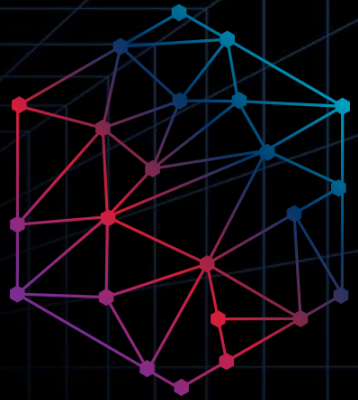
Model-Informed Drug Development

MIDD+

2021 Virtual Conference



Population Pharmacokinetic (PopPK) and Concentration-QTc Analysis of Quizartinib in Patients With FLT3-ITD–Positive Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML)

Dongwoo Kang,[1] Elizabeth Ludwig,[2] David Jaworowicz,[2] Hannah Huang,[2] Jill Fiedler-Kelly,[2] et al

[1]Daiichi Sankyo, Inc, Basking Ridge, NJ; [2]Cognigen Corporation, a Simulations Plus company, Buffalo, NY

SimulationsPlus

Cognigen | DILIsym Services | Lixoft

Background

- Fms-related tyrosine kinase 3 (*FLT3*) is expressed in hematopoietic progenitor cells; signaling through FLT3 promotes their proliferation and differentiation. *FLT3* is mutated in approximately 30% of patients with AML[1,2]
- The *FLT3*–internal tandem duplication (ITD) mutation represents the most common type of *FLT3* mutation and is associated with high relapse rates, decreased response to salvage therapy, and shorter overall survival (OS)[1-4]
- Quizartinib is an oral, once-daily, highly potent and selective, next-generation, type II FLT3 inhibitor that has shown high clinical activity in patients with *FLT3*-ITD–positive R/R AML[5,6]
- Single-agent quizartinib demonstrated a clinically meaningful OS benefit in patients with R/R *FLT3*-ITD AML vs salvage chemotherapy, with a 24% reduction in the risk of death in the phase 3 QuANTUM-R (AC220-007) trial[7]

Note: Based on poster presented in ACoP10, Oct. 2019

Objectives

- The objectives of the present analyses were to:*
  - Develop PopPK models for quizartinib and its major metabolite (AC886) in a pooled analysis of 7 trials
  - Evaluate the exposure-response relationship between quizartinib concentration and the QT interval by electrocardiogram (ECG) corrected for heart rate (QTc) in patients in the QuANTUM-R study

*The content of this presentation is limited to the conc-QTc analysis

Methods

- Data Included
  - Concentration-QTc model development included only data from the QuANTUM-R study
  - PK samples were obtained at matched time points at which ECGs were taken: pre-dose, 2, 4, and 6 hours post-dose on PK visit days, then less frequently on other visit days
    - Observed ECG data was corrected with heart rate using Fridericia's calculation
- Modeling Procedure
  - For the C-QTc model, various structural models were considered as the base model, including linear and nonlinear models. Forward addition ($\alpha = .01$) followed by backward elimination ($\alpha = .001$) was used to build the covariate model. Thorough evaluation of the model was considered, including circadian rhythm correction, evaluation of parameter distributions, test for hysteresis, and incorporation of effect from the AC886 metabolite
  - Nonlinear mixed-effects modeling in NONMEM version 7.3 (ICON Development Solutions) was used for PopPK and C-QTc analyses. SAS version 9.4 (SAS Institute), R software version 3.1.2 (The R Foundation), and KIWI Version 2 (Cognigen Corporation, a Simulations Plus company) were used for data manipulation and plotting, respectively

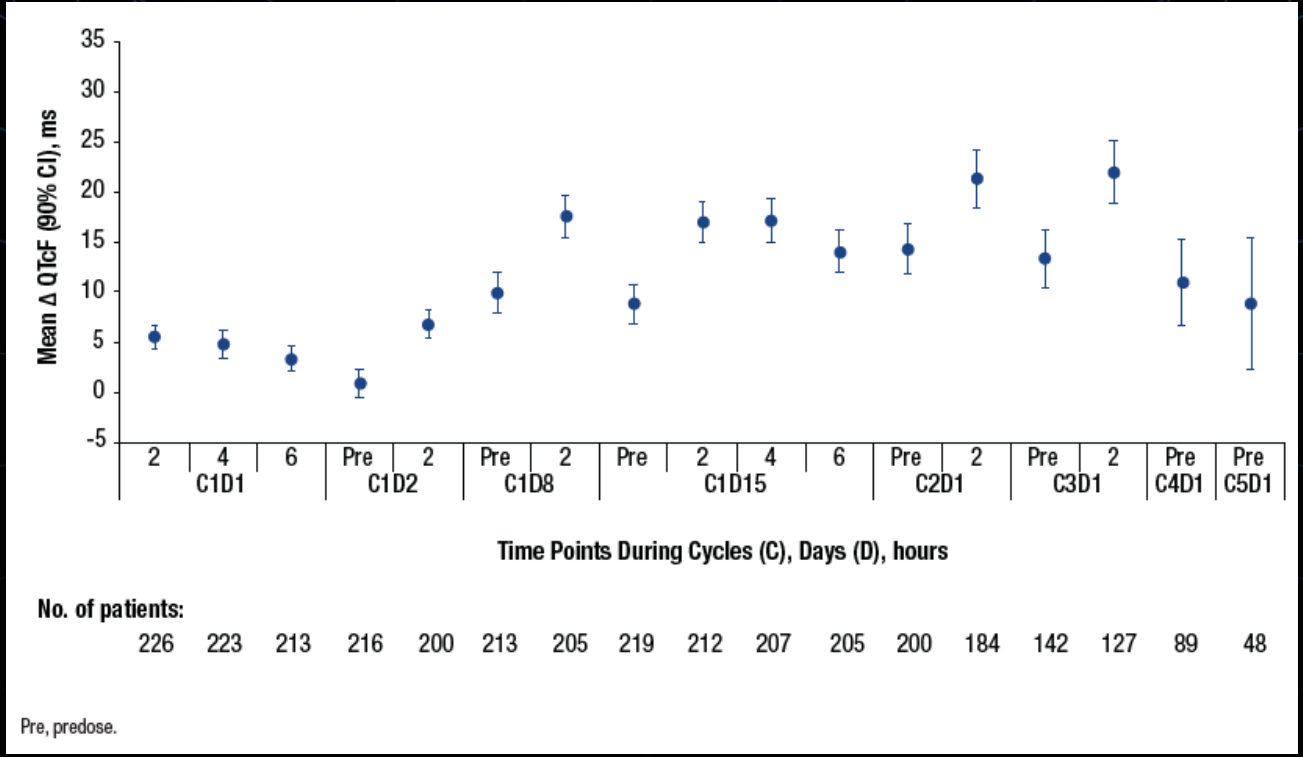
Results: Summary of Patient Characteristics

- A total of 2842 PK-matched mean QTcF samples were available from 226 participants for the C-QTc analysis
  - A 30-minute window was used to match PK and QTcF samples, except for 24-hour samples, for which a 90-minute window was used

Characteristic	N = 226
Age, median (range), years	55 (19, 81)
Sex, n (%)	
Male	104 (46.0)
Female	122 (54.0)
Race, n (%)	
White	168 (74.3)
Black or African American	8 (3.5)
Asian	24 (10.6)
American Indian or Alaska Native	1 (0.4)
Other	7 (3.1)
Unknown	18 (8.0)
Weight, median (range), kg	70.0 (39.5, 147)
QTcF, median (range), ms	414 (364, 471)
Hypocalcemia, n (%)	97 (42.9)
Hypokalemia, n (%)	35 (15.5)
Hypomagnesemia, n (%)	63 (27.9)
QT-prolonging drug use, n (%)	66 (29.2)

Summary of demographics and covariates for C-QTc data set. All factors were tested for covariate effects on slope and intercept except for baseline QTcF, which was tested for slope only.

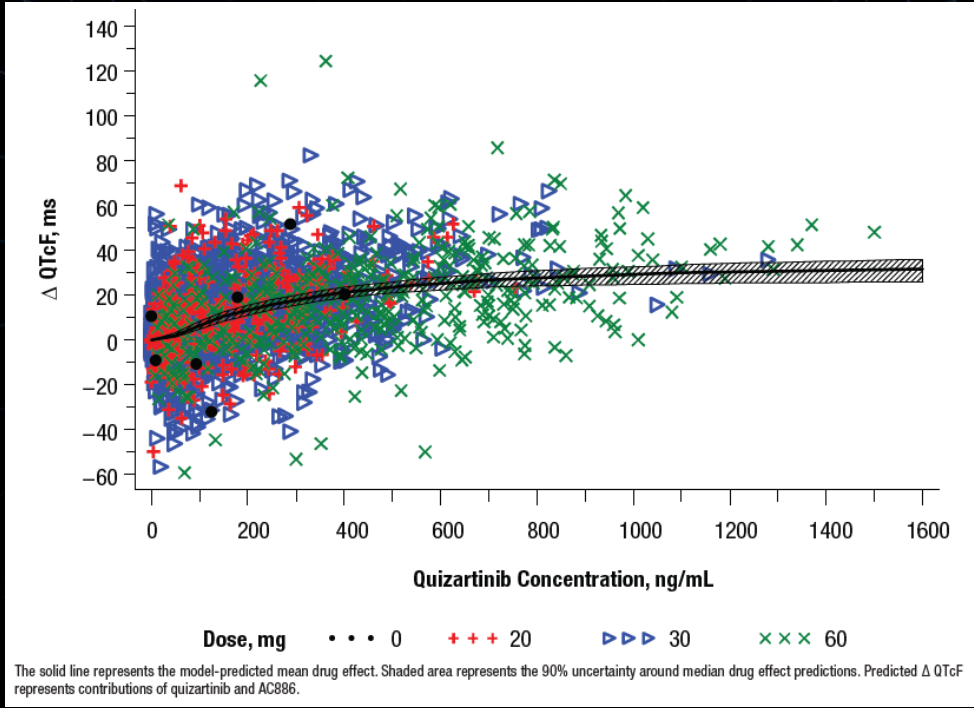
Results: Observed ΔQTcF Data with Respect to Visit Days



Results: C-QTc Analysis

- An exposure-response model described the relationship between quizartinib and AC886 concentrations and QTcF: the model was parameterized in terms of baseline QTcF, fixed time effect parameters for the circadian rhythm correction of baseline QTcF, and separate sigmoid maximum pharmacological effect (E_{max}) functions for quizartinib and AC886. The choice of E_{max} functions was driven by the observed data in QuANTUM-R and, hence, serves as "fit-for-purpose."
- QTc shows an exposure-dependent increase with respect to quizartinib and AC886 concentrations; the relative contribution from quizartinib and AC886 is ~ 12:1
- Hypokalemia (serum potassium < 3.5 mmol/L) was a statistically significant covariate on baseline QTcF, but not on E_{max}. In patients with hypokalemia, baseline QTcF was predicted to be prolonged by 6.15 msec compared with the population mean of 413 msec. At the same quizartinib and AC886 concentrations, ΔQTcF would be expected to be the same in patients with or without hypokalemia

Results: Scatterplot of ΔQTcF vs Quizartinib Concentration by Dose, With Mean (90%CI) ΔQTcF (Black)



The solid line represents the model-predicted mean drug effect. Shaded area represents the 90% uncertainty around median drug effect predictions. Predicted Δ QTcF represents contributions of quizartinib and AC886.

Results: C-QTc Analysis (cont'd)

- The predicted mean Δ QTcF at the geometric mean C_{max} of quizartinib (and the corresponding AC886 concentration) following 28 days of 60-mg, once-daily dosing in the actual study population is 21.1 ms (90% CI, 18.3-23.6 ms)
- The predicted mean Δ QTcF for nominal dosing of 60 mg once daily without dose adjustment and without the use of strong CYP3A inhibitors is higher, 22.4 ms (90% CI, 19.5-24.9 ms)

Dose	Mean Δ QTcF, ms	90% CI, ms
30 mg[a]	14.6	(12.3-17.0)
60 mg[b]	21.1	(18.3-23.6)
60 mg[a]	22.4	(19.5-24.9)

[a] 30 days of nominal dosing without the use of strong CYP3A inhibitors (n = 226).
[b] On day 28 following actual dosing used in the QuANTUM-R study, based on QT-based and other dose modifications (n = 109).

Conclusions

- QTcF showed an exposure-dependent increase with respect to quizartinib and AC886 concentration; however, no factors, including sex and age, were identified to have a clinically relevant effect on the concentration-QTc relationship

References

1. Daver N, et al. Leukemia. 2019;33(2):299-312.
2. Levis M. Hematology Am Soc Hematol Educ Program. 2013;2013:220-226.
3. Boissel N, et al. Leukemia. 2002;16(9):1699-1704.
4. Ravandi F, et al. Leuk Res. 2010;34(6):752-756.
5. Cortes J, et al. Lancet Oncol. 2018;19:889-903.
6. Cortes JE, et al. Blood. 2018;132:598-607.
7. Cortes JE, et al. Lancet Oncol. 2019;20(7):984-997.
8. Sandmaier BM, et al. Am J Hematol. 2018;93(2):222-231

Q&A

Questions & Answers

Model-Informed Drug Development

MIDD+

2021 Virtual Conference

Learn More! www.simulations-plus.com

SimulationsPlus

Cognigen | DILIsym Services | Lixoft