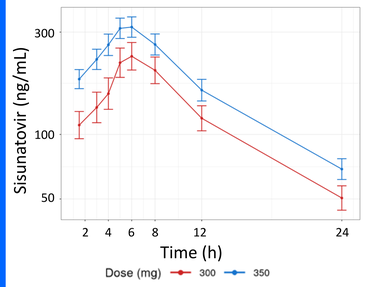



**Table 2: Plasma PK Parameters of 300 and 350 mg Q12h Sisunatovir**

| Parameter (unit)[a] | Sisunatovir 300 mg | Sisunatovir 350 mg |
|---|---|---|
| N | 13 | 29 |
| $AUC_{12}$ (ng.hr/mL) | 1978 (83) | 2870 (92) |
| $AUC_{24}$ (ng.hr/mL) | 2951 (79) | 4194 (94) |
| $C_{max}$ (ng/mL) | 238.0 (85) | 344.4 (87) |
| $T_{max}$ (hr) | 6.00 (5.00 - 8.32) | 6.00 (1.53 - 6.02) |

a. Geometric mean (geometric %coefficient of variation) for all except median (range) for Tmax.

## Results (C-QTc Modeling)

- No clinically significant effect of sisunatovir on HR (Figure 5 and Table 3) and QTc interval (Figure 6 and Table 4).

**Figure 5: ΔΔHR Predictions Over Range of Observed Concentrations**

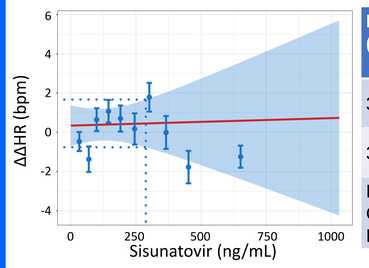



**Table 3: ΔΔHR Predictions at high clinical exposure**

| Dose (mg) | Geometric Mean $C_{max}$ (ng/mL) | ΔΔHR (bpm) | 90% CI |
|---|---|---|---|
| 300 | 238 | 0.43 | -0.59, 1.46 |
| 350 | 344 | 0.47 | -.098, 1.93 |
| High Clinical Exposure | 288 | 0.45 | -0.76, 1.67 |

**Figure 6: ΔΔQTcF Predictions Over Range of Observed Concentrations**

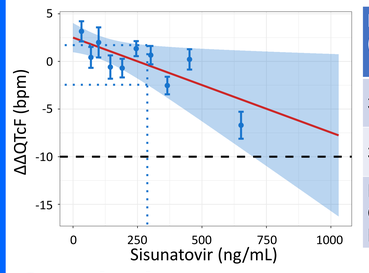



**Table 4: ΔΔQTcF Predictions at high clinical exposure**

| Dose (mg) | Geometric Mean $C_{max}$ (ng/mL) | ΔΔHR (bpm) | 90% CI |
|---|---|---|---|
| 300 | 238 | 0.13 | -1.6, 1.86 |
| 350 | 344 | -0.93 | -3.44, 1.58 |
| High Clinical Exposure | 288 | -0.37 | -2.45, 1.71 |

## Conclusions

**Preclinical models predicted that 200 mg sisunatovir Q12h for 5 days is unlikely to result in QTc prolongation. The clinical concentration-response analyses did not identify a QTc signal of potential clinical concern with sisunatovir.**