M-044

Concentration-QT Analysis of Quizartinib in Patients With Relapsed/Refractory AML

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BACKGROUND

- FMS-like tyrosine kinase 3 (FLT3) is expressed in hematopoietic progenitor cells, and signaling through FLT3 promotes these cells' proliferation and differentiation. FLT3 is mutated in approximately 30% of patients with acute myeloid leukemia (AML)
- The FLT3-ITD (internal tandem duplication) mutation is associated with a shorter duration of response, greater cumulative incidence of relapse, and shorter survival after relapse. It has been identified as the worst single prognostic factor for duration of complete remission and relapse-free survival in AML[1]
- Quizartinib is a novel oral second-generation class III receptor tyrosine kinase inhibitor that has shown potent and selective FLT3 inhibition and high clinical activity in patients with FLT3-ITD–positive relapsed/refractory AML
- Quizartinib has been shown to prolong survival in patients with relapsed/refractory AML (including those with hematopoietic stem cell transplant)[1] and is currently being studied along with chemotherapy in the first line

OBJECTIVE

- To evaluate the relationship between pharmacokinetic exposures of quizartinib (AC220) and active metabolite AC886 and QTc interval

METHODS

Data and Software

- Data were obtained from a phase 2 study (2689-CL-2004; ClinicalTrials.gov, NCT01565668) evaluating the safety and efficacy of quizartinib with planned doses of 30 and 60 mg/d in patients with relapsed/refractory AML with FLT3-ITD mutations
- Quizartinib doses of 30 or 60 mg were administered once daily for continuous 28-day cycles. Patients were instructed to take quizartinib on an empty stomach at least 1 hour before or 2 hours after a meal in the morning. Increases or reductions in quizartinib dose might have occurred as specified by the study protocol guidelines for dose modification
- Serial triplicate centrally reviewed electrocardiograms, together with time-matched PK samples, were collected over 24 hours following a single dose on cycle 1, day 1 and at steady state on cycle 1, day 15
- NONMEM 7.3 (ICON) was used for concentration-QT (C-QT) modeling analysis, and R software was used for statistical analysis and plotting

Concentration-QT Analysis Methods

- Nonlinear mixed-effect modeling was applied, including the evaluation of base structural models with linear and nonlinear functions, RR interval correction method (ie, Fridericia or population corrections), potential hysteresis trend, circadian rhythm correction, and model parameter distribution
- Extensive covariate modeling was performed on predefined covariates, baseline QTcF (QTc corrected by Fridericia's formula), patient demographics (sex, age, body weight, race), low electrolyte (Ca, K, Mg) levels, and concomitant use of QT prolonging agents
- Model-predicted QTcF was determined for the observed quizartinib concentrations

RESULTS

- The analysis included 868 time-matched mean QTc and concentration measurements from 73 patients (Table 1)
- The population correction method produced a QT interval more independent from RR duration than Fridericia correction (Figure 1). However, QTcF was chosen in the primary analysis because dose adjustment and safety monitoring during the study were done with QTcF and per the guidance from the recent scientific white paper.[2] The analysis was repeated with population-corrected QT data
- Circadian variation was observed. Because the QTc data covered a portion of the 24-hour time span (mostly occurring between 8:00 AM and 5:00 PM), a fixed time effect model was used to correct the baseline with respect to circadian rhythm (Figure 2)[2]
- Emax function of C-QTc produced a similar or better fit than linear function but had poor precision of parameter estimates. Therefore, linear function was chosen for the final model
- There was significant improvement in the model fitting with inclusion of both quizartinib and AC886 concentrations (Table 2), which was in agreement with the preclinical finding that both were active in affecting cardiac ion channels
- Normal distribution for the between-subject variability in baseline term and slopes (both for quizartinib and AC886) and proportional error for the residual error produced the best fit (Table 3)
- Based on the forward-selection (α = 0.01) and backward-elimination (α = 0.001) covariate modeling, race effect on the baseline QTcF was included in the final model. The baseline QTcF was approximately 4% higher in white patients than in patients of other races (Table 4)
- The final C-QTc model captures the trend in the observed data well (Figure 3) and indicates that QTcF increases linearly with respect to concentrations of quizartinib and AC886, with a 15-fold higher slope for quizartinib than for AC886 (Tables 4 and 5, Figure 4). Model-predicted mean QTcF increase from baseline was 7.36 and 19.3 ms (upper bound of 2-sided 90% CI: 8.90 and 23.3 ms), for quizartinib 30 and 60 mg/d, respectively (Table 6)
- An alternative model using quizartinib concentration alone as a predictor (Table 4 vs Table 5) or using QTcP data (not shown) provided similar results

Ca, calcium; ECG, electrocardiogram; Emax, maximum effect; K, potassium; Mg, magnesium PK, pharmacokinetic.

Table 1. Summary of Patient Characteristics for C-QT Analysis

Demographic Characteristics		Overall
Age, y	Mean (SD)	53.4 (15.0)
	Median	54.0
	Minimum, maximum	19.0, 77.0
	n	73
Baseline QTcF, ms	Mean (SD)	414.2 (21.8)
	Median	415.7
	Minimum, maximum	362.3, 455.0
Baseline QTcP, ms	Mean (SD)	432.9 (24.1)
	Median	434.0
	Minimum, maximum	367.1, 488.8
Weight, kg	Mean (SD)	75.8 (16.4)
	Median	76.5
	Minimum, maximum	40.4, 115.9
Race, n (%)	White	56 (76.7)
	Black or African American	3 (4.1)
	Asian	3 (4.1)
	Unknown	11 (15.1)
Sex, n (%)	Male	42 (57.5)
	Female	31 (42.5)
QTc prolongation drug, N (%)	No	322 (37.3)
	Yes	541 (62.7)
Hypocalcemia flag, N (%)	No	448 (51.9)
	Yes	415 (48.1)
Hypokalemia flag, N (%)	No	804 (93.2)
	Yes	59 (6.8)
Hypomagnesemia flag, N (%)	No	624 (72.3)
	Yes	239 (27.7)
Hypocalcemia flag (corrected), N (%)	No	672 (77.9)
	Yes	191 (22.1)

n, number of patients; N, number of records; QTc, QT interval corrected by electrocardiogram for heart rate; QTcF, QT interval corrected using Fridericia's formula; QTcP, QT interval corrected using population-based correction factor.

Table 2. Concentration-QTcF Base Structural Model Building Process

Model	Description	VOF	Δ VOF	AIC	Δ AIC	Reference Model	*P* Value
1	Baseline	5769.488	NA	5795.488	NA	NA	NA
2	Baseline + quizartinib	5589.763	–179.725	5619.763	–175.725	Model 1	6.95E-39
3	Baseline + AC886	5667.805	–101.683	5697.805	–97.683	Model 1	6.14E-22
4	Baseline + (quizartinib + AC886)	5592.625	–176.863	5622.625	–172.863	Model 1	2.91E-38
5	Baseline + quizartinib + AC886 (2 slopes)	5563.68	–26.083	5597.68	–22.083	Model 2	1.60E-05

AC886, compound code for active metabolite of quizartinib; Δ AIC, difference in Akaike information criteria values between the 2 models under comparison; NA, not applicable; QTcF, QT interval corrected using Fridericia's formula; Δ VOF, difference in the value of objective function between the 2 models under comparison.

Table 3. Evaluation of Functional Forms and Distributions for Interindividual and Residual Variability in the Base Structural Concentration-QTcF Model

Model	Functional Form for Error Model (RV)	Distribution for IIV on Baseline QTcF	Distribution for IIV on Slope for Quizartinib	Distribution for IIV on Slope for AC886	VOF
A	Additive	Normal	Normal	Normal	5563.680
B	Proportional	Normal	Normal	Normal	5548.688
C	Additive	Log-normal	Normal	Normal	5564.373
D	Additive	Normal	Log-normal	Normal	5568.788
E	Additive	Log-normal	Log-normal	Normal	5569.525
F	Proportional	Log-normal	Log-normal	Normal	5555.277
G	Proportional	Log-normal	Normal	Normal	5549.533

AC886, compound code for active metabolite of quizartinib; IIV, interindividual variability; QTcF, QT interval corrected using Fridericia's formula; RV, residual variability; VOF, value of objective function.

Table 4. Parameter Estimates of Final Concentration-QTcF Model (Including Quizartinib and AC886 Concentrations as Descriptors)

Parameter	Final Parameter Estimate		Interindividual Variability	
	Typical Value	%RSE	Magnitude	%RSE
BASE: baseline QTcF value, ms	418	0.677	16.8 SD	15.0
BASE: proportional shift of non-white patients on baseline QTcF	–0.0411	31.3		
Fixed time effect for 1st decile of clock time, ms	0.342	738	NE	NA
Fixed time effect for 2nd decile of clock time, ms	2.87	72.7		
Fixed time effect for 3rd decile of clock time, ms	0	Fixed		
Fixed time effect for 4th decile of clock time, ms	3.42	63.6		
Fixed time effect for 5th decile of clock time, ms	5.80	39.2		
Fixed time effect for 6th decile of clock time, ms	7.74	29.6		
Fixed time effect for 7th decile of clock time, ms	6.49	42.4		
Fixed time effect for 8th decile of clock time, ms	6.69	33.7		
Fixed time effect for 9th decile of clock time, ms	6.89	31.5		
Fixed time effect for 10th decile of clock time, ms	5.26	52.4		
PSLP: slope for observed quizartinib concentration, ms/(ng/mL)	0.0383	14.7	0.0226 SD	46.5
MSLP: slope for observed AC886 concentration, ms/(ng/mL)	0.00256	491	0.0584 SD	32.0
Residual variability	8.58E-04	12.7	2.93 %CV	NA
Minimum value of objective function = 5537.157				

AC886, compound code for active metabolite of quizartinib; %CV, coefficient of variation expressed as a percentage; NA, not applicable; NE, not estimated; QTcF, QT interval corrected using Fridericia's formula; %RSE, relative standard error expressed as a percentage.

Table 5. Parameter Estimates of Alternative Final Concentration-QTcF Model (Including Quizartinib Concentration Alone as Descriptor)

Parameter	Final Parameter Estimate		Interindividual Variability	
	Typical Value	%RSE	Magnitude	%RSE
BASE: baseline QTcF value, ms	419	0.646	15.4 SD	15.9
BASE: proportional shift of non-white patients on BASE	–0.0402	28.3		
BASE: exponent of age on BASE	0.0495	24.0		
Fixed time effect for 1st decile of clock time, ms	0.629	400	NE	NA
Fixed time effect for 2nd decile of clock time, ms	2.85	72.7		
Fixed time effect for 3rd decile of clock time, ms	0	Fixed		
Fixed time effect for 4th decile of clock time, ms	3.24	64.0		
Fixed time effect for 5th decile of clock time, ms	5.41	42.0		
Fixed time effect for 6th decile of clock time, ms	7.93	29.4		
Fixed time effect for 7th decile of clock time, ms	5.90	45.2		
Fixed time effect for 8th decile of clock time, ms	6.64	33.3		
Fixed time effect for 9th decile of clock time, ms	6.40	33.5		
Fixed time effect for 10th decile of clock time, ms	4.87	55.7		
PSLP: slope for observed quizartinib concentration, ms/(ng/mL)	0.0409	12.5	0.0283 SD	45.1
Residual variability	9.26E-04	11.5	3.04 %CV	NA
Minimum value of objective function = 5552.9				

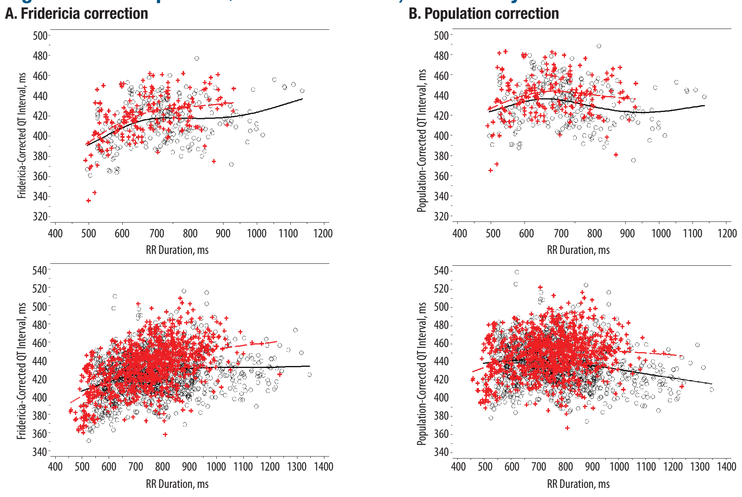
%CV, coefficient of variation expressed as a percentage; NA, not applicable; NE, not estimated; QTcF, QT interval corrected using Fridericia's formula; %RSE, relative standard error expressed as a percentage.

Table 6. Predicted Δ QTcF at Geometric Mean of Quizartinib $C_{max,ss}$ on Cycle 1, Day 15 and Corresponding AC886 Concentrations at T_{max} of Quizartinib Following Quizartinib 30- and 60-mg Once-Daily Doses

Dose, mg	Observed Geometric Mean of Quizartinib $C_{max,ss}$ on Cycle 1, Day 15, ng/mL	Calculated Geometric Mean of AC886 $C_{max,ss}$ on Cycle 1, Day 15, ng/mL	Final QTcF Model (Quizartinib and AC886)			Alternative Final QTcF Model (Quizartinib Only)		
			Mean Δ QTcF, ms	Lower Bound 90% CI, ms	Upper Bound 90% CI, ms	Mean Δ QTcF, ms	Lower Bound 90% CI, ms	Upper Bound 90% CI, ms
30	186[a]	93[b]	7.36	5.69	8.90	7.60	5.99	9.03
60	487[a]	243.5[b]	19.3	14.9	23.3	19.9	15.7	23.6

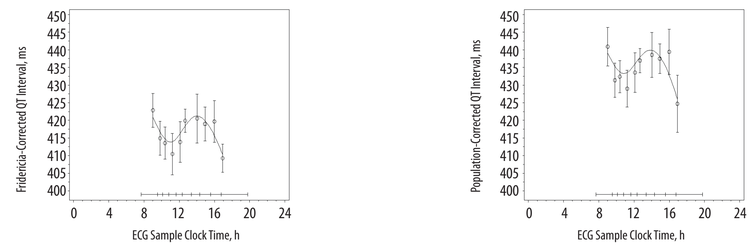
AC886, compound code for active metabolite of quizartinib; $C_{max,ss}$, peak plasma drug concentration after dosing at steady state; Δ QTcF, change from baseline QTcF; QTcF, QT interval corrected using Fridericia's formula; T_{max}, time to maximum plasma concentration.
[a] Obtained from noncompartmental analysis results of Study 2689-CL-2004.
[b] Obtained based on 0.5 metabolite-to-parent ratio.

Figure 1. Scatterplot of QTcF vs RR Interval, Stratified by Sex



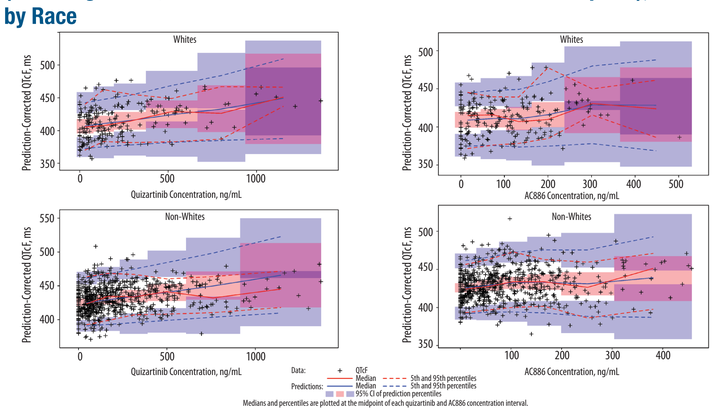
The lines represent smoothing splines fit to the data.
Upper panels show pretreatment QTcF and lower panels show post-treatment QTcF.

Figure 2. Pretreatment QTcF and QTcP vs Sampling Clock Time Within Each Decile Bin



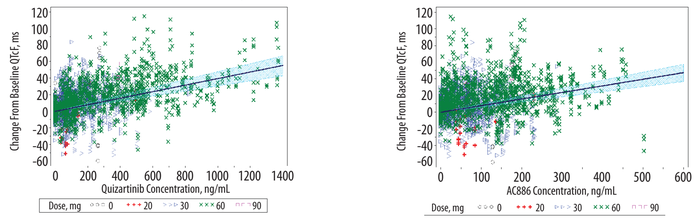
The lines represent smoothing splines fit to the median X and Y values within each X bin. The horizontal bars along the x-axis represent the minumum and maximum values for each X bin. The vertical bars represent the 90% confidence intervals for the mean of Y values within each X bin.

Figure 3. Prediction-Corrected Visual Predictive Check of the Final QTcF Model (Including Both Quizartinib and AC886 Concentrations as Descriptors), Stratified by Race



Medians and percentiles are plotted at the midpoint of each quizartinib and AC886 concentration interval.

Figure 4. Scatterplot of Δ QTcF vs Quizartinib Concentrations, With Model-Predicted Mean and 90% CI Overlaid, Based on the Final QTcF Model



The solid line and shaded region represent the model-predicted mean and 90% confidence interval of the mean, respectively (assuming that AC886 concentration is 50% of quizartinib concentration).

CONCLUSIONS

- This analysis suggests concentration-dependent QTc prolongation with quizartinib
- Results support the clinical recommendation of dose reduction in patients receiving strong cytochrome P450 3A inhibitors, for whom quizartinib exposure is increased 2-fold in the presence of such agents[3]

REFERENCES

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DISCLOSURES

D Kang and O Yin are employees of Daiichi Sankyo, Inc. K Lin and E Ludwig are employees of Cognigen Corporation, a Simulations Plus Company.

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