Abstract # C121

A Phase I QTc Study of Tivozanib in Patients with Advanced Solid Tumors

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Introduction

- Tivozanib (AV-951) is a potent, selective, long half-life, tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFRs) -1, -2, and -3
  - Preclinical and clinical studies have shown that tivozanib displays strong antiangiogenic and antitumor effects[1-4]
- Results from a Phase I study of tivozanib in patients with solid tumors, determined a maximum tolerated dose of tivozanib 1.5 mg/day, with responses observed in patients with renal cell carcinoma and other tumors[1]
- Tivozanib is currently being tested in a Phase III study in patients with renal cell carcinoma and Phase I/II studies of other solid tumors
- Tivozanib is associated with an acceptable safety profile consistent with that of a selective VEGFR inhibitor, with low incidences of off-target toxicities
- Evaluation of QT interval is expected to be a routine part of oncology development[5]
  - Preclinical (monkey telemetry and hERG patch clamp) studies of tivozanib and retrospective electrocardiogram (ECG) analyses did not suggest an effect on the QTc; however, this has not been assessed prospectively in humans as recommended by the International Conference on Harmonisation E14 guidelines for cardiac assessment of new drugs[6]
- This open-label, non-randomized, single-arm study prospectively investigated the proarrhythmogenic potential of tivozanib on the QTc interval, the potential effect of tivozanib on ECG morphology and ECG-pharmacokinetic (PK) relationship in patients with advanced solid tumors

Objectives

- To evaluate the ECG intervals and morphology following treatment with tivozanib in patients with advanced solid tumors
- To determine the relationship, if any, of the change in QTc duration based on Fridericia's correction (QTcF) with serum concentration of tivozanib over time in patients with advanced solid tumors

Methods

Study Design

- This was an open-label, non-randomized, exploratory single-arm trial
- Patients with advanced solid tumors were enrolled to receive 1.5 mg of tivozanib orally, once daily for 21 days
- Collection of serial blood samples for PK measurements and time-matched, triplicate, 12-lead ECGs is outlined in **Table 1**. These time points were selected to accommodate accumulation due to the long half-life of tivozanib and to achieve a wide range of drug concentrations until steady state was reached[7]

Table 1. ECG and PK Sampling Schedule

Time	Day 1	Day 2	Day 8 (±1 day)	Day 21
Predose	X	X	X	X
2.5 hours post dose	X		X	X
4 hours post dose	X			X
5 hours post dose	X		X	X
6 hours post dose	X			X
8 hours post dose	X		X	X
10 hours post dose	X			X
24 hours post dose				X

ECGs were taken as a single set of triplicate ECGs with the exception of two sets of triplicate ECGs at baseline. The first triplicate was done approximately 20 to 30 minutes predose, and the second set of triplicates was done immediately predose. ECGs were done prior to the PK draw.

- ECG evaluation, analysis, interpretation, and reporting were performed by a central laboratory under blinded conditions (eResearchTechnology, Inc., Philadelphia, PA, United States)
- Additional safety parameters were evaluated by assessment of clinical laboratory tests, physical examinations, vital signs, and recording of adverse events (AEs)

Study Endpoints

- Primary endpoint:
  - Change from baseline in the QTcF interval (QT interval corrected for heart rate [HR] using Fridericia's correction method)
- Secondary endpoints included:
  - Change from baseline in HR, PR interval, QRS interval, uncorrected QT interval, QT interval corrected for HR using Bazett's correction method (QTcB), and ECG morphological patterns and correlation between the QTcF change from baseline and serum concentrations of tivozanib

Key Eligibility Criteria

- Adult patients with advanced solid tumors, an Eastern Cooperative Oncology Group score ≤1, and life expectancy ≥3 months were eligible
- No clinically significant cardiac disease (New York Heart Association class >2), including unstable angina, acute myocardial infarction within 6 months of Day 1, congestive heart failure, or arrhythmia requiring therapy, with the exception of extra systoles or minor conduction abnormalities, per investigator judgment
- Baseline ECG QTcF <480 ms

Data Analysis and Statistical Methods

- ECG analysis population included all patients with at least one available baseline and on-treatment ECG measurement
- The following ECG parameters were assessed: HR, PR interval, QRS, and QT interval
- Baseline QTcF was determined as an average of all 6 predose ECGs on Day 1
  - As QTcF is considered the more accurate method,[5] it was used as the primary method for HR correction for QT used, with QTcB as the secondary method
- The time-averaged analysis for the ECG interval data was made using the endpoint "change from baseline" for each of the ECG intervals for all on-treatment ECG time points, as well as for Day 1 and Day 21 separately
- Day 21 assessments collected ≥2 days and Day 22 assessments collected ≥1 day past scheduled visit were excluded
- Exploratory outlier analysis was performed to identify exaggerated effect on any ECG parameter in individual patients. Specific outlier criteria for QT interval were new abnormal U waves, new absolute QTc duration >500 ms, and a >60 ms change in QTc from baseline

Exposure-effect Analyses

- ECG-PK analysis was performed using tivozanib serum concentrations paired with concomitant ECG QTc data
- A linear mixed-effects model was used to quantify the relationship between the serum concentration of tivozanib and ΔQTc (time-matched drug difference in QTc interval, baseline adjusted). Serum concentration, intercept, and patient were included as random effects. This model was used to estimate the population slope and the standard error of the slope of the relationship between the change from baseline in QTc intervals and serum concentrations of tivozanib. If this model did not converge, then serum concentration was included as a fixed effect with intercept and patient included as random effects
- The predicted population average expected ΔQTc and the corresponding upper 95% one-sided confidence interval (CI) were then estimated at relevant concentration levels (e.g. the mean maximum serum concentration [C_{max}] under doses). The exploration of the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration-response relationship was explored
- In addition to the usual PK parameters, the analysis explored the relationship between the mean change from baseline only for QTcF (and QTcB) vs serum concentrations of tivozanib

Results

- Fifty-one patients with advanced solid tumors were enrolled, and 50 patients received at least one dose of tivozanib and were evaluable: 17 male (34%) and 33 female (66%) patients with a median age of 63 years (range 41–84) and mean body mass index of 28.3 (±7.76). The majority (94%) were Caucasian

QTc Results

- No clinically significant QT prolongation was observed with tivozanib 1.5 mg daily dosing for 21 days
  - There were no QTcF values >500 ms; 2 patients (4%) had QTcF values >480 ms
  - Clinically non-significant QTcF prolongation of >60 ms change from baseline was observed in 1 patient (2%). Non-significant QTcF changes of 30 to 60 ms from baseline occurred in 6 patients (12%)
  - By time-averaged data, the central tendency mean change from baseline for QTcF duration for all post-dose time points showed a change of +2.2 ms (**Table 2**)
  - Time-point analysis of mean change from baseline for QTcF duration for Day 1 and Day 21 separately showed clinically insignificant changes of -1.1 ms and +6.8 ms, respectively (**Table 2**)

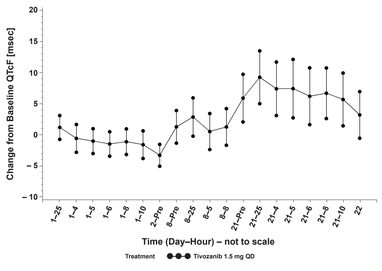
Table 2. ECG Parameters, Mean Change From Baseline

Parameter (mean change from baseline)	All Post-Dose Time Points	Day 1 (N=50)	Day 21 (N=43)
Heart rate (bpm)	-2.1	-1.6	-2.1
PR (ms)	1.2	2.5	0.2
QRS (ms)	2.1	1.7	2.5
QT (ms)	5.6	1.5	9.9
QTcF (ms)	2.2	-1.1	6.8
QTcB (ms)	0.4	-2.5	5.1

Bpm, beats per minute; ms, milliseconds.

- **Figure 1** shows the mean change in QTcF interval from baseline for all time points on treatment
  - The maximal mean increase in QTcF was 8.3 ms (upper CI 12.6 ms) noted at 2.5 hours post dose on Day 21
  - Most of the QTc changes observed occurred at the later time points by which patients had received up to 3 weeks of treatment; all were found to be not clinically significant (**Figure 1**)
  - Similar results were seen with QTcB interval (data not shown)

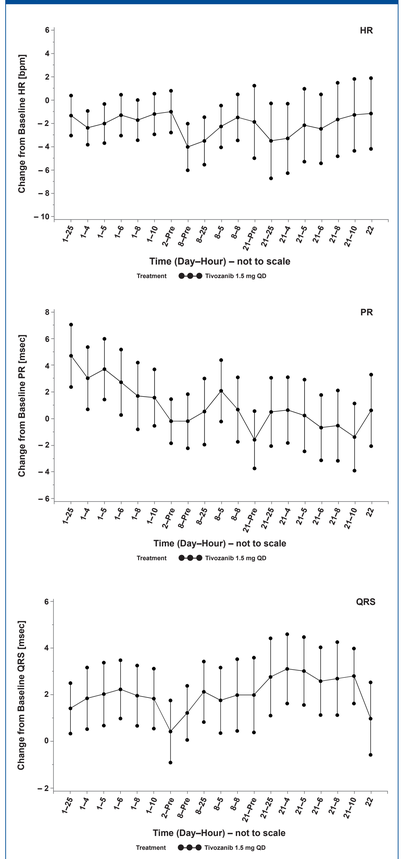
Figure 1. Mean change in QTcF (±90% CI) from baseline for all time points.



Effect on Other ECG Parameters

- No clinically relevant changes from baseline were observed in HR, PR interval, and QRS complex with tivozanib treatment (**Figure 2, Table 2**)
  - Clinically non-significant reduction in HR was observed
  - Outlier analysis revealed no tachycardic outliers and two (4%) bradycardic outliers of no clinical relevance
  - There were two (4%) outliers for QRS duration. A small effect on QRS was observed by time-point analysis; however, these changes are unlikely to be of clinical relevance
- Morphological analysis showed 4 patients (8%) had new ST depression and 4 patients (8%) had new T wave inversion, which were not noted to be clinically significant

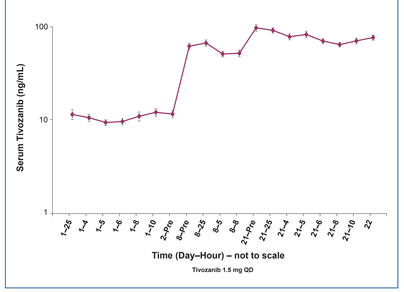
Figure 2. Mean change in HR, PR, and QRS (±90% CI) from baseline for all time points.



PK/QT Relationship

- **Figure 3** illustrates the mean serum concentration for all time points on treatment
  - Tivozanib accumulation observed after 3 weeks of treatment is consistent with previous studies

Figure 3. Mean tivozanib serum concentration (± SEM) for all time points.



SEM, standard error of mean.

- The linear mixed model estimate of the relationship between QTcF/QTcB and serum tivozanib concentration indicates that the slope for the QTcF vs serum tivozanib concentration was 0.08464 (**Table 3**)
  - This indicates a small exposure-effect relationship, with a predicted QTcF change of 8.27 at the average C_{max} of 118.1 ng/mL (upper CI 12.6 ms)

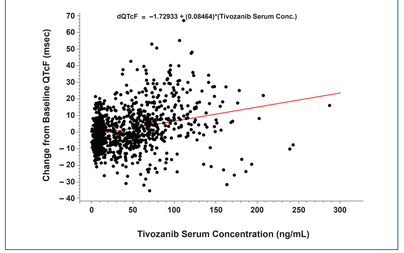
Table 3. ΔQTc vs Tivozanib Serum Concentration: Linear Mixed Model Estimates [A]

Parameter (ms)	Serum Concentration Effect on ΔQTc: Slope [A]	Standard Error [A]	Slope *P*-Value [A]	Predicted ΔQTc at Average C_{max} 118.1 ng/mL	One-sided Upper 95% CI of Predicted ΔQTc [B]	Overall Model Fit (*P*-value) [A]
QTcF	0.08464	0.02292	0.0006	8.2694	12.6493	<0.0001
QTcB	0.07298	0.02329	0.0031	5.4611	10.2234	<0.0001

[A] Linear mixed effects model is fit for change from baseline (i.e. subtracted) vs the serum concentration. Serum concentration, subject, and intercept are included in the model as random effects terms.
[B] Upper bound, upper one-sided 95% linear mixed model based confidence limit.

- The relationship between QTcF duration and serum concentration from paired samples taken for tivozanib is shown in the scatter plot in **Figure 4**
  - Similar results were seen with QTcB analysis (data not shown)
  - Observed variability in QTcF appears consistent with increased variability in QTc often noted in oncology patients[8]

Figure 4. QTcF changes from baseline vs tivozanib serum concentration.



- These data show a relationship between the concentration of tivozanib and QTcF; however, the relationship is of borderline clinical significance considering the significant comorbidities of the patient population. The onset of QT changes occurred late within the dosing period
  - Clinically significant QTcF interval prolongation is not expected at steady-state levels of tivozanib at the recommended dosing of 1.5 mg daily for 21 days

Safety

- Forty patients (80%) experienced at least one possibly, probably, or definitely treatment-related AE
- The most common AEs related to study treatment were hypertension (19 patients [38%]), fatigue (12 patients [24%]), headache (8 patients [16%]), and stomatitis (7 patients [14%])
  - The majority were Grade 1/2, with the exception of Grade 3 hypertension observed in 10 patients (20%) and Grade 3 fatigue observed in 1 patient (2%)
- Other treatment-related Grade 3 AEs were observed in 1 patient (2%) each: diarrhea, abdominal pain, gastrointestinal hemorrhage, dysaesthesia, dyspnea, prolonged QT, and increased aspartate aminotransferase, alanine aminotransferase, and bilirubin levels
- There were no treatment-related Grade 4 AEs. There were three deaths on study, all due to disease progression
- AEs leading to study discontinuation in 2 patients (4%) were: fatigue, anorexia (1 patient), and memory impairment (1 patient)
- Nine patients (18%) experienced treatment-emergent serious AEs, of which three were treatment related, consisting of gastrointestinal hemorrhage (resulting in treatment discontinuation), abdominal pain, and dyspnea

Conclusions

- This prospective study demonstrated that daily administration of 1.5 mg tivozanib for 21 days is not associated with clinically significant QT prolongation or any other important ECG findings
  - Tivozanib administration showed a mean increase of 8.3 ms (upper CI 12.6 ms) in the QTcF duration at C_{max} using an exposure-effect model with central tendency changes showing a 2.2 ms change, which is not suggestive of a clinically significant effect on cardiac repolarization. There were no occurrences of QTcF >500 ms. QTcF prolongation of >60 ms change from baseline was observed in 1 patient (2%), and QTcF changes of 30 to 60 ms from baseline occurred in 6 patients (12%)
  - A slight reduction in HR of no clinical significance was observed
  - There was no significant effect on atrioventricular conduction as measured by a mean increase in the PR interval
  - There was a small effect on depolarization as measured by a 2.1 ms increase in the QRS duration, which is unlikely to be of clinical relevance
  - Based on these results, future clinical trials may not require intensive ECG monitoring
- Data from this study suggest that the safety and PK profile of tivozanib was similar to that observed in previous studies

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