Comparison of pharmacokinetics and QTc effect of Quizartinib in Japanese and non-Japanese patients with Relapsed/Refractory (R/R) FLT3-ITD positive acute myeloid leukemia (AML) using population pharmacokinetic (PopPK) analyses

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BACKGROUND

- Quizartinib is an oral, once-daily, highly potent, and selective type II FLT3 inhibitor that has shown high levels of clinical activity in patients with FLT3-ITD-positive relapsed/refractory (R/R) acute myeloid leukemia (AML).[1]
- In the phase 3 QuANTUM-R (AC220-007, NCT02039726) including non-Japanese patients with relapsed/refractory FLT3-ITD R/R AML, single-agent quizartinib treatment demonstrated clinically meaningful overall survival benefit, with a 24% reduction in the risk of death as compared to salvage chemotherapy.[2]
- The phase 2 study (AC220-A-J201, NCT02984995) in Japanese patients with FLT3-ITD R/R AML showed that quizartinib monotherapy was well tolerated and resulted in clinically meaningful reductions in blast count. [3]
- The population PK and concentration-QT analyses previously performed demonstrated an exposure-dependent increase with respect to quizartinib and AC886 concentrations. [4] The results supported clinical recommendation of dose reduction in patients receiving strong CYP3A inhibitors.

OBJECTIVES

The objectives of this analyses were to compare the pharmacokinetic (PK) profiles and QTc effect of quizartinib and its metabolites AC886 in Japanese and non-Japanese patients and to support justification of quizartinib dose and dosing regimen in Japanese AML patients.

METHODS

Data and Software

- Data for PopPK analysis were obtained from 7 non-Japanese studies (4 studies in healthy subjects and 3 studies in patient with AML) and 2 Japanese studies in patient with AML. **(Table 1)** Quizartinib dosing regimens ranged from 20 mg/day to 90 mg/day as quizartinib dihydrochloride.
- Data for concentration-QT interval corrected using Fridericia's formula (C-QTcF) analysis were obtained from AC220-007 and AC220-A-J201. **(Table 2)** Serial triplicate centrally reviewed electrocardiograms and time-matched PK samples were collected over 24 hours following quizartinib administration on Cycle1 Day1 and on Cycle 1 Day15.
- NONMEM V.7.3 was used for PopPK and C-QTc modeling. SAS® Version 9.4 or KIWI™ Version 2 software was used for data preparation, statistical analysis and plotting data presentation.

PopPK Analysis

- The PK parameters of the previously developed PopPK models[5] for quizartinib and its metabolite AC886, **(Figure 1)** were updated with same model structure, using the pooled data including Japanese patients. The effect of Japanese population (race) was then evaluated as a covariate on relevant clearance and volume parameters.
- Quizartinib and AC886 steady-state exposures (AUC0-24,ss and Cmax,ss) for the Japanese AML patient population were simulated using the final PopPK model with predicted individual PK parameters and compared to the estimates for the reference AML patients.

Concentration-QT Analysis

- The previously developed C-QTcF model which described the relationship between quizartinib and AC886 concentrations and QTcF in terms of baseline QTcF, fixed time effect parameters for the circadian variation of baseline QTcF, separate sigmoid Emax functions for quizartinib and AC886, and covariate effect of hypokalemia on baseline QTcF was used.[4] A full model was formed by inclusion of the effect of Japanese population on baseline QTcF and Emax for quizartinib and AC886. Covariate assessment of the Japanese race effect was performed using backward elimination ($\alpha = 0.001$) from full model.
- Simulations were performed in Japanese patients to predict median ΔQTcF (change from baseline QTcF) and the 90% confidence interval (CI) across observed quizartinib and AC886 plasma concentrations in AC220-A-J201.

RESULTS

PopPK Analysis

- A total of 11,488 quizartinib concentrations collected from 638 individuals were include in analysis.
- The PK of quizartinib and AC886 in healthy volunteers and non-Japanese and Japanese patients with AML was well characterized by a 3-compartment model with sequential zero- and first-order absorption and linear elimination. **(Figure 1)**
- Japanese population was not found to be a statistically significant covariate on quizartinib and AC886 PK parameters.
- The pcVPC results suggest that the final PK model was able to reasonably capture the central tendency (median) of the PK profiles in non-Japanese and Japanese patients. **(Figure 2)**
- Comparisons of model-predicted steady-state exposures provide substantial evidence of considerable overlap in the quizartinib and AC886 exposures between non-Japanese and Japanese patients. **(Figure 3)**

Concentration-QT Analysis

- A total of 3371 mean time-matched QTcF and concentration measurements from 263 patients were used for C-QTcF analysis.
- The covariate effect of Japanese population was evaluated on baseline QTcF, Emax of quizartinib, and Emax of AC886 and was not statistically significant.
- The pcVPC results suggest that the final C-QTc model was able to reasonably capture the central tendency (median) of the C-QTcF relationship in AC220-007 with non-Japanese and AC220-A-J201 with Japanese data. **(Figure 4)**
- The C-QTcF relationship in Japanese patients was adequately described by the same structural model developed for the non-Japanese study with parameters updated. **(Figure 5)**
- The predicted median ΔQTcF was 16.7 msec [90% CI: 14.7, 18.7 msec] at the geometric mean peak plasma quizartinib concentration (285 ng/mL) and corresponding AC886 concentration (213 ng/mL) on Cycle 1 Day 28 in Japanese patients with actual dosing history of 60 mg quizartinib once-daily administration in AC220-A-J201. **(Table 3)**

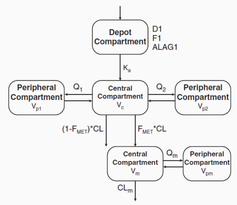
RESULTS (PopPK)

Table 1. Summary Statistics of Demographic Characteristics, Stratified by Healthy Subjects Versus Patients and by Japanese Versus Non-Japanese Subjects

Subject Characteristic	Statistic	Healthy Subjects From non-Japanese Studies#1	AML Patients From non-Japanese Studies#2	non-Japanese Studies#3	AML Patients From Japanese Studies#4
n		261	324	585	53
Age	Mean (SD)	35.4 (11.3)	53.2 (14.6)	45.3 (15.9)	61.4 (15.0)
Weight (kg)	Mean (SD)	76.7 (12.4)	74.5 (18.5)	75.5 (16.1)	53.3 (9.30)
Body Surface Area (m^2)	Mean (SD)	1.92 (0.192)	1.88 (0.258)	1.90 (0.232)	1.55 (0.168)
Sex, n (%)	Male	168 (64.4)	160 (49.4)	328 (56.1)	24 (45.3)
	Female	93 (35.6)	164 (50.6)	257 (43.9)	29 (54.7)
Race, n (%)	White	179 (68.6)	247 (76.2)	426 (72.8)	0 (0.0)
	Black or African American	62 (23.8)	12 (3.7)	74 (12.6)	0 (0.0)
	Asian – Non-Japanese	4 (1.5)	27 (8.3)	31 (5.3)	0 (0.0)
	American Indian or Alaska Native	5 (1.9)	1 (0.3)	6 (1.0)	0 (0.0)
	Native Hawaiian or Other Pacific Islander	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
	Other	10 (3.8)	8 (2.5)	18 (3.1)	0 (0.0)
	Asian - Japanese	0 (0.0)	0 (0.0)	0 (0.0)	53 (100.0)
	Unknown	0 (0.0)	29 (9.0)	29 (5.0)	0 (0.0)
CYP3A Inhibitors, n (%)	No or Mild	202 (77.4)	125 (38.6)	327 (55.9)	32 (60.4)
	Moderate	30 (11.5)	107 (33.0)	137 (23.4)	18 (34.0)
	Strong	29 (11.1)	92 (28.4)	121 (20.7)	3 (5.7)
CYP3A Inducers, n (%)	No or Mild	261 (100.0)	323 (99.7)	584 (99.8)	53 (100.0)
	Moderate	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)

#1: AC220-014; Relative Bioavailability Study, AC220-015; DDI Study with ketoconazole, AC220-016; hepatic impairment study, AC220-018; DDI study with lansoprazole, #2: 2689-CL-0011; Phase 1 Study of maintenance therapy in patient with AML, 2689-CL-2004; Phase 2 study in patients with R/R AML, AC220-007; Phase 3 in patients with R/R AML, #3: all patients in #1 and #2, #4: AC220-A-J101; Phase 1 study Japanese patients with R/R AML , AC220-A-J201; Phase 2 study Japanese patients with R/R AML
Abbreviations: AML, acute myeloid leukemia; CYP, cytochrome P450; n, number of subjects; SD, standard deviation.

Figure 1. Model Diagram and Equation with final parameters for Quizartinib and AC886 Population Pharmacokinetic Model



$$CL_i = 3.45 \times \left(1 + \left(0.761 \times flag_{PATIENT_i}\right)\right) + \left(-0.476 \times flag_{STRCYP}\right)$$

$$V_{c_i} = 218 \times \left(\frac{ALB_i}{4.1}\right)^{-1.45} \times \left(\frac{BSA_i}{1.9}\right)^{1.23} \times \left(1 + \left(0.382 \times flag_{PATIENT_i}\right)\right)$$

$$F1_i = 1 + \left(0.196 \times flag_{STRCYP_i}\right), \quad k_a = 0.925, \quad D1_i = 1.23$$

$$V_{p1_i} = 140 \times \left(1 + \left(1.37 \times flag_{PATIENT_i}\right)\right), \quad V_{p2_i} = 53.5, \quad Q1_i = 27.0, \quad Q2_i = 0.612$$

$$CL_{m_i} = 4.78 \times \left(\frac{BSA_i}{1.9}\right)^{1.25} \times \left(1 + \left(0.493 \times flag_{RACB_i}\right) + \left(0.251 \times flag_{STRCYP_i}\right)\right)$$

$$V_{cm_i} = 2.85 \times \left(1 + \left(7.54 \times flag_{STRCYP_i}\right)\right) + \left(1.54 \times flag_{PATIENT_i}\right)$$

$$F_{MET_i} = 0.5\ (Fixed), \quad V_{pm_i} = 56.7, \quad Q_{m_i} = 3.46$$

D1, duration of zero-order input; F1, bioavailability;ALAG1,absorption lag time; K_a, first-order absorption rate constant; V_c, central volume of distribution; V_{p1}, peripheral volume of distribution 1;V_{p2},peripheral volume of distribution 2;
Q1, intercompartmental clearance 1; Q_2, intercompartmental clearance 2; CL, clearance; FMET, parent-to-metabolite conversion fraction; V_m, central volume of distribution for metabolite; V_{pm}, peripheral volume of distribution for metabolite; Q_m, intercompartmental clearance for metabolite; CL_m, metabolite clearance.
ALB_i, serum albumin (g/dL); BSA_i, body surface area surface area (m^2); $flag_{PATIENT}$, the indicator variable for patient status (healthy subject or patient with AML); $flag_{STRCYP}$, the indicator variable for strong CYP3A inhibitor use; $flag_{RACB}$, the indicator variable for Black/African American race

Figure 2. Prediction-Corrected Visual Predictive Check for the Final Population Pharmacokinetic Model Stratified by Study for Quizartinib in AC220-007 with non-Japanese AML patient (A) , AC220-A-J201 with Japanese AML patient (B), and the corresponding figures for AC886 (C and D).

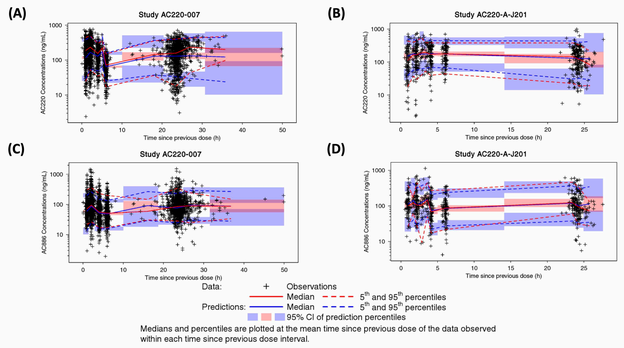
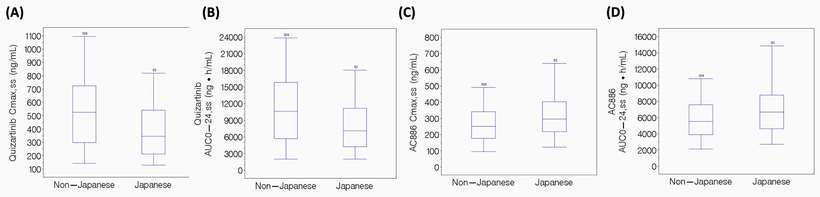


Figure 3. Model-Predicted Steady-State Quizartinib Cmax, AUC(0-24h) (A, B) and AC886 (C, D) Following 60 mg Once Daily Quizartinib Dosing in Non-Japanese Patients and Japanese Patients



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95 percentiles. The number of subjects is above each box.

RESULTS (C-QTc)

Table 2. Summary of Baseline Characteristics of Patient Demographics, Electrolyte Levels, and Concomitant Medication Use in Concentration-QTcF Analysis Dataset

Patient Characteristic	Statistic	Study AC220-007	Study AC220-A-J201	Overall
n		226	37	263
Age (y)	Mean (SD)	53.9 (14.4)	60.0 (14.6)	54.8 (14.6)
Baseline QTcF (msec)	Mean (SD)	415 (20.0)	415 (17.2)	415 (19.6)
Baseline Body Weight (kg)	Mean (SD)	74.1 (18.8)	53.5 (8.88)	71.2 (19.2)
Race, n (%)	White	168 (74.3)	0 (0.00)	168 (63.9)
	Black	8 (3.54)	0 (0.00)	8 (3.04)
	Asian	24 (10.6)	37 (100)	61 (23.2)
	American Indian or Alaska Native	1 (0.442)	0 (0.00)	1 (0.380)
	Other	7 (3.10)	0 (0.00)	7 (2.66)
	Unknown	18 (7.96)	0 (0.00)	18 (6.84)
Sex, n (%)	Male	104 (46.0)	15 (40.5)	119 (45.2)
	Female	122 (54.0)	22 (59.5)	144 (54.8)
Hypokalemia Flag[a], n (%)	No	191 (84.5)	34 (91.9)	225 (85.6)
	Yes	35 (15.5)	3 (8.11)	38 (14.4)
QTc Prolonging Drug Use, n (%)	No	160 (70.8)	23 (62.2)	183 (69.6)
	Yes	66 (29.2)	14 (37.8)	80 (30.4)

Abbreviations: n, number of patients; QTc, QT interval corrected for heart rate; QTcF, QT interval corrected using Fridericia's formula; SD, standard deviation.
[a] Hypokalemia flag: Serum potassium level of < 3.5 mM/L.

Figure 4. Prediction-Corrected Visual Predictive Check for the Final QTcF Model Stratified by Study AC220-007 (A) and Study AC220-A-J201 (B), With Observations Overlaid

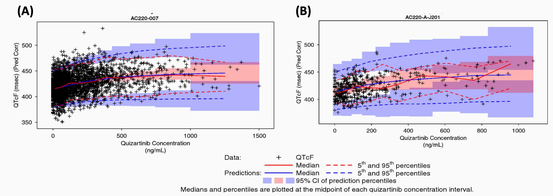
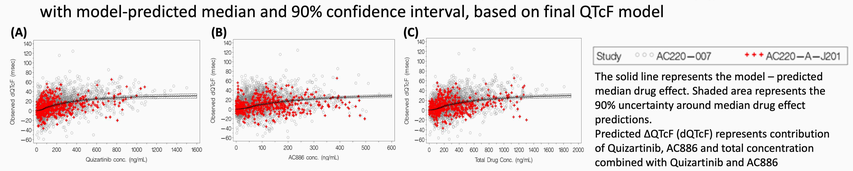


Figure 5. Scatterplots of ΔQTcF Versus Quizartinib (A), AC886 (B), and Total Concentrations (C), Overlaid with model-predicted median and 90% confidence interval, based on final QTcF model



The solid line represents the model – predicted median drug effect. Shaded area represents the 90% uncertainty around median drug effect predictions.
Predicted ΔQTcF (dQTcF) represents contribution of Quizartinib, AC886 and total concentration combined with Quizartinib and AC886

Table 3. Model-Predicted Median ΔQTcF at Steady State on Cycle 1 Day 28 in Studies With Japanese Patients

Simulation Population	Geo Mean of Simulated Individual Quizartinib Cmax,ss (ng/mL)[a]	Geo Mean of Simulated Individual AC886 Concentration (ng/mL)[b]	Final QTcF Model (Quizartinib and AC886)		
			Median Predicted ΔQTcF (msec)[c]	Lower Bound of 90% CI Around Median ΔQTcF (msec)	Upper Bound of 90% CI Around Median ΔQTcF (msec)
AC220-A-J201	285	213	16.7	14.7	18.7

a: Obtained from simulation of Cmax,ss of quizartinib in patients who were on 60 mg on Cycle 1 - Day 28 in Study AC220-A-J201 (n = 22) using their actual dosing history, including use of strong CYP3A inhibitors and dose escalation and reduction as per protocol.
b: Pharmacokinetic model-predicted AC886 concentration at the time of quizartinib Cmax,ss.
c: The ΔQTcF was calculated by applying geometric mean of quizartinib Cmax,ss and geometric mean of AC886 concentration to final C-QTcF model structure with 1000 replicates of parametric bootstrapping performed.

CONCLUSIONS

- The PopPK analysis demonstrated similar PK profiles of quizartinib and AC886 in Japanese and non-Japanese AML patients.
- There were no significant differences in the C-QTcF relationships for quizartinib and AC886 between the Japanese and non-Japanese AML patients.
- These results support the same dosing regimen for quizartinib in Japanese and non-Japanese AML patients.

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DISCLOSURES

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