

Assessment of Vactosertib effect on QT interval: A Retrospective Concentration-QTc Analysis in Oncology Patients

>>> Elodie Valade (1), Mingyu Heo (2), Saerom Kim (2), Marta Valle (1), Jungwon Woo (2)

>>> (1) Parexel Clinical Pharmacology, Modeling and Simulation
(2) MedPacto, Inc., Seoul, Republic of Korea

Background

- Vactosertib is a highly selective, potent inhibitor of the protein serine/threonine kinase activity of transforming growth factor (TGF)- β receptor type 1. Vactosertib is being developed as an anticancer agent for various solid and hematologic malignancies.
- Although vactosertib elicited concentration-dependent inhibition of human ether-à-go-go-related gene (hERG)-mediated potassium currents from 10 to 100 μ M (half maximal

inhibitory concentration (IC50) = 31.04 μ M or 12390 ng/mL), no pathophysiological effects on respiratory rate, CNS function, or cardiovascular system were observed after oral administration of vactosertib at doses of up to 100 mg/kg.

- To assess vactosertib QT interval prolongation potential, a concentration-QTc (conc-QTc) analysis was performed using retrospective data from available clinical trials in oncology patients.

Methods

Data

Two clinical studies in patients with advanced solid tumor or in patients with low and intermediate myelodysplastic syndrome were selected. Vactosertib was administered once daily (QD) or twice daily (BID) for 5 days on and 2 days off-treatment, repeated for 28-day cycles.

Dose levels included 30, 60, 100, 140, 200, 260 and 340 mg QD and 100, 200 and 300 mg BID.

No placebo data were available.

529 matched vactosertib plasma concentrations and baseline-adjusted Fridericia corrected QT interval (Δ QTcF) from 36 subjects were available for analysis (Table 1).

Table 1. Data available for conc-QTc analysis

Population	Dose Regimens	Time-matched PK and ECG measurements
Patients with advanced-stage solid tumors (n=34)	30, 60, 100, 140, 200, 260 and 340 mg QD 200 mg BID	Cycle 1 Day 1: 0.5, 1, 2, 4, 8, 12 and 24 h post-dose Cycle 1 Day 5: pre-dose, 0.5, 1, 2, 4, 8, 12 (and 24 if stay overnight) h post-dose Cycle 1 Day 22: pre-dose, 1 and 6 h post-dose Cycle 1 Day 26: pre-dose, 1 and 6 h post-dose
Patients with low or intermediate myelodysplastic syndromes (n=2)	300 mg BID	Cycle 1 Day 1: 0.5, 1 and 2 h post-dose Cycle 1 Day 5: pre-dose, 0.5, 1 and 2 h post-dose

Modeling steps

- Graphical analysis to evaluate underlying assumptions of pre-specified linear models (heart rate (HR) effects, hysteresis and linearity).
- An adapted pre-specified linear model for conc-QTc analysis was applied [1]. Sensitivity modelling analyses were performed when deemed appropriate.
- Model evaluation: The developed models were evaluated with goodness-of-fit and visual predictive checks. Predictions of mean Δ QTc and two-sided 90% confidence interval (CI) at concentrations of interest were calculated using nonparametric bootstraps.

Data management was performed using SAS. Graphical analyses were performed using R version 3.3.3. Model development and simulations used NONMEM version VII level 4.4 (ICON, Hanover, MD), compiled using the GNU Fortran 4.6.3 for Windows, and PerlSpeaks NONMEM (PsN) version 5.0.0.

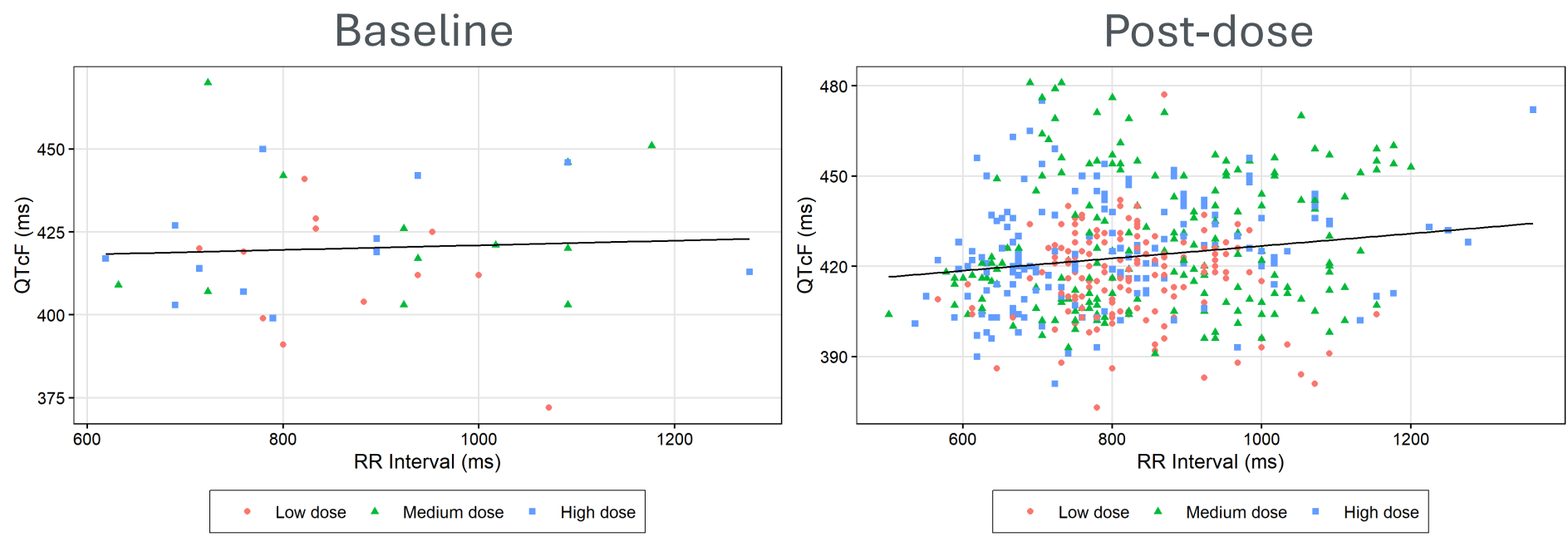
Results

Graphical analysis

A slight trend between change from baseline in HR (Δ HR) and vactosertib plasma concentrations was observed, suggesting vactosertib could potentially decrease HR.

QTcF was independent of RR interval at baseline but a slight trend was observed for post-dose, consistent with a potential effect of vactosertib on HR (Figure 1).

Figure 1. QTcF versus RR Interval Stratified by Period



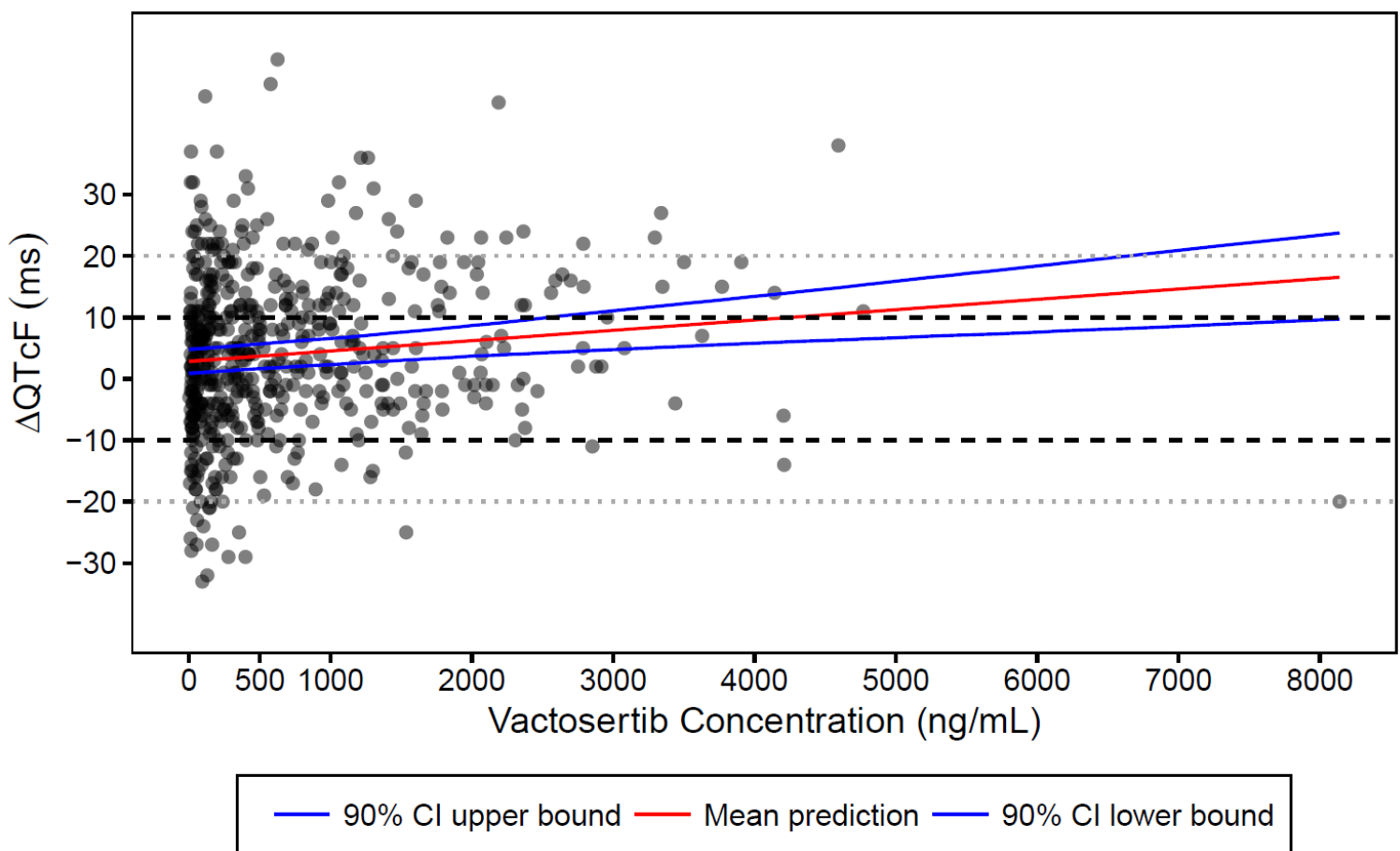
Fridericia's correction was considered to conduct the primary analysis. However, a subject-specific HR correction was estimated and was further explored in a sensitivity analysis.

Δ QTcF appears higher at 2 h post-dose whereas vactosertib C_{max} occurs at 0.5 h post-dose. Thus, the existence of a delay was further explored in a sensitivity analysis.

Primary Analysis

The parameters of the adapted pre-specified model are available in Table 2. The upper bounds of the two-sided 90% CI for the model-derived Δ QTcF at the steady state C_{max} for dosing regimens of interest were not predicted to reach the 10 ms threshold (Figure 2, Table 3).

Figure 2. Model-Derived Mean Δ QTcF versus Vactosertib Plasma Concentrations (primary analysis)



Sensitivity Analysis (delay – effect compartment)

Parameters of the linear model using predicted concentration in an effect compartment are available in Table 2.

Sensitivity Analysis (HR)

A subject-specific HR correction was estimated using on- and off- treatment data to derive individual-specific corrected QT interval (QTcI) [2]. Typical value of the correction factor to calculate QTcI was 0.301 (RSE 15.1%) with a BSV of 52.7%. Parameters of the model using QTcI are available in Table 2.

Table 2. Parameter Estimates for the Conc-QTc Models

Parameters	Estimates (RSE%)		
	Primary Analysis	Sensitivity Analysis (delay)	Sensitivity Analysis (HR)
Intercept (ms)	2.91 (46.5%)	0 fixed	0 fixed
Slope (ms per ng/mL)	0.00168 (34.5%)	0.00527 (20.0%)	0.00214 (40.5%)
QTcF Baseline effect	-0.210 (24.8%)	-0.209 (29.5%)	-0.586 (18.7%)
Effect compartment rate constat (1/h)	-	2.34 (30.2%)	-
BSV for intercept (ms)	7.90 (14.4%)	7.98 (13.4%)	7.17 (15.3%)
RUV (ms)	9.81 (4.8%)	9.63 (4.5%)	11.9 (5.2%)

BSV: between-subject variability; RSE: relative standard error; RUV: residual unexplained variability

Table 3. Predicted Δ QTc (90% CI) for C_{max} of dosing regimens of interest

Dosing Regimens	C_{max}	Predicted mean Δ QTc (90% CI) in ms		
		Primary Analysis	Sensitivity analysis (delay)	Sensitivity analysis (HR)
200 mg QD	C1D1 (1958 ng/mL)	6.14 (3.64–8.57)	9.23 (6.51–12.34)	4.09 (1.23–6.76)
	Steady state (1551 ng/mL)	5.46 (3.08–7.69)	7.31 (5.16–9.78)	3.24 (0.978–5.35)
200 mg BID	C1D1 (2047 ng/mL)	6.29 (3.75–8.78)	9.69 (6.83–13)	4.28 (1.29–7.07)
	Steady state (1625 ng/mL)	5.58 (3.17–7.84)	7.69 (5.42–10.28)	3.39 (1.02–5.61)
300 mg BID	C1D1 (3071 ng/mL)	8.01 (4.82–11.25)	14.52 (10.2–19.42)	6.42 (1.94–10.6)
	Steady state (2438 ng/mL)	6.95 (4.15–9.72)	11.52 (8.13–15.41)	5.09 (1.54–8.41)

C1D1: Cycle 1 Day 1

Conclusions

- The upper bound of the two-sided 90% CI for the model-derived Δ QTcF or Δ QTcI was not predicted to reach 10 ms for vactosertib geometric mean C_{max} at steady state. When accounting for a delay, the upper bound of the two-sided 90% CI for the model-derived Δ QTcF was predicted to reach the 10 ms threshold for the 200 mg BID and 300 mg BID dosing regimens.
- Regardless of the type of analysis, the upper bound of the two-sided 90% CI for the model derived Δ QTcF or Δ QTcI was not predicted to reach 20 ms for vactosertib geometric mean C_{max} at C1D1 or at steady state for the dosing regimens clinically relevant. Based on these results alone, vactosertib seems unlikely to result in clinically meaningful QT prolongation at the evaluated dosing regimens.
- The presented results may be refined through data cleaning, but overall conclusions will most probably remain unchanged.

References

- [1] Garnett C, Bonate P, Dang Q, Ferber G, Huang D, Liu J, Mehrotra D, Riley S, Sager P, Tornøe C, Wang Y. Scientific white paper on concentration-qtic modeling. Journal of Pharmacokinetics and Pharmacodynamics, 45:383–397, 2018.
- [2] Malik M, Hnatkova K, Batchvarov V. Differences between study-specific and subject specific heart rate corrections of the QT interval in investigations of drug induced QTc prolongation. Pacing Clin Electrophysiol., 27(6 Pt 1):791–800, 2004.