FDA Briefing Document

Oncologic Drugs Advisory Committee (ODAC) Meeting
May 14, 2019

NDA 212166
Quizartinib
Applicant: Daiichi-Sankyo, Inc.

DISCLAIMER STATEMENTS

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the quizartinib NDA to this Advisory Committee in order to gain the Committee's insights and opinions regarding the effectiveness and safety of the proposed drug product for the proposed oncologic indication. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the FDA for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

The doses of quizartinib quoted in this document are expressed as the salt form; 30 mg of the salt form is equivalent to the 26.5 mg dosage as free base, and 60 mg of the salt form is equivalent to the 53 mg dosage as free base.

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ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALL	Acute lymphoblastic leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
CR	Complete remission
DCAS	Direct Comparison Analysis Set
DFS	Disease-free survival
EFS	Event-free survival
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
IPD	Individual patient-level data
IPTW	Inverse Probability or Treatment Weight
sIPTW	Stabilized Inverse Probability or Treatment Weight
IRC	Independent Review Committee
MRD	Minimal residual disease
OR	Odds ratio
OS	Overall survival
PLT	Platelets
RFS	Relapse-free survival
SAE	Serious adverse event
SMQ	Standardized MedDRA query
VOD	Veno-occlusive disease

1. INTRODUCTION

1.1 Proposed Indication

The applicant is seeking approval of quizartinib, a multikinase inhibitor, for the indication "treatment of adults with relapsed or refractory acute myeloid leukemia (AML) which is FLT3-ITD positive, as detected by an FDA-approved test."

1.2 Purpose of the Meeting

The purpose of this Advisory Committee meeting is to discuss a) whether the overall survival (OS) results from Study AC220-007 are credible, b) what risk management strategies would be useful to reduce the risks of potentially fatal cardiac toxicity, and c) whether the small OS advantage for quizartinib outweighs the risks of treatment.

The applicant submitted the results of Study AC220-007 to support its marketing application. Study AC220-007 was a randomized trial comparing quizartinib, at a starting dose of 30 mg daily by mouth with an increase to 60 mg daily on day 15 in the absence of QTcF prolongation, to standard-of-care (SOC) chemotherapy for the treatment of adult patients with FLT3-ITD positive relapsed or refractory AML (R/R AML). The primary endpoint of the study was OS. There were 367 patients randomized. The analysis of OS on the ITT population showed a statistically significant improvement with a hazard ratio (HR) of 0.77 (95% CI 0.59, 0.99; p=0.019), but analysis of the secondary endpoint, event-free survival (EFS), did not show a statistically significant improvement (HR 0.9; 95% CI 0.71, 1.16; p=0.114). Complete remission (CR) rates were similar between the arms (4% on the quizartinib arm vs 1% on the SOC arm).

The credibility of the results of the primary efficacy endpoint analysis in Study AC220-007 were challenged by multiple findings. In the ITT population, 4 patients (2%) on the quizartinib arm were randomized and not treated, and 1 patient (0.4%) was censored for the OS endpoint prior to week 8. In contrast, 28 patients (23%) randomized to the SOC arm were not treated, and 9 patients (7%) were censored for the OS endpoint prior to week 8. Additionally, subgroup analyses for OS by investigator-preselected chemotherapy group (high-intensity vs low-intensity), a stratification factor for the study, revealed a HR of 0.59 (95% CI 0.36, 0.97) for the low-intensity subgroup, compared to a HR of 0.83 (95% CI 0.62, 1.11) for the high-intensity subgroup, such that the results appear to be driven by the low-intensity stratum. Differences between the study arms in subsequent poststudy therapies were also noted, including a much higher rate of allogeneic hematopoietic stem cell transplantation (HSCT) in the quizartinib arm (23%) than in the chemotherapy control arm (0%) in the low-intensity stratum.

Quizartinib is known to inhibit the slow delayed rectifier outward potassium current (IKs) and prolong QTc. In a concentration-QTcF analysis, the mean ΔQTcF was 12.0 ms with quizartinib 30 mg and 20.1 ms with quizartinib 60 mg; these prolongations of QTcF are consistent with an increased risk of arrhythmias. In AC220-007, there was a higher incidence of QT prolongation and associated adverse events in the quizartinib arm. Across the quizartinib clinical development program, the risk of on-treatment deaths due to cardiac events was estimated as 1-2%. If quizartinib is marketed, potential strategies to manage the risk of this cardiac toxicity might include a boxed warning, a contra-indication for use with other QT prolonging drugs, a recommendation for administration of beta blockers to prevent arrythmias, a medication guide to educate patients, and a Risk Evaluation and Mitigation Strategy comprised of a communication plan to inform healthcare providers.

When comparing treatment-related adverse reactions (TEAEs) between the arms on Study AC220-007, the quizartinib arm had a higher incidence of QT prolongation and arrhythmias, and a lower incidence of gastrointestinal events for the intensive chemotherapy stratum. For the low-intensity chemotherapy stratum, the quizartinib arm had a higher incidence of QT prolongation, arrhythmias, cytopenias and gastrointestinal disorders. Mild neutropenia could be prolonged. There was also a 7% risk of events on the spectrum of differentiation syndrome with or without acute febrile neutrophilic dermatosis in the patients treated with quizartinib, including fatal events.

FDA seeks input from the committee on whether the imbalance in early censoring and patients randomized but not treated between the arms on Study AC220-007, the inconsistency of the results across the stratification subgroups, and the effects of subsequent therapies on the primary endpoint impact the interpretation of the study results to a degree that renders them unreliable. The committee discussion will also assist the FDA in determining whether the 6.5 week OS benefit is sufficiently meaningful to outweigh the safety risks of therapy with quizartinib, and if marketed, what strategies might be effective in reducing the risk of fatal cardiac events.

2. ESTABLISHMENT OF EFFECTIVENESS

2.1 Background

To obtain marketing approval, the Food Drug and Cosmetics Act (FD&C Act) requires that sponsors provide substantial evidence of safety and efficacy of their products based on the conduct of adequate and well-controlled studies. For treatment of conditions that are not immediately life-threatening, or where there is not considered to be an unmet medical need, this generally understood to mean more than one randomized trial. In oncology in general, and in the treatment of AML in particular, where the conditions are serious or life-threatening and the

available therapies are limited, a single trial has been accepted to support a marketing application.[1] This does not reflect a lower standard for effectiveness than is used in other clinical contexts. For a single trial to be used as the basis for marketing approval, it must be well-designed, well-conducted and provide statistically-persuasive efficacy findings that are robust and so compelling as to make a second trial unethical or practically impossible to perform.

There are several clinical outcomes that have been used as measures of effectiveness for AML therapies. Overall survival (OS) has long been considered the optimal endpoint to establish efficacy for agents used in the treatment of AML. As discussed at the Oncologic Drugs Advisory Committee Meeting on July 11, 2017, however, with the emergence of multiple new effective drugs for AML that may be used as poststudy treatments, OS may no longer be an accurate reflection of the treatment effect in clinical trials. Event-free survival (EFS), which relies on events that would occur prior to use of poststudy treatments, has recently been accepted as a clinical benefit of new drugs for AML (Jen et al. 2018). Achievement of complete remission (CR) is generally considered reasonably likely to predict a clinical benefit such as OS, but in the noncurative setting, CR that is of long duration may be a clinical benefit in itself. Lastly, for therapies that are relatively nontoxic and not myelosuppressive, CR or CR with partial hematologic recovery (CR/CRh) associated transfusion independence may represent clinical benefit. No matter which endpoint is considered primary, for a single trial to constitute substantial evidence of efficacy, the results should be consistent across the efficacy endpoints.

2.2 Study AC220-007: FDA's Assessment of the Issues for the Efficacy Analysis

To support the marketing application for quizartinib for the proposed indication, the applicant submitted the results of the Study AC220-007, a randomized, open-label, active-control study of quizartinib compared to chemotherapy in adult patients with FLT3-ITD$^+$ AML that was refractory or that relapsed within 6 months of first remission. The chemotherapy to be used for an individual patient was declared prior to randomization, so that patients could be stratified by intensity of the preselected regimen [intensive chemotherapy [MEC or FLAG-IDA) or low-intensity chemotherapy (LDAC)]. The details of the study are as described in Section 9 of the Applicant's Briefing Document. The primary endpoint of the study was OS. The applicant seeks to use the OS results to provide evidence of efficacy for quizartinib based on a HR of 0.76 (95% CI 0.58, 0.98) with a 1.5 months difference in median OS between arms (median OS 6.2 months for the quizartinib arm and 4.7 months for the chemotherapy arm).

[1] "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Guidance for Industry" (December 2018) https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf

Upon review of the study results, FDA identified the following issues that raised doubts regarding the credibility of the OS results:

- Imbalances in the rates of patients who were early-censored for OS (prior to week 8 after randomization) and in the number of patients randomized but not treated (RNT);
- Inconsistent OS treatment effect by strata based on intensive vs low-intensity chemotherapy;
- Confounding of the assessment of OS by the follow-on therapies which patients received after discontinuation from Study AC220-007 study treatment; and
- Lack of treatment effect in additional efficacy endpoints.

The specific details and uncertainties raised by these issues are detailed below.

2.2.1 Early Censoring And Patients Randomized Not Treated

Study AC220-007 randomized patients 2:1 to receive quizartinib (n=245) or chemotherapy (n=122). FDA noted a imbalance between arms in the numbers of patients randomized but not treated (RNT) and in the numbers of patients censored early. On the quizartinib arm, there were 4 (2%) RNT patients, whereas on the chemotherapy control arm, there were 28 (23%) RNT patients. Additionally, there was 1 (<1%) patient on the quizartinib arm censored early and 9 (7%) patients on the chemotherapy arm censored early.

The discussion will make use of the following terminology:

- *early censoring* is defined as censoring < 8 weeks after randomization and abbreviated *EC8*.
- *early death* is defined as death < 8 weeks after randomization and abbreviated *ED8*.
- the patients with survival follow-up at least 8 weeks are abbreviated as *GE8*

ED8 is not statistically of interest with respect to the resampling analysis discussed below. The terminology is needed to understand that the set of patients who are not early-censored includes a) patients who die < 8 weeks after randomization (ED8) and b) patients with survival follow-up at least 8 weeks (GE8).

Table 1 shows a breakdown of the numbers of patients with early censoring by study arm and chemotherapy intensity stratum. It should be noted that FDA used an updated data file for these analyses, so there may be small differences in the results displayed in comparison to those reported in the Applicant's Briefing Document Sections 9.1.9 and 9.1.11.4.

Table 1. Summary of Numbers of Early-Censoring, Randomized-Not-Treated, and Randomized-Treated Patients By Chemotherapy Intensity Stratum

			RNT			RT		
Study Arm	**Stratum**	**N**	**EC8**	**ED8**	**GE8**	**EC8**	**ED8**	**GE8**
Quizartinib	LDAC	57	0	1	1	0	7	48
	MEC/FLAG-IDA	188	0	2	0	1	8	177
	Total	**245**	**0**	**3**	**1**	**1**	**15**	**225**
Chemotherapy	LDAC	29	1	2	4	0	8	14
	MEC/FLAG-IDA	93	6	3	12	2	13	57
	Total	**122**	**7**	**5**	**16**	**2**	**21**	**71**

Source: FDA analysis using updated data submitted 3/15/2019
Additional abbreviations:
RNT, randomized but not treated
RT, randomized and treated
EC8, censored < 8 weeks after randomization
ED8, died < 8 weeks after randomization
GE8, survived with follow-up at least 8 weeks after randomization

As patients who are early-censored do not provide (or provide very little) information relevant to the determination of the treatment effect, it is unknown to what extent the treatment effect could change and in what direction had early-censored patients remained observable beyond their early-censored time. It is also unknown to what extent the treatment effect could change and in what direction had RNT patients been treated with study therapy. FDA raised a question as to whether the substantial differences between study arms in early censoring and RNT rather than the treatment effect of quizartinib could have given rise to a small but statistically significant OS advantage. FDA therefore performed stress test analyses to assess whether the quizartinib survival advantage over chemotherapy observed in the primary OS analysis continues to hold under potentially reasonable sets of assumptions about early censoring and RNT.

FDA's stress tests employ a similar resampling methodology described in the Applicant's Statistical Analysis Plan but under a different set of assumptions than those of the Applicant. The assumptions that go into FDA's stress test simulation study are obtained by asking the following questions:

- **Question 1**. Per Table 1, consider the 6 patients in the chemotherapy arm in stratum "MEC/FLAG-IDA" who are RNT and EC8. What would these patients' event times and statuses look like had they been treated with study therapy and were not EC8? A reasonable assumption is that their survival times and statuses would resemble the 57 "MEC/FLAG-IDA" RT patients with follow-up time for at least 8 weeks (GE8).

- **Question 2**. Per Table 1, consider the 12 patients in the chemotherapy arm in stratum "MEC/FLAG-IDA" who are RNT and GE8. What would their survival times and statuses look like had they been treated with study therapy? A reasonable assumption is also that their survival times and statuses would resemble the 57 "MEC/FLAG-IDA" RT patients with follow-up time for at least 8 weeks. However, it is possible that for some of these patients, receiving study therapy in the study setting might not matter; their survival times and statuses could conceivably remain the same.

  We introduce a mixture probability, denoted as π, to cope with these two types of patients. However, as it is not known what π should be, we consider a range of values for π: from 0.10 to 0.95 with 0.95 indicating that for approximately 95% of RNT patients with follow-up for at least 8 weeks, treating them with study therapy would not change the outcome.

- **Question 3**. Per Table 1, consider the 2 patients in the chemotherapy arm in stratum "MEC/FLAG-IDA" who are RT and EC8. What would their survival times and statuses look like had they not been EC8? Again, a reasonable assumption is also that their survival times and statuses would resemble the 57 "MEC/FLAG-IDA" RT patients with follow-up time for at least 8 weeks.

- **Question 4**. Per Table 1, consider the 3 patients in the chemotherapy arm in stratum "MEC/FLAG-IDA" who are RNT and died < 8 post-randomization (ED8). What would their survival times and statuses look like had they been treated with study therapy? Since these are early-deaths, receiving study therapy is unlikely to change the outcome. Thus, for these RNT ED8 patients, it is reasonable to assume that treating them with study therapy would not change the outcome.

Details of the resampling algorithm are discussed in Appendix 1. Robustness of the primary OS results is assessed in three ways, by:

- the proportion of times (out of 20,000 simulations) that the stratified log-rank p values from the simulation, denoted by p^*, exceeds 0.02319, the prespecifed threshold for significance,
- the distribution of the estimated hazard ratios and estimated upper 95% confidence limit across 20,000 simulations,
- the distribution of the difference in estimated median OS across 20,000 simulations.

Table 2 provides a summary of FDA's simulation results with respect to the stratified log-rank test.

Table 2. Distribution of One-Sided *p and the Proportion of Failure to Achieve Statistical Significance in 20,000 Simulations**

	Proportion		Median			
Scenario	$p^* > 0.02319$	**Q1**	**p***	**Q3**	**P80**	**P90**
$\pi = 0.10$	**99.8%**	0.0859	**0.1236**	0.1738	0.1880	0.2284
$\pi = 0.40$	**96.9%**	0.0505	**0.0775**	0.1147	0.1257	0.1588
$\pi = 0.50$	**94.0%**	0.0418	**0.0639**	0.0959	0.1058	0.1354
$\pi = 0.60$	**90.1%**	0.0346	**0.0538**	0.0815	0.0898	0.1144
$\pi = 0.80$	**75.5%**	0.0234	**0.0355**	0.0536	0.0590	0.0765
$\pi = 0.90$	**63.7%**	0.0190	**0.0286**	0.0432	0.0476	0.0613
$\pi = 0.95$	**57.2%**	0.0174	**0.0259**	0.0381	0.0420	0.0538

Source: FDA analysis. For each row, 20,000 simulations were performed.

Note, that the value of π controls how many RNT GE8 patients have their survival times imputed. There are 16 RNT GE8 patients in the chemotherapy arm and 1 RNT GE8 patient in the quizartinib arm. When

- $\pi = 1$, the simulation does not impute survival times and statuses for any of the 16 RNT GE8 patients in the chemotherapy arm. That is, we assume that it would not have mattered had these 16 patients been treated with study therapy - their outcomes would have remained as is.
- $\pi = 0$, the simulation imputes survival times and statuses of all 16 RNT GE8 patients in the chemotherapy arm. That is, we assume that had these 16 RNT GE8 patients been treated with study therapy - their outcomes would resemble those of RT patients who are GE8.

The 2nd column in Table 2, labeled "Proportion $p^* > 0.02319$", provides information on the proportion of times that the log-rank test failed to achieve statistical significance. Note, even under the assumption that $\pi = 0.95$ (a scenario favorable to quizartinib where we assume that 95% of RNT patients with follow-up for at least 8 weeks would have the same survival information had they been treated with study therapy), the stratified logrank test failed to achieve statistical significance approximately 57% of the time. This is corroborated by the distribution of p^*:

- $\pi = 0.95$ - the median p^* is 0.0259
- $\pi = 0.10$ - the median p^* is 0.1236

Under the assumptions about EC8 and RNT that underlie Questions 1 through 4, the results in Table 2 suggest that the statistical OS advantage of quizartinib over chemotherapy observed in

the primary OS analysis, as assessed by the log-rank test, is not robust in the presence of differential early-censoring and randomized-not-treated.

Table 3 summarizes the behavior of the simulated hazard ratios (HR).

Table 3. Distribution of HR in 20,000 Simulations

	Estimated HR					Estimated 95% Upper CL				
Scenario	**Q1**	**Median**	**Q3**	**P80**	**P90**	**Q1**	**Median**	**Q3**	**P80**	**P90**
$\pi = 0.10$	0.84	**0.86**	0.89	0.89	0.91	1.08	**1.11**	1.14	1.15	1.17
$\pi = 0.40$	0.81	**0.84**	0.86	0.86	0.88	1.04	**1.07**	1.10	1.11	1.13
$\pi = 0.50$	0.80	**0.82**	0.85	0.85	0.87	1.03	**1.06**	1.09	1.10	1.12
$\pi = 0.60$	0.80	**0.82**	0.84	0.84	0.86	1.02	**1.05**	1.08	1.08	1.10
$\pi = 0.80$	0.78	**0.80**	0.82	0.82	0.83	1.00	**1.02**	1.05	1.05	1.07
$\pi = 0.90$	0.77	**0.79**	0.81	0.81	0.82	0.99	**1.01**	1.03	1.04	1.06
$\pi = 0.95$	0.77	**0.78**	0.80	0.80	0.82	0.98	**1.00**	1.02	1.03	1.05

Source: FDA analysis. For each row, 20000 simulations were performed.

The first set of columns in Table 3 (Estimated HR) pertains to the distribution of the HR point estimate, and the second set of columns (Estimated 95% Upper CL) pertains to that of the upper 95% confidence limit of the HR. Observe that the medians of the estimated upper 95% confidence limit are at least 1.0 for all scenarios, also raising questions about the survival advantage of quizartinib over chemotherapy as quantified by the hazard ratio.

Table 4 below summarizes the difference in estimated median OS across the simulations. The median values of the differences in the estimated OS medians (the difference between study arms) seem to range between 3.9 and 5.6 weeks.

Table 4. Distribution of Difference in Median OS in 20,000 Simulations

			Median OS				
Scenario	**Min**	**Q1**	**Difference (wks)**	**Q3**	**P80**	**P90**	**Max**
$\pi = 0.10$	-0.7	3.6	**3.9**	4.3	4.3	4.6	7.4
$\pi = 0.40$	0.3	4.0	**4.3**	5.0	5.0	5.6	7.4
$\pi = 0.50$	1.7	4.1	**4.3**	5.3	5.3	5.7	7.4
$\pi = 0.60$	1.6	4.3	**4.9**	5.4	5.6	6.4	7.4
$\pi = 0.80$	3.4	4.9	**5.4**	5.7	6.4	6.6	7.4
$\pi = 0.90$	3.4	5.0	**5.6**	6.4	6.6	6.9	7.4
$\pi = 0.95$	3.6	5.3	**5.6**	6.4	6.6	6.9	7.7

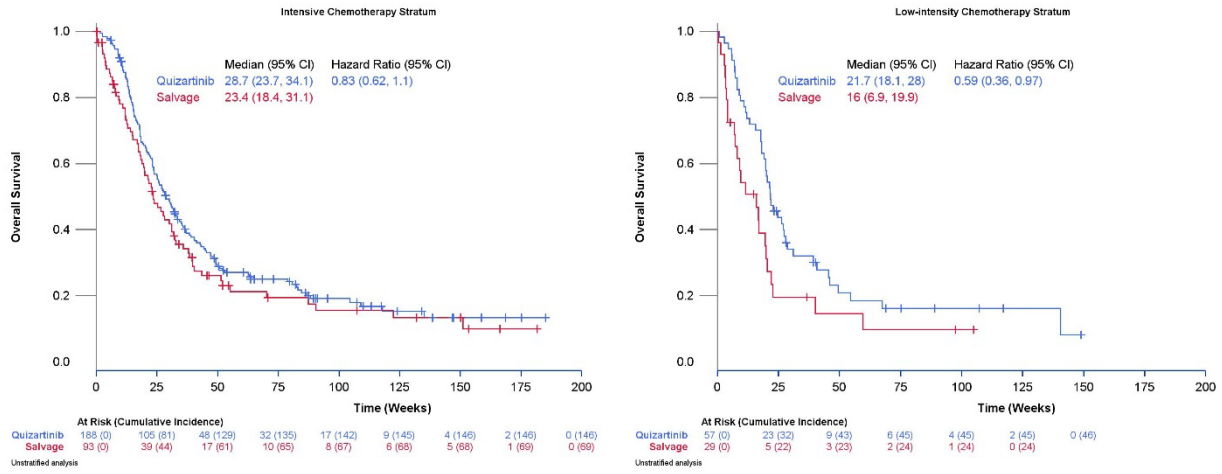
Source: FDA analysis. For each row, 20000 simulations were performed.

In summary, the simulations for the logrank p-value, HR and difference in OS suggest that the observed results are not robust.

2.2.2 Differences in Treatment Effect by Chemotherapy Intensity Stratum

For Study AC220-007, the chemotherapy to be used for an individual patient in the control arm was declared prior to randomization, so that patients could be stratified by intensity of the preselected regimen. The options included intensive chemotherapy (MEC or FLAG-IDA) or low-intensity chemotherapy (LDAC). It should be noted that the eligibility criteria were the same for both the intensive and low-intensity chemotherapy strata. Of the 367 patients who were randomized, 281 (77%) were preselected for intensive chemotherapy, and 86 (23%) were preselected for low-intensity chemotherapy. OS results by the preselected chemotherapy stratum are summarized in Figure 1 and Table 5 below.

Figure 1. Study AC220-007: Kaplan-Meier estimates for OS by Preselected Chemotherapy Stratum



Source: FDA analysis

Table 5. Study AC220-007: OS Results by Preselected Chemotherapy Stratum

	Intensive Stratum (MEC; FLAG-IDA)		Low intensity Stratum (LDAC)	
	Quizartinib (N = 188)	**Chemotherapy (N=93)**	**Quizartinib (N =57)**	**Chemotherapy (N=29)**
Median OS, weeks (95% CI)	28.7 (23.7, 34.1)	23.4 (18.4, 31.1)	21.7 (18.1, 28)	16 (6.9, 19.9)
Hazard Ratio (95% CI)	0.83 (0.62, 1.11)		0.59 (0.36, 0.97)	

Source: FDA analysis

FDA noted that the significance level of the OS results for the ITT population appear to be driven by the large effect in the much smaller low-intensity stratum. Consequently, there remains uncertainty regarding the generalizability of the study results.

2.2.3 Effect of Subsequent Therapies

One-hundred and fifty one patients (41%) treated on both arms of Study AC220-007 received a poststudy therapy for AML (additional nonstudy therapies after discontinuation of study treatment). These included 93 patients (38%) on the quizartinib arm and 58 patients (48%) on the control arm. No patients preselected for low intensity therapy on the chemotherapy control arm proceeded to allogeneic HSCT. The poststudy therapies included hypomethylating agents (HMAs) such as azacitidine and decitabine, cytotoxic chemotherapies, allogeneic HSCT, approved FLT3 inhibitors and investigational agents (identified and unidentified). Where sufficient information was available, FDA categorized each poststudy regimen by intensity.

Allogeneic HSCT, intensive chemotherapy and other FLT3 inhibitors were considered as poststudy therapies that might influence OS. Allogeneic HSCT was used for 86 (35%) patients on the quizartinib arm and 21 (17%) patients on the chemotherapy control arm. No patients on the control arm preselected for the low-intensity stratum proceeded to allogeneic HSCT. Table 6 shows the percentage of patients who underwent allogeneic HSCT or who received intensive chemotherapy or another FLT3 inhibitor as poststudy therapy.

Table 6. Study AC220-007: Poststudy Therapies

	Intensive Stratum (MEC; FLAG-IDA)				Low-Intensity Stratum (LDAC)			
	Quizartinib Arm (N = 188)		Chemotherapy Control Arm (N=93)		Quizartinib Arm (N =57)		Chemotherapy Control Arm (N=29)	
Poststudy Therapy	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Allogeneic HSCT	73	39%	21	22%	13	23%	0	
In CR	3	1.5%	0	0%	-		0	
Not in CR	70	37%	21	23%	13	23%	0	
Intensive chemotherapy	44	23%	17	18%	8	14%	7	24%
Other FLT3 inhibitor[a]	26	14%	22	24%	5	9%	7	24%
Sorafenib	21	11%	19	20%	4	7%	5	17%
Gilteritinib	5	3%	3	3%	1	2%	1	3%
Midostaurin	1	0.5%	1	1%	0		0	
Pacritinib	0		0		0		1	3%

Source: FDA reviewer; [a]1 patient on each arm got 2 subsequent FLT3 inhibitors.

Although the use of poststudy therapies is consistent with the ITT principle and is a prominent feature of trials in oncology, an imbalance in use raises questions about how the poststudy therapies when used in an imbalanced fashion contributed to the observed OS treatment effect. The open-label nature of Study AC220-007 may exacerbate this contribution issue; it is unknown how knowledge of the study treatment might influence a patient's choice to receive a particular poststudy therapy or the investigator's choice to recommend a particular poststudy therapy such as HSCT or a FLT3 inhibitor.

FDA observed that the increased rates of subsequent allogeneic HSCT in the quizartinib arm compared with the control arm were due to an increased rate of subsequent allogeneic HSCT in non-responders on the quizartinib arm compared to the chemotherapy control arm. The low CR rate in both study arms precludes a comparison of the rate of subsequent allogeneic HSCT in responders between the arms; the rate of subsequent allogeneic HSCT for nonresponders was 34% in the quizartinib arm and 16% in the chemotherapy control arm, with the greatest differential being in the low-intensity chemotherapy stratum.

FDA compared OS between quizartinib and chemotherapy among patients who initiated poststudy HSCT using a Cox regression model with linear predictor described by

$$1 + Z + H(t) + Z.H(t)$$

and where

- $H(t)$ is a poststudy HSCT indicator with value 1 if a patient initiated HSCT at time t and 0 otherwise. Note that a patient may initiate other anti-AML therapies (for example, other FLT3s or HMAs) regardless of whether they initiate HSCT.
- Z is a treatment indicator with value 1 if quizartinib and 0 if chemotherapy

From this model, among patients who underwent poststudy HSCT, the estimated OS hazard ratio for quizartinib vs the chemotherapy control arm is not significant (HR 0.95; 95% CI: 0.5, 1.79). FDA recognizes that this is not proof of no difference (i.e., the interaction term is not statistically significant). FDA also recognizes that the interpretability of models making use of time-dependent covariates is an open question. Nevertheless, there is a question of whether there is a quizartinib survival advantage over chemotherapy among patients who initiate HSCT poststudy. To the extent that there is no survival advantage between quizartinib and chemotherapy patients once they initiate HSCT, and to the extent that poststudy selection into HSCT is different between arms among nonresponders, it is not clear to FDA how much of the observed treatment effect is attributable to quizartinib. Adding to this complication is the differential initiation of

alternative FLT3 therapies; the number of patients that initiated poststudy FLT3 therapies was 31 (13%) in the quizartinib arm and 29 (24%) in the chemotherapy control arm.

The applicant presented a sensitivity analysis whereby patients who underwent subsequent allogeneic HSCT were censored at the time of HSCT, the results of which were similar to those from the primary analyses (see Applicant Briefing Document, Section 9.1.11.3). FDA noted that this approach does not address the uncertainty of attributing the treatment effect to quizartinib compared to the subsequent allogeneic HSCT due to the differential censoring between the arms, as well as differential application of other therapies between the arms. Since AC220-007 was an open-label study, the potential for informative censoring, and a bias for proceeding with transplant on the quizartinib arm when a CRi was achieved, or for an investigational agent when this was the case with a patient on the control arm, cannot be excluded or definitively adjudicated.

2.2.4 Internal Consistency Among Efficacy Endpoints

In Study AC220-007, the primary efficacy endpoint was OS, the key secondary endpoint was EFS, and exploratory endpoints included rates of CR, complete remission with incomplete platelet recovery (CRp) and complete remission with incomplete hematologic recovery (CRi). Although CRp and CRi are frequently used as additional measures of biological activity in early phase trials, CRp and CRi are not considered a clinical benefit or reasonably likely to predict clinical benefit in patients with AML. For drugs that are not myelosuppressive, durable CRh and transfusion independence on treatment may also represent a meaningful palliative effect, so FDA also assessed these outcomes in the quizartinib arm.

The results of FDA's analysis of OS, EFS, CR, CR/CRh and transfusion independence are summarized in Table 8. For this analysis, EFS was calculated as defined by the Applicant. It should be noted that CR and CRh reported here are as adjudicated independently by the FDA clinical reviewer, and there may be small difference in comparison to the results reported by the Applicant.

Table 7. Study AC220-007: FDA Analysis of Efficacy Endpoints

	Quizartinib Arm N=245	Chemotherapy Control Arm N=122
Median OS	26.9 weeks	20.4 weeks
(95% CI)	(23.1, 31)	(17, 25.2)
HR (95% CI)	0.77 (0.59, 0.99)	
	p = 0.019	
Median EFS	6.0 weeks	3.7 weeks
(95% CI)	(0.1, 8.3)	(0.4, 6.0)
HR (95% CI)	0.9 (0.71, 1.16)	
	p = 0.114	
CR rate, n (%; 95% CI)	10/245 (4%; 2, 7%)	1/122 (1%; 0.1, 5%)
CR/CRh rate, n (%; 95% CI)	27/245 (11%; 8, 16%)	-
Achieved transfusion independence*	26/99 (26%: 19, 36%)	-

Source: FDA analysis using updated data submitted 3/15/2019

* Transfusion independence (TI) is defined as no platelet or RBC transfusion documented for any consecutive 56-day period on treatment. The analysis applies only to patients who were transfusion-dependent (TD) at study baseline. FDA defined TD as having received a platelet or red blood cell (RBC) transfusion through study day -1; the Applicant's definition of TD differed slightly, which may account for the difference in results as reported in the Applicant's Briefing Document Section 9.1.11.6, Table 9.8.

The results of the EFS analysis did not demonstrate a significant advantage for quizartinib over control chemotherapy. Additionally, the 4% CR rate, 11% CR/CRh rate, and 27% achievement of transfusion independence are small.

In summary, the results for the secondary and additional efficacy endpoint on study AC220-007 do not provide substantial supportive evidence of effectiveness.

2.3 Summary of Issues for the Efficacy Analysis

FDA acknowledges that the analysis of OS in Study AC220-007 demonstrates a statistically significant survival advantage with a 6.5 week difference between study arms. However, FDA identified multiple issues that challenge the credibility, interpretation and generalizability of the results of Study AC220-007. The issues identified include:

- There are imbalances between study arms in early censoring for OS and in the proportion of patients randomized-not-treated, prevalent mainly in the chemotherapy control arm. FDA's simulations suggest that the observed OS results are not robust.

- The OS results for the ITT population appear to be driven by the low-intensity stratum.
- There is an imbalance between study arms in the poststudy therapies reported, including allogeneic HSCT. Since Study AC220-007 was an open-label study, there may have been bias in the selection of poststudy therapies that could impact OS.
- Treatment with quizartinib did not have a substantial effect on the key secondary and additional efficacy endpoints.

3. CARDIAC TOXICITY

3.1 Background

The action potential of cardiac muscle is controlled by ion channels that conduct inward and outward flowing current. Small molecule drugs may interfere with these ion channels and predispose to cardiac arrhythmias. Two of these ion channels, IKr (the rapid delayed rectifier outward potassium current) and IKs (the slow delayed rectifier outward potassium current) are involved mainly in cardiac repolarization. With two channels for control, there is a safety reserve for repolarization when one of the currents is blocked. Most drugs that prolong the QTc interval and cause torsades de pointes do so by inhibiting IKr. IKs is increased by sympathetic activation and by heart rate increases which are essential for QT adaptation. If IKs is impaired, the QT interval will fail to shorten appropriately during tachycardia, which creates a highly arrhythmogenic condition.

We are not aware of any approved drugs that are predominant IKs blockers with QTc prolongation at clinical exposures. Therefore, insights into the clinical presentation of IKs blockade are gleaned from experience with patients with Long QT (LQT) 1 Syndrome (i.e., loss of function mutation in the KCNQ1 gene resulting in decreased IKs). The clinical presentation of LQT1 patients is repeated episodes of syncope or loss of consciousness precipitated by abrupt increases in heart rate, such as with exercise and emotional distress. This is the major distinction between patients with LQT1 vs. those with LQT2 (e.g., loss of function mutation in the hERG gene resulting in decreased IKr); LQT1 patients are at greatest risk for arrhythmias whenever the heart rate accelerates. Among LQT1 patients with QTc > 500 ms, risk is driven by the prolonged QTc and heart rate is less important; however, among patients with QTc ≤ 500 ms, those with lower heart rate (< 60 bpm) have fewer cardiac events (e.g., syncope or aborted cardiac arrest) than those patients with higher heart rates (>60 bpm) (Schwartz et al. 2008). Beta blocker therapy is used to reduce the risk of cardiac events (syncope, aborted cardiac arrest, sudden cardiac death) in LQT patients with normal resting QTc.

It is thought that IKs blockade acts synergistically with inhibition of IKr to cause interference with repolarization, reflected as prolonged QTc (Veerman et al. 2013). Therefore, there is

expected to be an increased risk of arrhythmias with use of drugs that reduce IKr concomitantly with drugs that reduce IKs, because this drug combination would result in reduction of both repolarizing potassium currents (So et al. 2006). Additionally, a reduction in extracellular potassium (e.g., clinical hypokalemia) reduces the cell surface density of hERG channels (IKr) and prolongs the QTc interval (Guo J et al. 2011).

3.2 FDA's Analysis of Cardiac Toxicity with Quizartinib

As shown in Table 4.1 of the Applicant's Briefing Document, quizartinib inhibits the IKs (hKVLQT1/minK) channel current with an IC50 < 300 nM. Although the Applicant indicated that allowed a 45-fold safety margin, their calculation was based on free concentration of quizartinib; FDA review teams have calculated the safety margin using estimates of both total and free drug concentrations. The safety margin as calculated by FDA could be very low when $IC50/Cmax_{total}$ is used, or up to only 12.7-fold when $IC50/Cmax_{free}$ is used. Additionally, as described by the Applicant in Section 4 of their Briefing Document, in a telemetry study in nonhuman primates, a single oral dose of quizartinib at 10, 30, 100 or 200 mg/kg induced dose-related prolongation of QTc intervals. FDA review also noted that 2 of 4 animals experienced ventricular premature complexes close to the Tmax time point.

Given these findings from the nonclinical studies, FDA proceeded with a more detailed assessment of the risk of clinical cardiac toxicity with focus in two areas, a) a concentration-QTcF analysis and b) an evaluation of observed adverse events potentially related to delayed cardiac repolarization.

3.2.1 Exposure-Response for QTcF Prolongation

Regarding assessment of the risks from drug-induced delayed cardiac repolarization, FDA has observed in the ICH E14 guidance that "...the risk of arrhythmias appears to increase with the extent of QT/QTc prolongation. Drugs that prolong the mean QT/QTc interval by around 5 ms or less do not appear to cause TdP. Whether this signifies that no increased risk exists for these compounds or simply that the increased risk has been too small to detect is not clear. The data on drugs that prolong the mean QT/QTc interval by more than around 5 and less than 20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk. Drugs that prolong the mean QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic..."[2] For the review of quizartinib, FDA's evaluation of the potential for

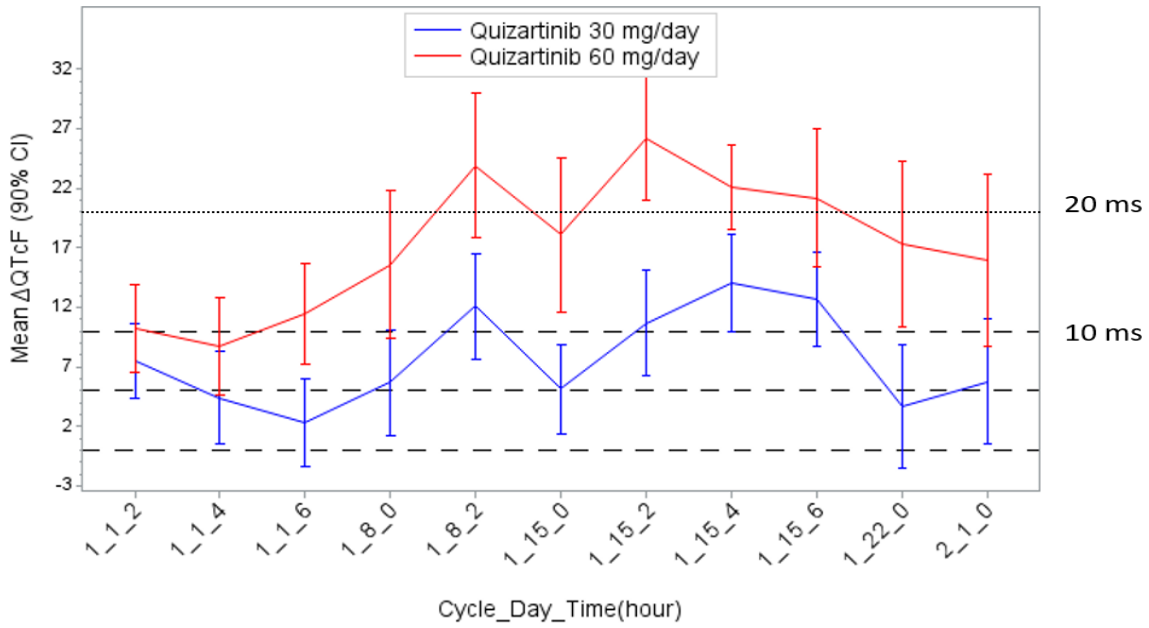
[2] "Guidance for Industry. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (October 2005)
https://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf

delayed cardiac repolarization included an exposure-response analysis for QTc prolongation and a determination of the incidence of outliers.

FDA reviewed ECG and PK data from Study 2689-CL-2004, a randomized dose-finding study in patients with relapsed or refractory AML, and from the pivotal trial Study AC220-007. The design of the trials are described in detail in Sections 8.2 and 9.1, respectively, of the Applicant's Briefing Document. The complete review from the Interdisciplinary Review Team (IRT) is provided in Appendix 3. The key findings from the analyses are described here.

Figure 2 shows the mean and 90% CI for ΔQTcF ordered by cycle, day and timepoints observed in Study 2689-CL-2004. The largest upper bound of ΔQTcF for quizartinib 30 mg/day was 18.07 ms and that for quizartinib 60 mg/day was 32.81 ms.

Figure 2. Study 2689-CL-2004: Time Course of ΔQTcF at 30 mg and 60 mg Quizartinib



Source: IRT Review Figure 1. Only timepoints at which the sample size is at least 70% of total population are used for this representation.

Table 8 shows the summary statistics for ΔQTcF as observed in Study 2689-CL-2004 and as predicted on the basis of the population PK model. These analyses show that most patients treated with quizartinib 60 mg dose had a ΔQTcF greater than 20 ms (Table 8), and the ΔQTcF was sustained at greater than 10 ms (Figure 2).

Table 8. ΔQTcF Summary Statistics at Quizartinib Mean Peak Concentration

Source	Quizartinib Dose	Cmax_ss (ng/mL)	ΔQTcF Mean (ms)	ΔQTcF 90% CI (ms)
Study 2689-CL-2004	30 mg/day	241	12.0	9.8 - 14.2
Study 2689-CL-2004	60 mg/day	457	20.1	16.4 - 23.7
popPK prediction	30 mg/day	256*	12.6	10.3 - 14.9
popPK prediction	60 mg/day	512*	22.1	18.0 – 26.1

Source: IRT Review Table 1
*Population PK model-predicted steady state Cmax, which assumes no adjustment in dosing.

The FDA outlier analyses also showed that the effect on ΔQTcF could be attributed to quizartinib as it was observed at a much lesser extent in the chemotherapy control arm (Table 9).

Table 9. Study AC220-007: QTcF Outlier Analysis

	Quizartinib	Chemotherapy
Absolute QTcF	**(n=239)**	**(n=84)**
≤ 450 ms	116 (49%)	79 (94%)
> 450 - 480 ms	86 (36%)	5 (6%)
> 480 - 500 ms	30 (13%)	0
> 500 ms	7 (3%)	0
Increase in QTcF	**(n=233)**	**(n=57)**
≤ 30 ms	85 (37%)	54 (95%)
> 30 - 60 ms	118 (51%)	2 (4%)
> 60 ms	30 (13%)	1 (2%)

Source: IRT Review Tables 7 and 8

Overall, the analyses demonstrate that quizartinib treatment was associated with concentration-dependent prolongation of QTcF to levels consistent with an increased risk of arrhythmias as described in the ICH E14 guidance.

3.2.3 Cardiac Adverse Events

The analysis of safety of quizartinib utilized data from the pivotal trial Study AC220-007 as well as data from 483 patients with AML treated on 4 trials of quizartinib monotherapy, and 168 patients on a trial of quizartinib in combination with intensive induction chemotherapy. See Section 6.2 and Table 6.1 in the Applicant's Briefing Document for a list of trials included in the quizartinib clinical development program used for FDA's review of safety.

Table 10 shows the results of a customized query for QT prolongation and arrhythmia events in Study AC220-007. There was a higher incidence of QT prolongation, fall and syncope on the quizartinib arm. Within the cardiac arrhythmia SMQ, atrial fibrillation was the most frequently reported TEAE and was reported in 12 (5%) patients on the quizartinib arm and 2 (2%) patients on the chemotherapy control arm. Two of the atrial fibrillation events were serious.

Table 10. Study AC220-007: QT Prolongation/Arrhythmia Events

Events	Quizartinib (n=241)	Chemotherapy (n=94)
Cardiac arrest	0	1 (1.1%)
Electrocardiogram QT prolonged	64 (26.6%)	2 (2.1%)
Fall	11 (4.6%)	2 (2.1%)
Syncope	12 (5.0%)	2 (2.1%)
Ventricular tachycardia	1 (0.4%)	3 (3.1%)

Source: IRT Review Section 4.7
*Uses grouped terms

Due to differences in exposure between the quizartinib and control arms on the pivotal study (Applicant Briefing Document, section 9.1.12.1), FDA deemed a comparison of cycle 1 treatment-emergent adverse events (TEAEs) between the arms relevant for safety analyses. However, as quizartinib is a chronically-administered therapy with the potential for cumulative toxicity and/or decreased tolerability over time (Thanarajasingam et al. 2018), an analysis of TEAEs on the quizartinib arm over multiple cycles is critical. Additionally, FDA viewed the preselected chemotherapy strata as subgroups with different toxicity profiles and analyzed toxicity separately for each stratum.

FDA's analysis of cardiac events by arm and by preselected chemotherapy stratum during cycle 1 and for the duration of quizartinib therapy are summarized below. Table 11 summarizes these events during cycle 1 for patients preselected for LDAC.

Table 11. Study AC220-007: Cardiac Events in Cycle 1 for Patients Preselected for LDAC

	All Grades		Grades 3-5	
	Quizartinib	Control	Quizartinib	Control
TEAE[a]	N=55	N=22	N=55	N=22
ECG Abnormal	11 20%	0 0%	1 2%	0 0%
Edema	10 18%	1 5%	0 0%	0 0%
Fatigue	7 13%	4 18%	1 2%	0 0%
Hypotension	6 11%	1 5%	2 4%	0 0%
Dyspnea/Resp Failure	4 7%	2 9%	0 0%	1 5%
Headache	4 7%	0 0%	0 0%	0 0%

Table 11. Study AC220-007: Cardiac Events in Cycle 1 for Patients Preselected for LDAC

	All Grades		Grades 3-5	
	Quizartinib	Control	Quizartinib	Control
TEAE[a]	N=55	N=22	N=55	N=22
Palpitations/Arrhythmia	3 5%	0 0%	1 2%	0 0%
Presyncope/Syncope	2 4%	0 0%	1 2%	0 0%
Dizziness	1 2%	2 9%	0 0%	0 0%
Fall	1 2%	1 5%	0 0%	0 0%

Source: FDA analysis
[a]Includes grouped terms, see Appendix 2

When looking beyond cycle 1, the rates of fatigue (36%), edema (25%), ECG abnormality (25%), dyspnea (18%), hypotension (20%), dizziness (11%), headache (15%), presyncope/ syncope (9%), fall (7%) and palpitations/arrhythmia (9%) continued to increase; angina (4%) and cardiac failure, hypoxia and heart block (2%) all occurred exclusively in the quizartinib arm over the course of exposure.

For patients preselected for the intensive chemotherapy stratum, when looking at cardiac AEs only over cycle 1, the only event that occurred at a higher rate in the quizartinib arm was ECG abnormal (19% vs 4%) (Table 12).

Table 12. Study AC220-007: Cardiac Events in Cycle 1 for Patients Preselected for Intensive Chemotherapy

	All Grades		Grades 3-5	
	Quizartinib	Control	Quizartinib	Control
TEAE[a]	N=186	N=72	N=186	N=72
Fatigue	43 23%	21 29%	4 2%	1 1%
ECG abnormal	35 19%	3 4%	3 2%	0 0%
Edema	20 11%	23 32%	1 1%	0 0%
Headache	20 11%	16 22%	0 0%	0 0%
Dyspnea/resp failure	20 11%	7 10%	4 2%	3 4%
Hypotension	14 8%	7 10%	2 1%	2 3%
Dizziness	15 8%	5 7%	0 0%	0 0%
Palpitations/arrhythmia	13 7%	13 18%	2 1%	1 1%
Presyncope/syncope	7 4%	2 3%	2 1%	1 1%
Angina	6 3%	2 3%	0 0%	0 0%
Cardiac murmur	3 2%	0 0%	0 0%	0 0%
Hypoxia	3 2%	0 0%	1 1%	0 0%
Fall	1 1%	1 1%	0 0%	0 0%
Hypotension	1 1%	0 0%	0 0%	0 0%

Source: FDA analysis
[a]Includes grouped terms, see Appendix 2

When looking beyond cycle 1 at the entire duration of exposure, the incidence of cardiac events continued to increase in the intensive chemotherapy stratum as well, and occurred at the following rates: fatigue (41%), edema and ECG abnormality (27%), dyspnea (25%), headache (24%), palpitations/arrhythmia (20%), dizziness (19%), hypotension (12%), angina and presyncope/ syncope (6% each), fall (4%), hypoxia (3%), rales, cardiac failure/cardiomyopathy, lethargy and cardiac murmur (2% each), and pericarditis/myocarditis, myocardial infarction, gait disturbance and heart block (1% each).

In summary, QT prolongation occurred in over 25% of patients on the quizartinib arm, and it was the most common TEAE during cycle 1 overall and in each preselected chemotherapy stratum.

Since the most serious clinical consequence of the pro-arrhythmic potential of quizartinib would be sudden cardiac death or cardiac arrest, FDA performed an analysis of this event in the pivotal Study AC220-007 and the larger quizartinib safety population for these critical events. The larger safety population consisted of the 724 patients with AML not in remission treated with quizartinib monotherapy across 5 clinical studies, and 169 patients with newly-diagnosed AML from the on-going Phase 3 trial Study AC220-A-U302 (see section 13.2.7.4 of the Applicant's Briefing Document for details). The data used for these analyses came from the 120-day safety update in the NDA.

FDA identified four deaths on Study AC220-007 attributed to quizartinib. In 3 cases, a sudden death, specifically described cardiac-related death, or a fall in a relatively young patient, two of whom were in patients who experienced QTcF prolongation with quizartinib therapy, are considered at least possibly related to quizartinib. In the fourth, a history of QTcF prolongation, electrolyte abnormalities and septic shock leading to death cannot be definitively distinguished from each other in their contribution to the young patient's death. Even without a history of QTcF prolongation, the unique mechanism of IKs blockade and the clinical experience with LQT1 syndrome do not allow for the exclusion of a pro-arrhythmic state, precipitated by any of a number of clinical conditions that are not uncommon in patients being treated for AML (sepsis, anemia, dehydration) and cause tachycardia, and others (electrolyte disturbances), which may even in isolation contribute to cardiac conduction abnormalities. Overall, there was a 1.7% incidence of on-treatment deaths due to acute or subacute cardiac events alone on the pivotal Study AC220-007.

FDA identified three additional deaths attributed to quizartinib in the larger safety population. Thus, in the integrated safety population of patients with R/R AML who were treated with quizartinib monotherapy, there were 7/724 patients (1%) who died on treatment with a root cause of death that was considered at least possibly cardiac in nature.

Lastly, there were 5 additional cases in Study AC220-A-U302, the on-going Phase 3 trial of standard intensive chemotherapy with or without quizartinib. There were 168 patients treated on each arm at the time of the data cut-off. Based on FDA review of these data, there were 2 fatal cardiac arrests, 1 sudden death, 1 fatal ventricular fibrillation, and 1 fatal ventricular dysfunction on the quizartinib arm; none of these terms were reported in the placebo arm. In summary, on the ongoing randomized phase 3 combination study, 3% of those enrolled as of the data cut-off above on the quizartinib arm had on-treatment deaths that are at least possibly due to acute cardiac events.

3.3 Summary of Cardiac Toxicity

The evidence available underscores the serious risk of fatal and life-threatening events with quizartinib.

- The nonclinical data identified the potential mechanism of QT prolongation as IKs blockade.
- The QTcF analyses showed that quizartinib treatment was associated with prolongation of QTcF to levels consistent with a risk of arrhythmias.
- In the safety database, QT prolongation was the most common cardiac adverse event.
- In Study AC220-007, there was a higher incidence of QT prolongation, fall and syncope reported in the quizartinib arm than in the chemotherapy control arm.
- The risk of on-treatment deaths due to cardiac events is estimated as 1-2%.

FDA notes that although the presence of electrolyte abnormalities may increase the risk of arrhythmias or fatal cardiac events, and sepsis or other complications may contribute to cardiac arrest, a causal relationship with quizartinib therapy is biologically plausible and cannot be definitively excluded. Occurrence of fatal cardiac events early in the treatment course supports the notion that these events are more than a theoretical risk in the context of quizartinib therapy.

The proposed step-dose regimen based on day 15 QTcF and dose modification instructions in the protocol for the pivotal study did not prevent these events from occurring at a significant rate. In fact, FDA review found that 22 patients at 18 sites did not have dose modifications despite the results of predose ECG results. There is also a heightened risk for sudden death by concurrent IKr blockade with concomitant use of other approved agents associated with QT prolongation. The pivotal study also recommended against the use of concomitant QT-prolonging agents (although these were not absolutely prohibited), yet over 70% of patients received at least one of these agents over the course of quizartinib therapy. The impact of the lack of adherence to dose modifications and the use of concomitant QT-prolonging agents highlight the need for education of practitioners of the unique risks associated with IKs blockade. Product labeling alone may not be sufficient to accomplish this.

Due to its unique mechanism for QT prolongation (IKs blockade), quizartinib has the potential for sudden death at the time of a rapid rise in heart rate, even without antecedent observed QTcF prolongation. Extrapolating from the only known analogous clinical scenario, that of LQT1 syndrome, prophylactic beta-blockade would be a possible strategy to prevent sudden death in patients treated with quizartinib.

FDA has indicated that for drugs with a demonstrated effect on QTc, "...the outcome of the risk-benefit assessment will generally be influenced by the size of the QT/QTc interval prolongation effect, whether the effect occurs in most patients or only in certain defined outliers, the overall benefit of the drug, and the utility and feasibility of risk management options."[3] If quizartinib is marketed, a strong risk management would be needed to support safe use. Strategies to consider would include specific notation in labeling (including a boxed warning, contra-indication for use with other QT prolonging drugs, and a recommendation for beta blockers to prevent arrythmias), a medication guide to educate patients, and a communication plan to inform healthcare providers about the risks and recommended management to prevent fatal and life-threatening cardiac events.

4. SAFETY PROFILE

4.1 FDA's Review of Adverse Reactions

FDA largely confirmed the Applicant's analysis of treatment-related adverse events (TEAE) in Study AC220-007. As described in Section 9.1.2 of the Applicant's Briefing Document, the most common ($\geq$ 10%) TEAE in cycle 1 reported for patients on quizartinib were nausea, anemia, electrocardiogram QT prolonged, thrombocytopenia, pyrexia, hypokalemia, febrile neutropenia, vomiting, fatigue, diarrhea, neutropenia, white blood cell count decreased, platelet count decreased, neutrophil count decreased, headache and decreased appetite. The adverse events of special interest identified by the Applicant included infection (77%), hemorrhage (49%), hepatic disorders (32%), QT prolongation (31%), cardiac arrhythmias (12%), and cardiac failure (2%) (Applicant's Briefing Document Section 9.1.12.12).

To assist with the risk-benefit assessment, FDA's safety analysis focused on early mortality, comparisons to the control chemotherapy, and identification of new safety issues as described below (in addition to the delayed cardiac polarization risk described in Section 3 above).

[3] "Guidance for Industry. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (October 2005)
https://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf

Early Mortality

There were 262 patient deaths on Study AC220-007, 186 (77%) on the quizartinib arm and 76 (81%) on the control arm. FDA adjudicated the root causes of death based on all available data and review of written narratives for all patients who died within 30 days of the last dose of therapy; these analyses are summarized in Table 13 below.

Table 13. Study AC220-007: Causes of Death

	Quizartinib (N=241)	Chemotherapy (N=94)
Mortality		
By day 30	2 (0.8%)	13 (14%)
By day 60	16 (7%)	23 (24%)
Died on Study	186 (77%)	76 (81%)
Cause of Death		
Lack of efficacy	147 (61%)	62 (66%)
Adverse event	25 (10%)	9 (10%)
Other/unknown	14 (6%)	5 (5%)
Died Within 30 days of Last Dose	80 (33%)	16 (17%)
Cause of Death		
Lack of efficacy	61 (25%)	9 (10%)
Adverse event	16 (7%)	7 (7%)
Other/unknown	3 (1%)	-

Source: FDA analysis; COD, cause of death; AE, adverse event; TRM, transplant-related mortality

Early mortality, especially day-30 deaths, was low in the quizartinib arm (0.8%) (Table 13). The majority of deaths on study were due to AML, and incidence of deaths due to fatal adverse events was similar in the two study arms.

Common Adverse Reactions

For the comparison of adverse reactions between study arms, FDA analyzed TEAEs at the preferred term level and level 1 Standardized MedDRA Queries (SMQs). Events with large incidence differences between arms were of interest. Since the preselected chemotherapy would be expected to have different safety profiles based on intensity, the results were assessed separately for the intensive chemotherapy stratum and the low-intensity chemotherapy stratum.

Table 14 shows a comparison of the TEAEs that occurred in Cycle 1 in the intensive chemotherapy stratum. The display includes only those TEAEs with a $\geq$ 10% risk difference

between study arms. QT prolonged is the only TEAE with at least a 10% higher incidence in the quizartinib arm than in the control arm.

Table 14. Study AC220-007: Comparison of Cycle 1 TEAEs in Patients Preselected for Intensive Chemotherapy

TEAE	Quizartinib (n=186)		Intensive Chemotherapy (n=72)		% Risk Difference
	n	(%)	n	(%)	
QT prolonged	41	22	2	3	+19
Febrile neutropenia	35	19	22	31	-12
Abdominal pain	13	7	14	19	-12
Insomnia	5	3	11	15	-13
Constipation	20	11	18	25	-14
Nausea	61	33	35	49	-16
Peripheral edema	17	9	20	28	-19
Stomatitis	10	5	18	25	-20
Diarrhea	33	18	30	42	-24
Pyrexia	38	20	37	51	-31

Source: FDA analysis

Table 15 shows a comparison of level 1 narrow SMQs that occurred in Cycle 1 in the intensive chemotherapy stratum. The display includes only those SMQs with a $\geq$ 15% risk difference between study arm.

Table 15. Study AC220-007: Comparison of Cycle 1 SMQs in Patients Preselected for Intensive Chemotherapy

SMQ (Narrow)	Quizartinib (n=186)		Intensive Chemotherapy (n=72)		% Risk Difference
	n	(%)	n	(%)	
Cardiac arrhythmias	45	24	4	6	+19
Torsade de pointes/QT prolongation	42	23	4	6	+17
Shock	44	24	6	8	+15
Hemodynamic edema, effusions and fluid overload	30	16	26	36	-20
Noninfectious diarrhea	33	18	30	42	-24
Oropharyngeal disorders	42	23	35	49	-26
Gastrointestinal nonspecific inflammation and dysfunctional conditions	93	50	59	82	-32

Source: FDA analysis

Table 16 shows a comparison of the TEAEs that occurred in Cycle 1 in the low-intensity stratum. The display includes only those TEAEs with a ≥ 10% risk difference between study arm. Dizziness was the only TEAE with an incidence > 10% higher in the control arm.

Table 16. Study AC220-007: Comparison of Cycle 1 TEAE in Patients Preselected for LDAC

TEAE	Quizartinib (n=55)		Low-Intensity Chemotherapy (n=22)		% Risk Difference
	n	(%)	n	(%)	
Anemia	20	36	3	14	+23
QT prolonged	11	20	0	0	+20
Neutropenia	10	18	0	0	+18
Vomiting	11	20	1	5	+15
Thrombocytopenia	13	24	2	9	+15
Peripheral edema	8	15	0	0	+15
Nausea	15	27	3	14	+14
Stomatitis	7	13	0	0	+13
Dizziness	0	0	3	14	-14

Source: FDA analysis

Table 17 shows a comparison of level 1 narrow SMQs that occurred in Cycle 1 in the low-intensity stratum. The display includes only those SMQs with a ≥ 15% risk difference between study arm. There were no SMQs with more than a 15% higher incidence in the control arm than in the quizartinib arm.

Table 17. Study AC220-007: Comparison of Cycle 1 SMQs in Patients Preselected for LDAC

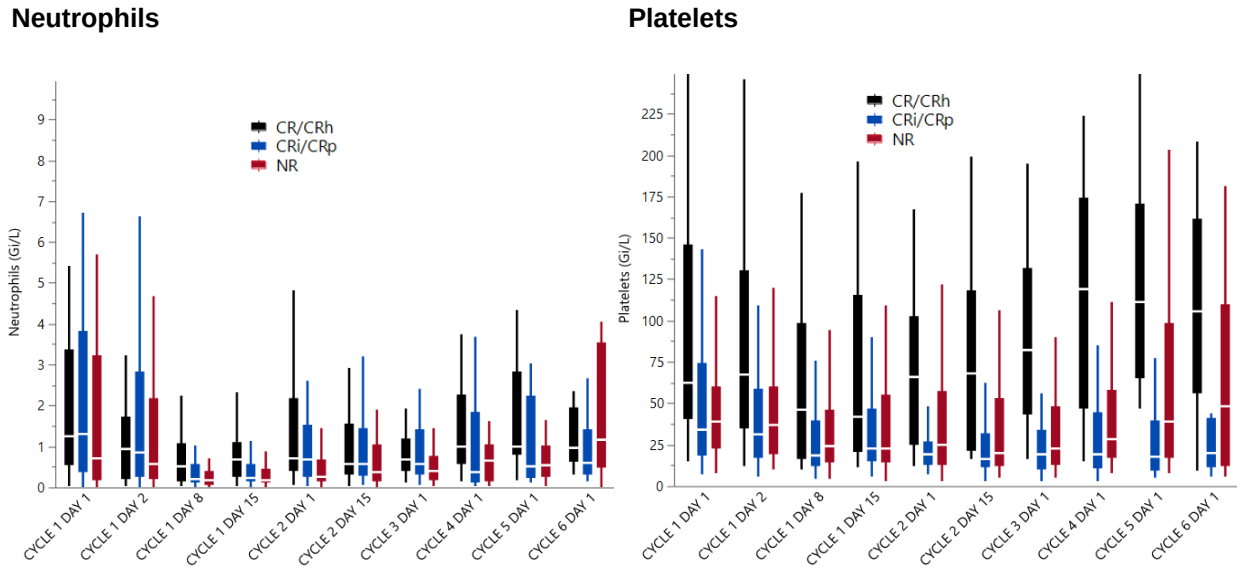
SMQ (Narrow)	Quizartinib (n=55)		Low-Intensity Chemotherapy (n=22)		% Risk Difference
	n	(%)	n	(%)	
Hematopoietic cytopenias	32	58	7	32	+26
Cardiac arrhythmias	13	24	0	0	+24
Torsade de pointes/QT prolongation	11	20	0	0	+20
Shock	12	22	1	5	+17
Gastrointestinal nonspecific inflammation and dysfunctional conditions	32	58	9	41	+17
Hemodynamic edema, effusions and fluid overload	12	22	1	5	+17

Source: FDA analysis

In summary, for the comparisons of TEAE and narrow SMQs in the intensive chemotherapy stratum, the quizartinib arm had a higher incidence of QT prolongation and arrhythmias, and a lower incidence of gastrointestinal events (Tables 14 and 15). For the low-intensity chemotherapy stratum, the quizartinib arm had a higher incidence of QT prolongation, arrhythmias, cytopenias and gastrointestinal disorders (Tables 16 and 17).

The difference in the rate of cytopenias in the low-intensity chemotherapy stratum warranted further investigation. Figure 3 shows the median (95% CI) of the neutrophil and platelet counts over time for the patients treated with quizartinib on Study AC220-007 grouped by best response (CR/CRh, CRi/CRp, or no response). Even in patients who achieve a CR/CRh, the neutrophil counts trended low for an extended period. In responders, platelets are appear to trend higher over time.

Figure 3. Study AC220-007: Neutrophil and Platelet Counts in the Quizartinib-Treated Patients by Study Visit Grouped by Best Response



Source: FDA Analysis

In the assessment of adverse reactions due to quizartinib, cardiac events and cytopenias are the main concerns.

4.2 Differentiation Syndrome/Acute Febrile Neutrophilic Dermatosis

Differentiation syndrome (DS) is a clinical syndrome characterized by dyspnea, unexplained fever, weight gain, unexplained hypotension, acute kidney injury, and pulmonary infiltrate or

pleuropericardial effusions first described in the context of treatment of acute promyelocytic leukemia (APL) with all-trans retinoic acid (ATRA), and classically thought to be limited to this clinical context (Frankel 1992). Subsequently, the incidence of DS with other therapies in the treatment of non-APL AML has been described (Norsworthy K, ASH 2018), including a 1% incidence with the approved FLT3-inhibitor gilteritinib (Gilteritinib Prescribing Information 2018). Fatal DS has been associated with both IDH- and FLT3-targeted therapies.

Montesinos et al (2009) described the criteria above to allow for more objective diagnosis of this syndrome. The Applicant applied the Montesinos criteria to the pooled quizartinib safety population and found a 10% incidence of possible or probable DS, including 12 (5%) cases on the pivotal study.

FDA review identified 20 cases of acute febrile neutrophilic dermatosis (AFND), or Sweet's syndrome, in the pooled quizartinib safety population. In Study AC220-007, the incidence of AFND was 4% on the quizartinib arm and 2% on the chemotherapy control arm. Most cases were not associated with active or progressive AML. Given literature reports of the phenomenon of AFND with FLT3-targeted therapies that were biopsy-proven to be differentiated myeloid cells without evidence of blasts (Sexauer et al 2012), FDA noted that this may be a phenomenon related to or part of DS for patients treated with quizartinib.

During adjudication of the cases detected using the Montesinos criteria, FDA identified 11 cases (5%) of DS on the pivotal study. There were an additional 4 cases (2%) who met Montesinos criteria only partially but who had cutaneous manifestations. In addition to establishing DS as an adverse reaction of quizartinib, FDA is considering AFND as a potential additional manifestation of DS.

FDA estimated that 7% of patients on the pivotal trial experienced an event considered to be on the DS/AFND spectrum. Given the potentially fatal course of DS/AFND, and the fact that steroids were not administered and quizartinib was not interrupted in 2 of the fatal cases on the pivotal study, it appears that this toxicity is underrecognized.

4.3 Summary of the Safety Profile

FDA agrees with the general safety profile of quizartinib as described by the Applicant, but FDA also identified potentially life-threatening or fatal differentiation syndrome and acute febrile neutrophilic dermatosis as additional adverse reactions associated with quizartinib therapy. Prolonged cytopenias were also observed.

5. POINTS FOR THE ADVISORY COMMITTEE TO CONSIDER

The Applicant is seeking an indication for the use of quizartinib for the treatment of adults with FLT3-ITD-positive relapsed or refractory AML based on the OS results from a single pivotal trial, Study AC220-007. Although the study was positive (HR 0.77; 95% CI 0.59, 0.99; p=0.019 as calculated by FDA), the significance was marginal, the OS results were not robust, the OS treatment effect appeared to be driven by the stratum of patients preselected for low-intensity chemotherapy and may have been confounded by imbalances in poststudy therapy, and the results of analyses of other efficacy endpoints were either not statistically significant or provided for a magnitude of effect that might not be considered clinically meaningful. These inconsistencies and imbalances undermine the reliability of the trial results.

The nonclinical studies provided by the Applicant and FDA's concentration-QTcF analysis demonstrated that quizartinib causes QT prolongation via a unique mechanism, namely IKs blockade. Blockade of IKs by quizartinib results in the potential for fatal cardiac arrhythmias. In Study AC220-007, 27% of patients experienced at least one event of QT-prolongation. When compared to intensive chemotherapy or LDAC, the risk of cardiac events was substantially higher with quizartinib. Across the quizartinib clinical development program, the risk of on-treatment deaths due to cardiac events was estimated as 1-2%. These results occurred despite instructions in the protocol regarding patient management to reduce the risks; FDA noted multiple instances where such instructions were not followed by the investigators. Other strategies to consider might include contra-indicating concomitant use with drugs that prolong QT via the complementary IKr channel and a recommendation for co-administration of beta blockers to prevent arrhythmias.

In addition to the cardiac toxicity, quizartinib treatment was associated with 7% risk of events on the spectrum of differentiation syndrome with or without acute febrile neutrophilic dermatosis. Use of quizartinib was also associated with other more common toxicities seen with anticancer therapies such as nausea, vomiting, diarrhea, liver enzyme abnormalities and cytopenias that predisposed to hemorrhagic events and infections. If considered in the context of the concerns raised above with regard to establishment of effectiveness in the proposed population, it is not clear to FDA that the risks of treatment with quizartinib are outweighed by potential benefit.

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7. APPENDICES

Appendix 1: Resampling Details

Table 18 is a shell of Table 1. To illustrate the resampling procedure, consider only the chemotherapy control arm. Since we assume that patients who experienced early death would fare no better even if they were treated, event times for all RNT early deaths are not imputed. That is, even if they were treated with study therapy, it is unlikely to change the outcome.

Table 18. Summary of Early-Censoring, Randomized-Not-Treated, and Randomized-Treated

Cohort	Stratum	EC8	ED8	GE8	EC8	ED8	GE8
Quizartinib	LDAC	A1		B1	C1		S1
	MEC/FLAG-IDA	A2		B2	C2		S2
Chemotherapy	LDAC	A3		B3	C3		S3
	MEC/FLAG-IDA	A4		B4	C4		S4

Source: FDA analysis

Resampling is performed by stratum, using the levels of preselected chemotherapy:

- LDAC (non-intensive chemo)
- MEC/FLAG-IDA (intensive chemo)

To illustrate the stress test based on resampling, consider chemotherapy patients in the "LDAC" stratum:

1. **RNT, EC8**. For each patient in cell A3, toss out the early-censored time/status and replace them with a survival time/status from a patient randomly-sampled from cell S3.
2. **RNT, GE8**. For each patient in cell B3,
   - Flip a coin with probability π.
   - Heads, do nothing to the patient's current survival time/status.
   - Tails, toss out the survival time/status and replace it with a survival time/status from a patient randomly-sampled from cell S3.
3. **RT, EC8**. For each patient in cell C3, toss out the survival time/status and replace them with a survival time/status from a patient randomly-sampled from cell S3.
4. Do this for all strata and for all study arms.
5. Analyze the data using the resampled values; record p-value, hazard ratio, median OS.
6. Repeat 20,000 times.

Additional Details. The resampling is performed in a way so as to not make a patient worse off. To illustrate, consider a RNT patient in cell B3. Suppose he died 17 weeks after randomization.

- if 17 weeks ≥ all survival times in S3, then the patient's survival time is kept as is. That is, the patient cannot die or be censored earlier than 17 weeks had he been randomized and treated.
- if 17 weeks < than the largest survival time in S3, then sample from among patients in S3 whose survival times are at least 17 weeks. This is consistent with the notion that treating the patient with study therapy does not make them worse off in the sense of reducing their survival time.

Appendix 2: Table of Grouped Terms Used for Adverse Reactions

Grouped Term	Preferred Terms Included In Grouped Term
Angina	Angina pectoris, chest discomfort, chest pain
Dizziness	Dizziness, dizziness postural, vertigo
Dyspnea/Respiratory Failure	Dyspnoea, dyspnoea exertional, respiratory failure tachypnoea
ECG abnormality	Electrocardiogram QRS complex prolonged, Electrocardiogram QT prolonged, Electrocardiogram T wave inversion
Fatigue	Asthenia, fatigue, malaise
Hemorrhagic events	Anal haemorrhage, catheter site haemorrhage, cerebral haemorrhage, coagulopathy, conjunctival haemorrhage, Contusion, epistaxis, eye haemorrhage, gastrointestinal haemorrhage, gingival bleeding, haematemesis, haematochezia, haematoma, haematuria, haemoptysis, haemorrhage, haemorrhage intracranial, haemorrhoidal haemorrhage, increased tendency to bruise, melaena, mouth haemorrhage, mucosal haemorrhage, post procedural haematoma, post procedural haemorrhage, purpura, rectal haemorrhage, retinal haemorrhage, scleral haemorrhage, subarachnoid haemorrhage, subdural haemorrhage, upper gastrointestinal haemorrhage, vaginal haemorrhage
Hepatotoxicity	Hepatic failure, hepatitis toxic, hepatotoxicity, liver disorder
Hypotension	Hypotension, hypovolemia

Grouped Term	Preferred Terms Included In Grouped Term
Hypertransaminasemia	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme, increased, liver function test abnormal, transaminases increased
Infection, pathogen unspecified	All PTs in the MedDRA HLGT
Neutropenia	Neutropenia, neutrophil count decreased
Edema	Eyelid oedema, face oedema, fluid overload,fluid retention, generalised oedema, oedema, oedema peripheral, swelling, swelling face
Palpitations/Arrhythmia	Arrhythmia, atrial fibrillation, bradycardia, palpitations, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, tachycardia, ventricular tachycardia
Pneumonia (excluding fungal)	Lung consolidation, lung infection, pneumonia, pneumonia aspiration, pneumonia respiratory syncytial viral
Sepsis (excluding fungal)	Device related sepsis, Escherichia sepsis, Klebsiella sepsis neutropenic sepsis, sepsis, septic shock, staphylococcal sepsis, streptococcal sepsis, urosepsis

Appendix 3: IRT Review Document for NDA 212166

Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 212166
Submission Number	SDN 004
Submission Date	9/25/2018
Date Consult Received	10/11/2018
Generic Name	Quizartinib
Clinical Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation submitted under NDA 212166. The QT-IRT reviewed the following materials:

- Previous QT-IRT review under IND 74552 dated 09/27/2011, 01/22/2013, and 06/22/2018 in DARRTS;
- Summary of Clinical Pharmacology Studies (Submission 0004);
- Study 2689-CL-2004 clinical study report and QT report (Submission 0004);
- Study AC220-007 clinical study report and QT report (Submission 0004); and
- Proposed label (Submission 0004).

1 SUMMARY AND RECOMMENDATIONS

1.1 OVERALL FINDINGS

Quizartinib is a predominant inhibitor of the slow potassium current (see section 5 for more details), IKs, and is associated with concentration-dependent QTc interval prolongation >20 ms at the 60 mg/day dose. In study AC220-007, 3.3% patients had QTc >500 ms and 12% had QTc increase >60 ms from baseline based on centrally read ECGs. An additional 3 subjects in the quizartinib arm had QTcF >500 ms based on local ECG reading at the investigator site and 1 subject experienced palpitations and presyncope. There was an imbalance of serious cardiac events associated with QT prolongation/cardiac arrhythmia in the quizartinib arm, including syncope and fall (with loss of consciousness). The risk of these AEs may not reflect the cardiac safety of this product because patients with increased risk for torsades de pointes were excluded from the clinical trial and the concomitant use of QT prolonging medications was generally prohibited.

In the clinical development program, there was an imbalance of serious cardiac adverse events in subjects taking > 60 mg quizartinib including 1 report of torsades de pointes, and 1 report of cardiac arrest with QTc prolongation (see section 3.3.3.3 for more details).

- A 63 y/o female subject ((b) (6) :) taking quizartinib 90 mg QD had Grade 4 QTc prolongation (QTcF of 543 ms) with torsades de pointes. Both events resolved after discontinuing treatment.
- A 39 y/o female ((b) (6)) died from a cardiac arrest. The event occurred on Day 40, 4 days after the starting quizartinib dose of 90 mg was increased to 135

mg. The QTcF had increased from baseline of 408 ms to a maximum of 496 ms 4 days before the cardiac arrest but was reportedly 471 ms the day before death.

The effect of quizartinib on cardiac repolarization was evaluated in Study 2689-CL-2004 using exposure-response analysis as the primary analysis. The highest dose that was evaluated was 60 mg/day, which covers therapeutic exposure at the highest recommended dose level (i.e. 60 mg/day). The overall analysis results are shown by study in Table 1. The findings of this analysis are further supported by the available nonclinical data (section 5), sponsor's exposure-response analysis which was based on data from Study CA220-007 (aka Study QuANTUM-R or Study AC220-PMX002) (section 3.3.4), and categorical analysis of the two studies (section 4.5).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

Study	ECG parameter	Treatment*	Quizartinib $C_{max,ss}$	Δ (ms)	90% CI (ms)
2689-CL-2004	QTc	30 mg/day	241.2 ng/mL	12.0	9.8 - 14.2
	QTc	60 mg/day	457.3 ng/mL	20.1	16.4 - 23.7
Population PK Prediction	QTc	30 mg/day without dose adjustment	256 ng/mL	12.6	10.3 - 14.9
	QTc	60 mg/day without dose adjustment	512 ng/mL	22 1	**18.0 – 26.1**

* Dose levels in the proposed label are expressed in the free base form. Dose levels in the rest of the review are expressed in the salt form.

1.2 COMMENTS TO THE REVIEW DIVISION

Most drugs that prolong the QTc interval and cause torsades de pointes do so by inhibiting the outward delayed rectifier potassium current, IKr. Quizartinib is a predominant inhibitor of the slow potassium current, IKs. IKs is increased by sympathetic activation and by heart rate increases which are essential for QT adaptation. If IKs is impaired, the QT interval will fail to shorten appropriately during tachycardia which creates a highly arrhythmogenic condition. [*J Am Coll Cardiol*. 2008;51:920-29].

We are not aware of any approved products that are predominant IKs blockers with QTc prolongation at clinical exposures. Therefore, insights into the clinical presentation of IKs blockade are gleaned from experience with patients with Long QT (LQT) 1 syndrome (i.e., loss of function mutation in the KCNQ1 gene resulting in decreased IKs). The clinical presentation of LQT1 patients is repeated episodes of syncope or loss of conscious precipitated by abrupt increases in heart rate, such as with exercise and emotional distress. This is the major distinction between patients with LQT1 vs. those with LQT2 (e.g., loss of function mutation in the hERG gene resulting in decreased IKr) — LQT1 patients are at greatest risk for arrhythmias whenever heart rate accelerates. Among LQT1 patients with QTc >500 ms, heart rate is rather unimportant; however, among patients with QTc ≤ 500 ms, those with lower heart rate (<60 bpm) have fewer cardiac events (e.g., syncope or aborted cardiac arrest) than those patients with higher heart rates (>60 bpm) [*J Am Coll Cardiol*. 2008;51:920-29]. Beta-blocker therapy is used to reduce the risk of cardiac events (syncope, aborted cardiac arrest, sudden cardiac death) in LQT patients with normal resting QTc [for more details, see HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes, *Heart Rhythm*. 2013; 10:1932-

63]. Randomized clinical trials to assess comparative efficacy of specific beta blockers are unavailable.

Cardiac repolarization is controlled by both IKr and IKs, which provides a safety reserve for repolarization when one of the currents is blocked ("repolarization reserve") [*PACE* 1998;21(5):1029-34]. There is increased risk of arrhythmias with concomitant use of quizartinib and drugs that reduce IKr because this drug combination results in a reduction in both repolarizing potassium currents. In animal models, blockade of IKs increased the reverse rate-dependent prolongation of action potential duration of dofetilide [*Br J Pharmacol*. 2006;48:255-63]. It is thought that IKs blockade acts synergistically with inhibition of IKr to cause interference with repolarization, reflected as prolonged QTc [*Circ Arrhythm Electrophysiol*. 2013;6:1002-1009]. Therefore, patients taking quizartinib should not take other drugs that delay cardiac repolarization, especially under pathological conditions with diminished repolarization reserve (such as with hypokalemia). In study AC220-007, concomitant use of QT prolonging medications was prohibited and patients with risk factors for torsades de pointes were excluded, including those patients with Long QT syndrome, history of ventricular arrhythmias and torsades de pointes, bradycardia, heart block, recent MI, and congestive heart failure/left ventricular dysfunction. Additionally, a reduction in extracellular potassium (i.e., clinical hypokalemia) reduces the cell surface density of hERG channels (IKr) and prolongs the QTc interval [*J Bio Chem*. 2011;286:34664-74]. Therefore, it is important that patients have normal levels of serum potassium when taking quizartinib.

IKs contributes to the repolarization in both ventricles and atria. Atrial tachyarrhythmias have recently been associated with LQT syndrome [*J Cardiovasc Electrophysiol*. 2003; 14:1027-33]; however, the mechanism explaining the association of atrial fibrillation and QT prolongation in LQT is not fully understood [*J Cardiovasc Electrophysiol*. 2015; 26:715-23; *Heart Rhythm*. 2013;10:1351-53]. The imbalance in atrial fibrillation events in the quizartinib arm could be drug-related, and this potential signal should be evaluated in ongoing clinical trials.

2 RECOMMENDATIONS

2.1 ADDITIONAL CLINICAL STUDIES

If quizartinib is further developed for other hematology/oncology diseases with longer survival times or tested at doses >60 mg/day, we recommend that the sponsor conducts a Holter ECG study to evaluate the QTc effects and safety in the presence of heart rate increases with exertion. Inclusion of beta blocker therapy could provide valuable insight into the clinical management and prevention of excessive QTc prolongation with heart rate increases.

2.2 PRODUCT LABEL

We have reviewed the most recent label available (Submission 0004, dated 09/25/2018) and we have some suggestions (*addition*, ~~*deletion*~~) for the language in Highlights, Sections 2.2, 2.4, 2.5, 5.1 and 12.2. The proposed changes are for suggestions only and we defer final labeling decisions to the Division.

Given that this drug prolongs the QTc interval >20 ms by inhibition the IKs current and at higher doses there are imbalances in serious cardiac events in the clinical development program including syncope, torsades de pointes and cardiac arrest with QTc prolongation, we recommend that the sponsor includes a box warning for QT prolongation and increased risk of torsades de pointes with abrupt heart rate increases in high risk patients.

The sponsor proposes using a 470 ms QTc threshold to guide treatment decisions. Study AC220-007, however, used a 450 ms QTc threshold. QTc intervals of 440 ms to 460 ms in men and 440 ms to 470 ms in women are considered borderline QTc prolongation. Therefore, it is reasonable to guide treatment initiation and dose titration for a life-threatening disease using a 470 ms threshold in patients who do not have risk factors for QTc prolongation or torsades de pointes. It is generally recognized that patients with QTc >500 ms are at high risk of developing arrhythmias and risk mitigation strategies should be in place to avoid exceeding 500 ms.

HIGHLIGHTS **----------DOSAGE AND ADMINISTRATION----------** Initiate treatment only if QTcF ≤ 470 ms. (2.2)
Reviewer's comment: We agree with sponsor's proposal to initiate treatment with baseline QTcF ≤ 470 ms. The mean effect on QTcF at the initial treatment (i.e. 30 mg QD) is around 13 ms (90% CI: 11-16 ms). The product labels for many other oncology drugs with a positive exposure-response relationship and a mean effect between 10 and 20 ms at the therapeutic dose level do not include a requirement on baseline QTcF. These drugs include ivosidenib (16.1 ms, 90%CI: 13.3-18.9 ms), apalutamide (12.4 ms, 90% upper CI: 16.0 ms), rucaparib (14.9 ms, 90% CI: 11.1-18.7 ms), encorafenib (18 ms, 90% CI: 14-22 ms), nilotinib (10.4 ms, 90% CI: 2.9-18 ms), and osimertinib (16.2 ms, 90% upper CI: 17.6 ms). *At this stage there are very few examples of FDA approved, oncology drug products that require baseline QTc <450 ms. Two of the examples are ribociclib (mean effect: 22.0, 23.7, or 34.7 ms in combination with an aromatase inhibitor, fulvestrant, or tamoxifen) and vandetanib (mean effect: 35 ms). Unlike these drug products, quizartinib is administered based on titration scheme, therefore, the risks of QT prolongation are lower despite of a mean effect >20 ms at the highest therapeutic dose (i.e., 60 mg QD)*
HIGHLIGHTS **----------WARNINGS AND PRECAUTIONS----------** QTc Interval Prolongation: Monitor electrocardiograms and electrolytes. If QTc interval prolongation occurs, ~~*dose reduce or*~~ interrupt, then resume dose or permanently discontinue. (2.4, 5.1)
Reviewer's comment: Revised to be consistent with recommendations in 2.4 and 5.1
HIGHLIGHTS **---------- DRUG INTERACTIONS----------**

QT Interval Prolonging Drugs: *Avoid* ~~*Use caution with*~~ coadministration. *Use caution when coadministration cannot be avoided.* (5.1, 7)

Reviewer's comment: We recommend avoid using VANFLYTA with drugs known to prolong the QT interval. If such drugs are given to patients already receiving VANFLYTA and no alternative therapy exists, perform ECG monitoring of the QT interval more frequently. (Refer to proposed language for 5.1)

2.2 Recommended Dosage

VANFLYTA should be initiated at a starting dose of 26.5 mg once daily only if QT interval corrected by Fridericia's formula (QTcF) ≤ 470 ms [see Warnings and Precautions (5.1)].

After two weeks:

The starting dose should be increased to the recommended dose of 53 mg once daily if QTcF ≤ 470 ms.

For patients with QTcF > 470 ms and ≤ 500 ms, continue at the same starting dose.

If QTcF > 500 ms, see Table 1.

Reviewer's comment: We agree with sponsor's proposal to allow dose escalation at QTcF ≤ 470 ms. The ECG evaluation after 2 weeks of 30 mg QD treatment should be considered as the baseline QTcF for the dose escalation phase. With dose escalation, a patient is expected to experience additional QT prolongation of approximately 10 ms. The product labels for many other oncology drugs with a positive exposure-response relationship and a mean effect between 10 and 20 ms do not include a requirement on baseline QTcF.

2.4 Monitoring and Dosage Modifications for Toxicities

Table 1: Recommended Dose Modifications for Toxicities

Adverse Reaction	Recommended Action
QTcF > 500 ms	Interrupt VANFLYTA for up to two weeks, correct hypokalemia or hypomagnesemia as needed, and ~~*avoid*~~ *discontinue* concomitant administration of drugs that prolong the QTc interval. Resume VANFLYTA at a reduced dose (see Table 2) when QTcF returns to ≤ 470 ms. If after 2 weeks of interruption QTcF does not return to ≤ 470 ms, permanently discontinue.
QTc prolongation with signs/symptoms of life-threatening arrhythmia	Permanently discontinue VANFLYTA.

Reviewer's comment: Acceptable.

2.5 Concomitant Use with Strong CYP3A Inhibitors

Table 3: Dose for Concomitant Use with Strong CYP3A Inhibitors

Concomitant Use with Strong CYP3A inhibitors	VANFLYTA Dose Modification
Patients taking a strong CYP3A inhibitor prior to initiation of VANFLYTA	Initiate treatment with a starting dose of 17.7 mg once daily. After 2 weeks, increase the dose to 26.5 mg once daily, if QTcF ≤ 470 ms. For patients with QTcF > 470 and ≤ 500 ms, continue at their current dose.

Reviewer's comment: We defer to the Division of Clinical Pharmacology regarding dose modification in the presence of strong CYP3A inhibitors.

5.1 QT~~c Interval~~ **Prolongation** *and Torsades de Pointes*

VANFLYTA ~~is associated with~~ *can prolong the QTc interval in a concentration-dependent manner [see Clinical Pharmacology (12.2)]. Torsades de pointes and cardiac arrest have occurred in patients treated with VANFLYTA. Patients with abrupt increases in heart rate are more susceptible to the proarrhythmic effects [see Clinical Pharmacology (12.2)].* ~~prolongation QTc interval prolongation may increase the risk of ventricular arrhythmias or torsade de pointes~~. ~~Of the 241 patients treated with VANFLYTA in the phase 3 clinical trial, 3.3% were found to have a QTcF interval greater than 500 ms, 12.4% had an increase from baseline QTcF greater than 60 ms based on central review of ECG data, and there were no cases of torsade de pointes or sudden death reported at the recommended doses (i.e., 26.5 mg or 53 mg)~~. ~~One patient in a phase 2 clinical trial developed torsades de pointes while receiving 79.5 mg. The event resolved following discontinuation of VANFLYTA.~~

ECGs should be performed and electrolyte abnormalities should be corrected prior to initiation of treatment. Do not start treatment with VANFLYTA if the QTcF interval is greater than 470 ms. Following dose initiation and escalation, ECGs should be performed at least once weekly for two weeks then once monthly thereafter, and as clinically indicated. Permanently discontinue VANFLYTA in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia [see Dosage and Administration (2.4)].

Do not use in patients with hypokalemia, hypomagnesemia, congenital Long QT Syndrome or in patients with a history of ventricular arrhythmias or torsades de pointes. Perform ECG monitoring of the QT interval more frequently ~~VANFLYTA should be used with caution~~ in patients who are at significant risk of developing QTc interval prolongation *and torsades de pointes*. These include patients with uncontrolled or significant cardiovascular disease, congestive heart failure, *atrial fibrillation, and structural heart disease.* ~~congenital Long QT Syndrome, hypokalemia and hypomagnesimia, history of clinically relevant ventricular arrhythmias or torsade de pointes. and patients receiving concomitant drugs known to prolong the QTc interval.~~

Avoid using VANFLYTA with drugs known to prolong the QT interval (including but not limited to anti-arrhythmic drugs, chloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, and pimozide). If such drugs are given to patients already receiving VANFLYTA and no alternative therapy exists, perform ECG monitoring of the QT interval more frequently.

Electrolytes should be maintained in the normal range. *Monitor electrolytes and ECGs more frequently in patients who experience diarrhea or vomiting.*

Concomitant use with strong CYP3A inhibitors may increase quizartinib exposure and therefore the dose of VANFLYTA should be reduced *[see Dosage and Administration (2.5)]*.

~~*ECGs should be performed and electrolyte abnormalities should be corrected prior to initiation of treatment. Do not start treatment with VANFLYTA if the QTcF interval is greater than 470 ms. Following dose initiation and escalation, ECGs should be performed at least once weekly for two weeks then once monthly thereafter, and as clinically indicated. Permanently discontinue VANFLYTA in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia [see Dosage and Administration (2.4)].*~~

Reviewer's comment: In LQT1, beta-blocker therapy is used to reduce the risk of cardiac events (syncope, aborted cardiac arrest, sudden cardiac death). Although these agents were not used in the clinical trials, they could be considered as part of the clinical treatment of high-risk patients taking VANFLYTA.

The listing of QT prolonging drugs to avoid came from the CAPRELSA label. If possible, this listing should be tailored to drugs that the patient population will most likely use.

7 Drug Interactions

QT Interval Prolonging Drugs	
Clinical Impact	Coadministration of VANFLYTA with other drugs that prolong the QT interval may further increase the incidence of QT prolongation.
Prevention or Management	*Avoid* ~~*Use caution when*~~ coadministering drugs that prolong the QT interval with VANFLYTA. *Use caution when coadministration cannot be avoided.*

Reviewer's comment: We recommend avoid using VANFLYTA with drugs known to prolong the QT interval. If such drugs are given to patients already receiving VANFLYTA and no alternative therapy exists, perform ECG monitoring of the QT interval more frequently. (Refer to proposed language for 5.1)

12.2 Pharmacodynamics

Cardiac Electrophysiology

In vitro studies have shown that quizartinib is a predominant inhibitor of the slow delayed rectifier potassium current, IKs. If IKs is blocked, the QT interval will fail to shorten appropriately during tachycardia which creates a highly arrhythmogenic condition.

The exposure-response analysis ~~*of QuANTUM-R*~~ predicted a concentration-dependent QTcF interval prolongation of *13 ms (upper bound of two-sided 90% CI: 15 ms) or* ~~*21*~~ *22* ms (upper bound of two-sided 90% CI: ~~*24*~~ *26* ms) at the steady-state Cmax of quizartinib *at the 27.5 mg or 53 mg dose levels* ~~*(53 mg)*~~. *Of the 241 patients treated with VANFLYTA in the phase 3 clinical trial, 3.3% were found to have a QTcF interval greater than 500 ms, 12.4% had an increase from baseline QTcF greater than 60 ms based on central review of ECG data. Cases of torsades de pointes and cardiac arrest have occurred at doses greater than 53 mg/day.*
Reviewer's comment: Sponsor's values were predicted based on the actual dosing history in study AC220-007. The dosing history is under the influence of QTc-based titration scheme. We recommend presenting the predicted values without dose modification; this represents the highest exposure at the proposed 30 mg or 60 mg QD dose levels.

3 SPONSOR'S SUBMISSION

3.2 OVERVIEW

Under IND 074552, the QT-IRT reviewed the protocol for Study AC220-007 and provided recommendations regarding QT-related exclusion criteria, intensive ECG monitoring plan and other risk mitigation strategies (DARRTS 09/27/2011 and 01/22/2013). In addition, the QT-IRT provided input on the proposed concentration-QTc approach at the pre-NDA meeting (DARRTS 08/09/2018). The QT-IRT agreed with the sponsor's proposal to not pool the data from two studies (i.e. Studies 2689-CL-2004 and AC220-007) for conducting the concentration-QTc analyses. However, it was noted to the sponsor that the QTc-based dose titration approach utilized in Study AC220-007 might confound the interpretation of QTc effects. Thus, the sponsor was recommended to submit the datasets and report for the concentration-QT analysis from both studies.

The sponsor submitted the concentration-QTc analysis along with the electronic datasets and source codes for the two studies:

- **Study 2689-CL-2004:** A Phase 2, randomized, open label study of two doses of quizartinib in patients with FLT3-ITD positive relapsed or refractory acute myeloid leukemia (AML). Approximately 70 patients were randomized equally to starting doses of quizartinib 30 mg/day or 60 mg/day, with escalation to 60 mg/day or 90 mg/day, respectively, after at least one 28-day cycle. 12-lead ECGs were collected in triplicate at Screening, predose and 2, 4 and 6 hours postdose on Cycle 1 Day 1 and 15, predose and 2 hours post dose on Day 8±1, predose on Cycle 1 Day 22 ±1, and Day 1 of every subsequent cycle.
- **Study AC220-007:** A Phase 3, open-label randomized study of quizartinib monotherapy (N=245) versus salvage chemotherapy (N=122) in subjects with FLT3-ITD positive AML refractory to or relapsed after first-line treatment with or without hematopoietic stem cell transplantation (HSCT) consolidation. Quizartinib monotherapy was started at 30 mg/day for 2 weeks with dose escalation at Day 16 (±1 day) to 60 mg if QTcF was ≤450 ms on Day 15. The starting dose for subjects on concomitant strong CYP3A inhibitors was 20 mg for 2 weeks with dose escalation to

30 mg if QTcF was ≤450 ms. In patients receiving quizartinib, triplicate 12-lead ECGs were performed prior to randomization, predose, 2, 4 and 6 hours postdose on C1D1 and C1D15, predose and 2 to 4 hours postdose on C1D2, C1D8, C2D1 and C3D1, and on Day 1 for all subsequent cycles with no time restriction. In patients receiving salvage chemotherapy, ECG data were collected at screening, and predose in Cycle 1 Day 1, 2, 8 and 15, and Day 1 in subsequent cycles. In patients receiving quizartinib after HSCT, ECG data were collected at predose, 2 and 4 hours postdose on C1D1 post-HSCT, predose on C1D15, and post-HSCT on C1D8, C2D1, and Day 1 in all subsequent cycles. The patients receiving quizartinib after HSCT is a subgroup of patients receiving quizartinib monotherapy.

Time-matched quizartinib and AC886 concentrations were collected in the studies. ECG data were analyzed in a central center laboratory. There were no placebo or positive control in either study for QT assessment purposes.

3.3 SPONSOR'S RESULTS

3.3.1 Central tendency analysis

Sponsor did not provide any central tendency analysis for pharmacodynamic data set.

3.3.1.1 Assay Sensitivity

Not applicable.

3.3.1.1.1 QT bias assessment

Not applicable.

3.3.2 Categorical Analysis

This reviewer's results are similar to sponsor's results for study 2689-CL-2004. But for the study AC220-007, there are some differences between the reviewer's and sponsor's results. Please see section 4.5 for FDA standard categorical analyses for Study 2689-CL-2004 and Study AC220-007.

Table 2. Categorical Analysis Based on Central ECG Reading (Study AC220-007)

Parameter	Quizartinib Monotherapy (N = 241) n (%)	Salvage Chemotherapy (N = 94) n (%)
QTcF		
>450 ms	114 (47.3)	6 (6.4)
>480 ms	38 (15.8)	0 (0.0)
>500 ms	8 (3.3)	0 (0.0)
Increase From Baseline >30 ms	151 (62.7)	14 (14.9)
Increase From Baseline >60 ms	30 (12.4)	1 (1.1)
PR		
Increase From Baseline >25% and PR >200 ms	2 (0.8)	0 (0.0)
QRS		
Increase From Baseline >25% and QRS >100 ms	2 (0.8)	0 (0.0)
Heart rate		
Decrease From Baseline >25% and heart rate <50 bpm	4 (1.7)	0 (0.0)
Increase From Baseline >25% and heart rate >100 bpm	32 (13.3)	7 (7.4)

bpm = beats per minute; ECG = electrocardiogram; n = number of subjects in the category; N = population size; PR = interval between the P and R wave; QRS = interval between the R and S wave; QT = interval between the start of the Q wave and the end of the T wave; QTcF = QTc with Fridericia's correction factor.
Notes: Assessments performed more than 30 days after discontinuation of study drug are not summarized.
Baseline for the ECG parameter is defined as the average of the last 3 ECG measurements taken prior to first dose at study drug.
"New" implies a newly occurring notable ECG value, which is defined as an abnormal ECG finding at post-baseline that is not present at baseline.

Source: Sponsor's Table 10.29 in CSR

3.3.3 Safety Analysis

3.3.3.1 Study AC220-007

Adverse events in the Torsade de Pointes/QT prolongation SMQ occurred with a higher frequency in the quizartinib arm than in the salvage chemotherapy arm (Table 3). In the quizartinib arm, there were 10 (4%) subjects with Grade ≥3 ECG QT prolonged (>500 ms). There were no Grade 4 events (QTcF >500 ms associated with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia). ECG QT prolonged was reported as serious for 5 (2%) subjects. The TEAEs of ECG QT prolonged were associated with study drug interruption for 11 (5%) subjects, dose reduction for 23 (10%) subjects, and study treatment discontinuation for 2 (1%) subjects.

Table 3. AEs in Torades de Pointes/QTc Prolongation Standard MedDRA Query

AESI Category	Quizartinib Monotherapy (N = 241)				Salvage Chemotherapy (N = 94)	
	TEAE n (%)	Grade ≥3 n (%)	Serious n (%)	Study Drug Discontinuation n (%)	TEAE n (%)	Grade ≥3 n (%)
Subjects with any Torsade de pointes/ QT prolongation	74 (30.7)	19 (7.9)	10 (4.1)	2 (0.8)	7 (7.4)	0
Electrocardiogram QT prolonged	64 (26.6)	10 (4.1)	5 (2.1)	2 (0.8)	2 (2.1)	0
Syncope	12 (5.0)	9 (3.7)	5 (2.1)	0	2 (2.1)	1 (1.1)
Ventricular tachycardia	1 (0.4)	0	0	0	2 (2.1)	1 (1.1)
Cardiac arrest	0	0	0	0	1 (1.1)	1 (1.1)

AE = adverse event; AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with an event; N = population size; PT = preferred term; QT = interval between the start of the Q wave and the end of the T wave; SAP = Statistical Analysis Plan; SMG = Standardized MedDRA Queries; SOC = system organ class; TEAE = treatment-emergent adverse event

Notes: A TEAE is defined as an AE that occurs, having been absent before the first dose of study drug or worsened in severity after the first dose of study drug, on or after the first dose of study drug and up to 30 days after the last dose of study drug. Subjects may have more than 1 event per category of interest and PT. At each level of subject summarization, a subject was counted once if he/she reported 1 or more AEs. AEs were coded using MedDRA Version 16.1. AEs of special interest are defined by selecting specific SMQ or SOC, and/or PTs as defined in the SAP.

No subjects in the salvage chemotherapy arm had an event that was serious or associated with discontinuation of study drug.

Source: Table 10.16 in CSR

There were 5 (2%) subjects reporting SAE of syncope in the quizartinib arm and none in the chemotherapy arm. The syncope events were not associated with QTc >470 ms or cardiac arrhythmias, but abrupt increases in heart rate are possible for those cases with hypotension.

- Subject (b) (6) is a 56 y/o female receiving quizartinib, 30 mg. On (b) (6) (b) (6)), the subject presented with CTCAE Grade 3 Syncope. At the time of the event, the subject was receiving 30 mg of quizartinib; the subjects subsequently missed two doses of quizartinib. On the same day, the subject presented to the emergency department with complaints of syncopal episodes at home. The subject reported pain to back of head. A computerized tomography (CT) scan of the head was negative. There was no evidence of acute intracranial hemorrhage or mass effect and no acute cervical spine fracture or traumatic subluxation. A CT scan of the cervical spine was also negative and showed small right parieto-occipital subgaleal hematoma without acute calvarial fracture. The subject's QTcF intervals were within normal limits prior and after the event; no ECG results at the event onset. No action was taken with the subject's quizartinib treatment as a result of the event. The following medication was given for the treatment of nausea: ondansetron 4 mg IV (from CIOMS). On the same day, the event resolved, and the subject was discharged. The subject was not receiving any relevant concomitant medication at the time of the event.
- Subject (b) (6) is a 45 y/o white female. On (b) (6) the subject presented with CTCAE Grade 3 Syncope. At the time of the event, the subject was not receiving quizartinib as it was previously permanently discontinued. The subject was admitted to the intensive care unit due to Syncope accompanied by hypotension and vertigo. On (b) (6) (b) (6) Syncope resolved, and the subject was discharged home. Per central electrocardiogram, the subject did not have any episodes of QTcF interval prolongation above 450 ms during the study.

- Subject (b) (6) is a 67 y/o female. On 09 MAR 2015 (Day 57), the subject presented with CTCAE Grade 3 Syncope. At the time of the event, the subject was receiving quizartinib 60 mg. On the same day, the subject was found on the floor. The subject had a fixed stare and was unblinking. The subject's body then became rigid. After less than 2 minutes, the subject regained consciousness and was covered with sweat. On the same day, the subject presented to the clinic as scheduled. The subject denied headache or dizziness. A predose ECG revealed mean QTcF of 447 ms (≥30 ms change from baseline), and a 2-hour postdose ECG revealed mean QTcF of 441 ms (≥30 ms change from baseline); the subject's mean heart rate were 73 bpm and 74 bpm, respectively. No action was taken with the subject's quizartinib treatment as a result of the event. No treatment was reported for the event. The event of Syncope resolved on the same day.
- Subject (b) (6) is a 60 y/o female. On 03 SEP 2015 (Day 36), the subject presented with CTCAE Grade 3 Febrile Neutropenia and CTCAE Grade 3 Syncope. At the time of the events, the subject was receiving quizartinib 60 mg. On 27 AUG 2015 (Day 29), an ECG showed normal sinus rhythm and no QTcF interval prolongation. On (b) (6) the subject presented to the emergency department due to syncopal episode at home and neutropenic fever (temperature not reported). Laboratory test results showed hematocrit of 16% (normal range 41% to 51%), hemoglobin of 5.5 g/dL (normal range 13.7 to 17.5 g/dL), platelets of 14 thou/µL (normal range 50 to 330 thou/µL), and neutrophils of 0.00 thou/µL (normal range 1.8 to 5.4 thou/µL) (from the CIOMS**). The subject was transfused with 2 units of packed red blood cells and 1 unit of platelets. No vital signs were reported. The ECG done prior to the transfer to the center revealed normal sinus rhythm (from the CIOMS). No treatment medication was reported for the event of Syncope. No action was taken with the subject's quizartinib treatment as a result of the events.
- Subject (b) (6) is 44 y/o male. On (b) (6) the subject presented with CTCAE Grade 3 Syncope. At the time of the event, the subject was receiving quizartinib 60 mg. The subject felt dizzy while in the shower, fell on his back, and lost consciousness for about 10 seconds. The subject rested in bed but fell again, without losing consciousness, when trying to stand up. The subject presented to an outside emergency department and was hypotensive (systolic pressure in the 70 to 80s mmHg). Hemoglobin was 7.3 g/dL and platelet count was 18000 (from the CIOMS**; normal ranges not provided). The subject had a back bruise and complained of pain. It was noted that 6 days prior to the event, the subject had received a platelet transfusion of 2 units of packed red blood cells and 1 unit of platelets for a platelet count of 12000 (from the CIOMS). A computed tomographic (CT) scan of the abdomen revealed left abdominal wall and lower back hematomas, as well as minimal left retroperitoneal hemorrhage. A CT scan of the brain/head was negative. On (b) (6) (b) (6) a CT scan of the chest revealed a small left pleural effusion. The medical impression was that of syncope related to underlying disease, hypovolemia, and anemia.

One subject in the quizartinib arm and 2 subjects in the salvage chemotherapy arm had TEAEs of ventricular tachycardia. The event of ventricular tachycardia in the quizartinib arm occurred in Subject (b) (6) on Day 23. The investigator attributed the event to electrolyte imbalance due to vomiting. Quizartinib had been interrupted 3 days earlier due to vomiting. This subject also experienced a serious syncope event on Day 1067 while on quizartinib (narrative above).

A total of 8 (3.3%) subjects in the quizartinib treatment arm had QTcF >500 ms and 30 (12.4%) subjects had QTcF >60 ms from baseline. QTc prolongation was reported as a serious AE in 5 subjects listed below. There were no reports of cardiac arrhythmias for these subjects; however, one subject had loss of consciousness.

- Subject (b) (6) is a 54 y/o male receiving 60 mg of quizartinib, who experienced a fall (serious event) associated with loss of consciousness on Day 46, and central ECG revealed a QTcF of 503.3 ms later that day. The subject was also found to have low hemoglobin (70 g/L; normal range: 130 to 170 g/L) and was transfused with 3 units of packed RBCs. No vital signs were recorded that day. However, vital signs the day before (on Day 45) showed a blood pressure of 81/50 mmHg and a pulse rate of 102 bpm. No action was taken with the subject's quizartinib treatment, and subsequent QTcF measurements until the EOT (Day 101) were all <450 ms. The investigator reported that the fall was caused by hypotension and anaemia and was unrelated to the study drug.
- Subject (b) (6) is 57 y/o female. On 03 JUL 2016 (Day 27), the subject presented with CTCAE Grade 3 Electrocardiogram QT Prolonged. At the time of the event, the subject was not receiving quizartinib as it was previously interrupted. Serum electrolyte levels were not provided on the same day. On the same day, ECG results showed QTc interval was > 524 ms (from the CIOMS). On 04 JUL 2016 (Day 28), the subject's QTc interval improved to 459 ms (from the CIOMS). The event of Electrocardiogram QT Prolonged resolved on the same day.
- Subject (b) (6) is 72 y/o male. On 09 NOV 2016 (Day 136), the subject experienced a nonserious CTCAE Grade 2 diarrhoea. Metronidazole was continued as treatment for the diarrhoea. On 16 NOV 2016 (Day 143), the subject presented with CTCAE Grade 3 Electrocardiogram QT Prolonged. At the time of the event, the subject was receiving quizartinib 60 mg. The subject also presented with nonserious CTCAE Grade 1 hypokalaemia, while the diarrhea resolved on the same day. ECG results showed mean QTcF of 537 ms (normal range < 450 ms) at 15:24, 531 ms at 15:27, and 510 ms at 15:30 (from the CIOMS). On the same day, laboratory results showed potassium 3.3 mmol/L (normal range 3.5 to 5.0 mmol/L), calcium 8.5 mg/dL (normal range 8.5 to 10.2 mg/dL), and magnesium 1.8 mg/dL (normal range 1.6 to 2.2 mg/dL) (from the CIOMS). The subject's quizartinib treatment was interrupted on 19 NOV 2016 (Day 146) as a result of the event. The subject's recent diarrhoea, from C. difficile colitis, resulted in hypokalemia which likely precipitated the QT prolongation. Treatment for hypokalaemia included potassium chloride. On 21 NOV 2016 (Day 148), ECG results showed mean QTcF of 435 ms at 13:01, 438 ms at 13:04, and 434 ms at 13:07 (from the CIOMS). Laboratory results showed potassium 4.3 mmol/L and calcium 8.6 mg/dL (from the CIOMS). No treatment was reported for this event. The event of Electrocardiogram QT Prolonged and hypokalaemia resolved on 21 NOV 2016 (Day 148). At the time of the event, the subject was receiving the following relevant concomitant medication: amlodipine (started on 31 MAY 2016 [Day -27]).
- Subject (b) (6) is a 41 y/o female. On 22 SEP 2015 (Day 15), the subject presented with CTCAE Grade 3 Electrocardiogram QT Prolonged. This was a serious adverse event as it was an important medical event. The event was also an AE of special interest. At the time of the event, the subject was receiving quizartinib 30 mg. On the same day, the subject experienced nonserious CTCAE Grade 1 nausea. Ondansetron 8 mg PRN was being given prophylactically for the nausea since 31 AUG 2015 (Day -8). On 04 SEP 2015 (Day -4), the subject's baseline electrocardiogram (ECG) showed QTcF was 424.7 ms. See the ECG Central Laboratory table and Line Plot of QTcF Results over Time below for additional relevant values. On 22 SEP 2015 (Day 15), ECGs collected before dosing and 2, 4, and 6 hours after dosing showed prolonged QT interval with an average 4 hour post dose QTc of 516 ms (517 ms at 14:58:01, 519 ms at 15:01:05, and 512 ms at 15:04:05; 487 ms at 16:58:00, 488 ms at 17:01:00, and 483 ms at 17:04:00) (from the CIOMS**). Laboratory results showed hemoglobin was 60 g/L (normal range 120 to 156 g/L), calcium was 1.88 mmol/L (normal range 2.12 to 2.56 mmol/L), sodium was 134 mmol/L (normal range 135 to 146 mmol/L), and potassium was 3.0 mmol/L (normal range 3.5 to 5.3 mmol/L); magnesium

was within normal range. See the Hematology and Serum Chemistry Part 2 tables below for additional relevant values. The subject's quizartinib dose was reduced from 30 mg to 20 mg on 23 SEP 2015 (Day 16) due to the Electrocardiogram QT Prolonged. The nausea resolved on 29 SEP 2015 (Day 22).

- Subject (b) (6) is 41 y/o female. On (b) (6) the subject presented with a CTCAE Grade 3 Electrocardiogram QT Prolonged, which had worsened from a CTCAE Grade 1. This was a serious adverse event as it required hospitalization and was also an AE of special interest. At the time of the event, the subject was receiving quizartinib 30 mg. On the same day, central laboratory results revealed Ca, K, and Mg values were within normal ranges. Additional local laboratory results at the time of event showed K was 3.2 mEq/L (normal range 3.3 to 5.1 mEq/L). ECG done on the day of the event was normal at predose with heart rate of 87.7 bpm and QTcF 454 ms; ECG was abnormal at 2 hours postdose with heart rate of 85.3 bpm and QTcF 502 ms (normal range <450 ms [from the CIOMS]). ECG at 7 hours postdose showed QTcF was 452 ms (from the CIOMS). The subject received magnesium sulfate 1 g once and potassium chloride 60 mEq once as treatment for the event. On (b) (6) QTcF was 461 ms (from the CIOMS); the event was considered resolved, and the subject was discharged from the hospital. On the same day, the subject's quizartinib treatment was interrupted due to Electrocardiogram QT Prolonged and was restarted on 10 OCT 2016 (Day 34) at a reduced dose of 20 mg. At the time of the event, the subject was receiving the following relevant concomitant medication: ranitidine (started on 16 AUG 2016 [Day -22]) and ciprofloxacin (started on 20 SEP 2016 [Day 14]). The subject was taking the following QT-prolonging medication within 30 days prior to the onset of Electrocardiogram QT Prolonged that was discontinued prior to the onset of the event: posaconazole (started on 17 AUG 2016 [Day -21] to 05 SEP 2016 [Day -2]).

In addition, 3 subjects in the quizartinib treatment arm had QTcF >500 ms based on local ECG reading at the investigator site. One subject experience palpitations and presyncope.

- Subject (b) (6) is a 63-year-old female who experienced palpitations and presyncope (both non-serious) on Day 23. No ECG data were reported on this date. Quizartinib dose was reduced to 20 mg in response to these events. Three days later, on Day 26, the subject experienced Grade 3 QT prolongation (non-serious), with a maximum QTcF interval of 514 ms (based on local reading). There were no central ECG data reported on Day 26. Quizartinib was interrupted, and the event resolved (central ECG QTcF values were 457 and 452 ms on Day 27 and 462 ms on Day 28). Study drug was not restarted, as the subject was withdrawn from the study on Day 28 due to AML disease progression.

3.3.3.2 Study 2689-CL-2004

Nineteen (25.7%) subjects had events in the Cardiac Disorders SOC during this study. The most frequently reported cardiac events were in the preferred terms tachycardia (10 subjects, 13.5%) and ECG QT prolonged (8 subjects, 10.8%). None of the reported AEs of ≥ Grade 3 were reported at a frequency of >10% in either dose group.

Of the 10 subjects who experienced tachycardia, 6 (16.7%) were in the 60 mg dose group. None were Grade 3 or more, an SAE, led to discontinuation of study drug or death.

Of the 8 subjects who experienced ECG QT prolonged, 6 of the subjects were in the 60 mg dose group. No event of ECG QT prolonged was Grade 4 or fatal, and the majority of these events (5 subjects, 6.8%) were Grade 1. All subjects who experienced ECG QT prolonged developed it within Cycle 1. Of the 8 subjects who experienced ECG QT

prolonged, 7 (9.5%) were considered by the Investigator to be related to study drug and 2 of those was an SAE.

Cardiac treatment-emergent AEs that led to dose interruption occurred in 2 subjects and were only observed in the 60 mg dose group (1 subject with ECG QT prolonged, ECG T-wave inversion, and cardiac failure; and 1 subject with ECG QT prolonged). Treatment-emergent AEs that led to dose reduction occurred in 2 subjects, one subject in each dose group (ECG QT prolonged, each).

3.3.3.3 Other Studies: RR AML Pooled Group

The RR AML pooled group includes a total of 673 subjects with RR AML from 4 studies (including 241 subjects from AC220-007), all of which enrolled subjects with RR AML who received quizartinib dihydrochloride QD, at doses ranging from 30 mg to 300 mg QD, depending on the study.

A dose-repose relationship of the TEAEs in the Torsade de Pointes/QT prolongation AESI category was evaluated using data from the RR AML pooled group. Few subjects in the 30-mg dose group (2.6%) and similar proportions of subjects in the 60 mg and >60-mg dose groups (29% and 32%, respectively) had TEAEs within the Torsades de Pointes/QT prolongation SMQ. The proportion of subjects in each dose group with TEAEs of Grade ≥3 were 3%, 8%, and 13%, respectively. The 2 most frequent SAEs were ECG QT prolonged (6% subjects) and syncope (1% subjects). Of the 3 subjects with an SAE of cardiac arrest, only one had some evidence of QT prolongation. One subject had torsades de pointes.

- Subject (b) (6) is a 63 y/o female subject receiving quizartinib, 90 mg. She had a Grade 4 SAE of ECG QT prolonged reported (QTcF 543 ms) with an episode of torsades de pointes on Day 20, which resolved spontaneously after treatment discontinuation. There were multiple contributing factors in this case, including hypocalcaemia, sepsis with episodes of respiratory arrest, and underlying atrial fibrillation.
- Subject (b) (6) is a 39 y/o female subject receiving quizartinib, 90 mg. Cardiac arrest occurred on Day 40, 4 days after the starting quizartinib dose of 90 mg was increased to 135 mg. The QTcF had increased from baseline of 408 ms to a maximum of 496 ms 4 days before the cardiac arrest but was reportedly 471 ms the day before death. Staphylococcal sepsis was also present and treated with piperacillin-tazobactam and voriconazole starting the day before death, and TEAEs of pain, vomiting, haemoptysis, epistaxis, and conjunctival haemorrhage were reported at the time of cardiac arrest.

3.3.4 Exposure-Response Analysis

The sponsor submitted concentration-QTcF analysis results based on data from studies 2689-CL-2004 and AC220-007 in separate study reports. In each report, the sponsor developed population-PK/PD models using a direct effect model to describe the relationship between QTcF vs. quizartinib concentration alone, AC886 concentration alone, or both quizartinib and AC886 concentrations. Both linear and nonlinear models were tested. The final model for Study AC220-007 was a sigmoid E_{max} model including estimates of baseline, a shift in baseline for patients with hypokalemia (i.e. a proportional increase of 1.5%), fixed time effect, and separate Emax, EC50, and Hill coefficients for quizartinib and AC886, as well as inter-individual variability in baseline and Emax for quizartinib and AC886. The final model for Study 2689-CL-2004 was a linear model

with baseline, fixed time effect, race effect on baseline (i.e. a proportional decrease of 4.1% in non-White patients), and separate slopes for quizartinib and AC886. Both models were evaluated based on goodness-of-fit and visual predictive check and were found acceptable for describing the observed QTcF data in individual studies.

Based on the final model for Study AC220-007, simulations were performed using the actual dosing history for the patients in Study AC220-007 who received 60 mg once daily at Cycle 1 Day 28 (n = 109). The final QTcF model predicted a mean ΔQTcF associated with geometric mean quizartinib $C_{max,ss}$ and geometric mean AC886 concentration at the time of the quizartinib $C_{max,ss}$ of 21.1 ms (90% CI: 18.3, 23.6 ms). Following the once-daily administration of quizartinib 30 mg and 60 mg for 30 days with no dose adjustment and without strong CYP3A inhibitor use, the model predicts a mean ΔQTcF of 15.9 ms (90% CI: 13.5, 18.4 ms) and 23.7 ms (90% CI: 20.6, 26.2 ms), respectively.

As the QTc effects were confounded by the QTc-based dose titration approach utilized in the Study AC220-007, the reviewer conducted concentration-QTc analysis using first cycle data from Study 2689-CL-2004. In addition, because quizartinib demonstrates comparable potency on Ikr inhibition but significantly higher potency on Iks inhibition as compared with AC860 (section 5), the reviewer used quizartinib as the only exposure metrics in the concentration-QTc analysis. Please see section 4.6 for additional details. In reviewer's analysis, the predicted ΔQTcF values at steady state in patients taking 30 mg QD or 60 mg QD doses (without dose modification) are similar to those predicted based on sponsor's final model from Study AC220-007.

4 REVIEWERS' ASSESSMENT

4.2 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. A dose dependent decrease in HR was observed in Study 2689-CL-2004. The decrease for the 60 mg QD dose level was approximately 10 bpm and it is therefore possible that the effects on HR could have impacted the precision of QTcF. However, the observed linearity of the concentration-QTc relationship suggests that the decrease in HR at the 60 mg QD dose level is unlikely to have impacted the evaluation of concentration-QTc relationship (see section 4.5). Therefore, we agree with using QTcF for the primary analysis.

4.3 ECG ASSESSMENTS

4.3.1 Overall

Overall ECG acquisition and interpretation in these two studies (2689-CL-2004 and AC220-007) appears acceptable.

4.3.2 QT bias assessment

Not applicable.

4.4 CENTRAL TENDENCY ANALYSIS

4.4.1 QTc

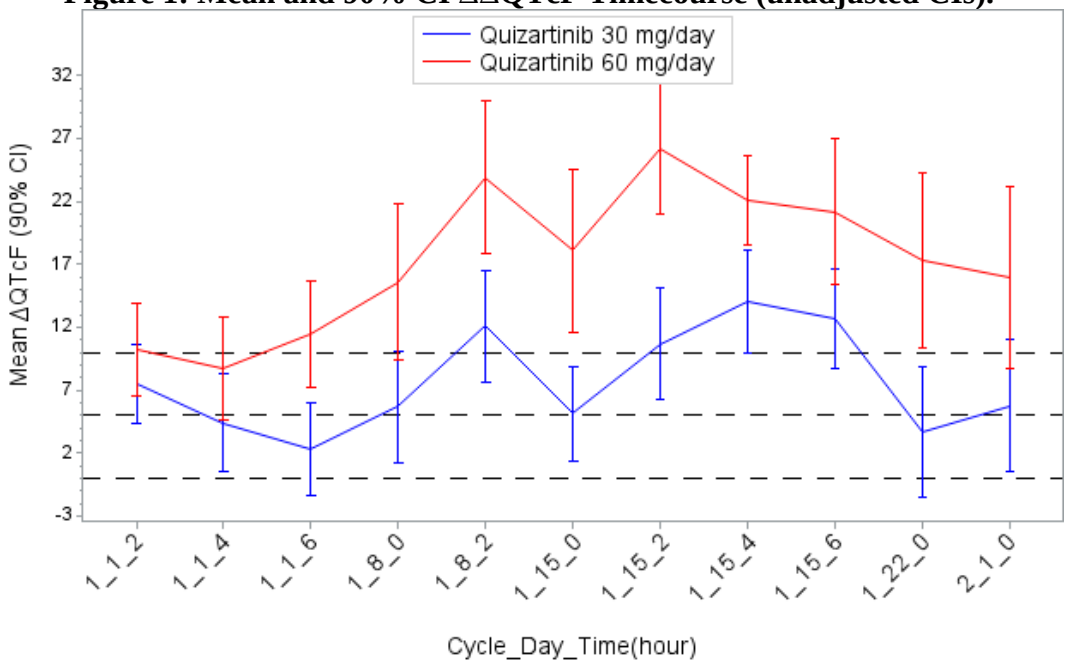
Study 2689-CL-2004:

Table 4 presents the descriptive statistics (mean and 90% CI) for ΔQTcF ordered by cycle, day and time points. The results are also graphically presented in Figure 1 (Note: only timepoints at which the sample size is at least 70% of total population are used for this representation). The largest upper bound for quizartinib 30 mg/day was 18.07 ms and that for quizartinib 60 mg/day was 32.81 ms.

Table 4: Descriptive Statistics for ΔQTcF

Treatment	Cycle	Day	Time (hr)	N	Mean	90% LCLM	90% UCLM
Quizartinib 30 mg/day	1	1	2	37	7.48	4.37	10.60
Quizartinib 60 mg/day	1	1	2	36	10.22	6.54	13.90
Quizartinib 30 mg/day	1	1	4	37	4.41	0.54	8.27
Quizartinib 60 mg/day	1	1	4	36	8.71	4.65	12.76
Quizartinib 30 mg/day	1	1	6	34	2.31	-1.39	6.00
Quizartinib 60 mg/day	1	1	6	33	11.42	7.16	15.69
Quizartinib 30 mg/day	1	8	0	36	5.67	1.24	10.09
Quizartinib 60 mg/day	1	8	0	34	15.59	9.39	21.78
Quizartinib 30 mg/day	1	8	2	37	12.06	7.69	16.43
Quizartinib 60 mg/day	1	8	2	33	23.88	17.79	29.98
Quizartinib 30 mg/day	1	15	0	38	5.12	1.37	8.87
Quizartinib 60 mg/day	1	15	0	32	18.07	11.58	24.55
Quizartinib 30 mg/day	1	15	2	38	10.67	6.25	15.10
Quizartinib 60 mg/day	1	15	2	32	26.19	20.95	31.42
Quizartinib 30 mg/day	1	15	4	38	14.04	10.00	18.07
Quizartinib 60 mg/day	1	15	4	30	25.65	18.48	32.81
Quizartinib 30 mg/day	1	15	6	38	12.64	8.73	16.56
Quizartinib 60 mg/day	1	15	6	27	21.19	15.39	26.99
Quizartinib 30 mg/day	1	22	0	35	3.69	-1.47	8.85
Quizartinib 60 mg/day	1	22	0	30	17.28	10.33	24.23
Quizartinib 30 mg/day	2	1	0	36	5.75	0.48	11.02
Quizartinib 60 mg/day	2	1	0	28	15.96	8.77	23.15

Figure 1: Mean and 90% CI ΔΔQTcF Timecourse (unadjusted CIs).



4.4.1.1 Assay sensitivity

Not applicable.

4.5 CATEGORICAL ANALYSIS

4.5.1 QTc

Study 2689-CL-2004:

Table 5 lists the number of subjects as well as the number of observations whose QTcF values are less than 450 ms, greater than 450 ms and less than or equal to 480 ms, greater than 480 ms and less than or equal to 500 ms, or greater than 500 ms. Two subjects' QTcF were above 500 ms in quizartinib 30 mg/day group.

Table 5: Categorical Analysis for QTcF

	Total (N)		Value<=450 ms		450 ms<Value<=480 ms		480 ms<Value<=500 ms		Value>500 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Quizartinib 30 mg/day	38	366	21 (55.3%)	300 (82.0%)	13 (34.2%)	60 (16.4%)	2 (5.3%)	4 (1.1%)	2 (5.3%)	2 (0.5%)
Quizartinib 60 mg/day	36	309	13 (36.1%)	240 (77.7%)	19 (52.8%)	63 (20.4%)	4 (11.1%)	6 (1.9%)	0 (0.0%)	0 (0.0%)

Table 6 lists the categorical analysis results for ΔQTcF. Two subjects' ΔQTcF in quizartinib 30 mg/day group and four subjects' ΔQTcF in quizartinib 60 mg/day group were above 60 ms.

Table 6: Categorical Analysis of ΔQTcF

	Total (N)		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.

	Total (N)		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Quizartinib 30 mg/day	38	366	23 (60.5%)	328 (89.6%)	13 (34.2%)	36 (9.8%)	2 (5.3%)	2 (0.5%)
Quizartinib 60 mg/day	36	309	14 (38.9%)	236 (76.4%)	18 (50.0%)	66 (21.4%)	4 (11.1%)	7 (2.3%)

Study AC220-007:

Table 7 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, greater than 450 ms and less or equal 480 ms, greater than 480 ms and less or equal 500 ms and greater than 500 ms. One subject's QTcF was above 500 ms in Post-HSCT quizartinib group and seven subjects' QTcF was above 500 ms in quizartinib group.

Table 7: Categorical Analysis for QTcF

	Total (N)		Value<=450 ms		450 ms<Value<=480 ms		480 ms<Value<=500 ms		Value>500	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
QUIZARTINIB	239	3987	116 (48.5%)	3395 (85.2%)	86 (36.0%)	532 (13.3%)	30 (12.6%)	51 (1.3%)	7 (2.9%)	9 (0.2%)
Salvage Chemotherapy	84	157	79 (94.0%)	151 (96.2%)	5 (6.0%)	6 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Post-HSCT QUIZARTINIB	48	694	39 (81.3%)	636 (91.6%)	7 (14.6%)	56 (8.1%)	1 (2.1%)	1 (0.1%)	1 (2.1%)	1 (0.1%)

Table 8 lists the categorical analysis results for ΔQTcF for this study. One subject in Post-HSCT quizartinib group, thirty subjects in quizartinib group and one subject in salvage chemotherapy group experienced ΔQTcF above 60 ms.

Table 8: Categorical Analysis of ΔQTcF

	Total (N)		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
QUIZARTINIB	233	3702	85 (36.5%)	3129 (84.5%)	118 (50.6%)	528 (14.3%)	30 (12.9%)	45 (1.2%)
Salvage Chemotherapy	57	91	54 (94.7%)	85 (93.4%)	2 (3.5%)	4 (4.4%)	1 (1.8%)	2 (2.2%)
Post-HSCT QUIZARTINIB	46	682	30 (65.2%)	623 (91.3%)	15 (32.6%)	58 (8.5%)	1 (2.2%)	1 (0.1%)

4.5.2 PR

Study 2689-CL-2004:

The outlier analysis results for PR are presented in Table 9. Two subjects who experienced PR interval greater than 220 ms in quizartinib 30 mg/day group.

Table 9: Categorical Analysis for PR

	Total (N)		Value<=200 ms		200 ms<Value<=220 ms		Value>220 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Quizartinib 30 mg/day	38	366	34 (89.5%)	346 (94.5%)	2 (5.3%)	17 (4.6%)	2 (5.3%)	3 (0.8%)
Quizartinib 60 mg/day	36	309	34 (94.4%)	303 (98.1%)	2 (5.6%)	6 (1.9%)	0 (0.0%)	0 (0.0%)

Study AC220-007:

The outlier analysis results for PR are presented in Table 10. Nine subjects experienced PR interval greater than 220 ms in quizartinib group. Note: Two subjects in salvage chemotherapy group and two subjects in quizartinib group had missing PR values.

Table 10: Categorical Analysis for PR

	Total (N)		Value<=200 ms		200 ms<Value<=220 ms		Value>220 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
QUIZARTINIB	237	3934	215 (90.7%)	3756 (95.5%)	13 (5.5%)	114 (2.9%)	9 (3.8%)	64 (1.6%)
Salvage Chemotherapy	82	154	79 (96.3%)	150 (97.4%)	3 (3.7%)	4 (2.6%)	0 (0.0%)	0 (0.0%)
Post-HSCT QUIZARTINIB	48	694	44 (91.7%)	675 (97.3%)	4 (8.3%)	19 (2.7%)	0 (0.0%)	0 (0.0%)

4.5.3 QRS

Study 2689-CL-2004:

The outlier analysis results for QRS are presented in Table 11. There are 4 subjects who experienced QRS interval greater than 110 ms in both quizartinib 30 mg/day and quizartinib 60 mg/day groups.

Table 11: Categorical Analysis for QRS

	Total (N)		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Quizartinib 30 mg/day	38	367	26 (68.4%)	327 (89.1%)	10 (26.3%)	31 (8.4%)	2 (5.3%)	9 (2.5%)
Quizartinib 60 mg/day	36	309	29 (80.6%)	277 (89.6%)	5 (13.9%)	18 (5.8%)	2 (5.6%)	14 (4.5%)

Study AC220-007:

The outlier analysis results for QRS are presented in Table 12. There are 2 subjects who experienced QRS interval greater than 110 ms in Post-HSCT quizartinib group and 15 subjects who experienced QRS interval greater than 110 ms in quizartinib group.

Table 12: Categorical Analysis for QRS

	Total (N)		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
QUIZARTINIB	239	3987	161 (67.4%)	3471 (87.1%)	63 (26.4%)	434 (10.9%)	15 (6.3%)	82 (2.1%)
Salvage Chemotherapy	84	157	70 (83.3%)	138 (87.9%)	14 (16.7%)	19 (12.1%)	0 (0.0%)	0 (0.0%)
Post-HSCT QUIZARTINIB	48	694	37 (77.1%)	612 (88.2%)	9 (18.8%)	75 (10.8%)	2 (4.2%)	7 (1.0%)

4.5.4 HR

Study 2689-CL-2004:

The outlier analysis results for HR are presented in Table 13. There are 9 subjects who experienced HR greater than 100 bpm in quizartinib 30 mg/day group and there are 15 subjects who experienced HR greater than 100 bpm in quizartinib 60 mg/day groups. 6

patients in the 30 mg/day group and 10 patients in the 60 mg/day group have baseline HR greater than 100 bpm.

Table 13: Categorical Analysis for HR

	Total (N)		Value<=100 bpm		Value>100 bpm	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Quizartinib 30 mg/day	38	367	29 (76.3%)	335 (91.3%)	9 (23.7%)	32 (8.7%)
Quizartinib 60 mg/day	36	309	21 (58.3%)	265 (85.8%)	15 (41.7%)	44 (14.2%)

Study AC220-007:

The outlier analysis results for HR are presented in Table 14. There are 10 subjects in Post-HSCT quizartinib group, 77 subjects in quizartinib group and 30 subjects in salvage chemotherapy group who experienced HR greater than 100 bpm. 1 patient in Post-HSC quizartinib group, 39 patients in quizartinib group, and 23 patients in salvage chemotherapy group have baseline HR greater than 100 bpm.

Table 14: Categorical Analysis for HR

	Total N		Value<=100 bpm		Value>100 bpm	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
QUIZARTINIB	239	3987	162 (67.8%)	3653 (91.6%)	77 (32.2%)	334 (8.4%)
Salvage Chemotherapy	84	157	54 (64.3%)	112 (71.3%)	30 (35.7%)	45 (28.7%)
Post-HSCT QUIZARTINIB	48	694	38 (79.2%)	673 (97.0%)	10 (20.8%)	21 (3.0%)

4.6 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between ΔQTcF and the concentrations of quizartinib based on data from Study 2689-CL-2004.

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF and 3) presence of non-linear relationship.

An evaluation of the time-course of quizartinib concentration and changes in ΔHR and ΔQTcF is shown in Figure 2, which shows dose-dependent decrease in HR and dose-dependent increase in ΔQTcF. Figure 2 does not appear to show significant hysteresis between ΔQTcF and the concentrations of quizartinib. The maximum ΔQTcF generally occurred at 2 hours postdose (i.e. Tmax of quizartinib) on Day 1 and on Day 15. Figure 3 shows the relationship between ΔQTcF and quizartinib concentrations, and it suggest a linear relationship between ΔQTcF and quizartinib concentrations.

Figure 2: Time course of drug concentration, heart rate, and QTcF.

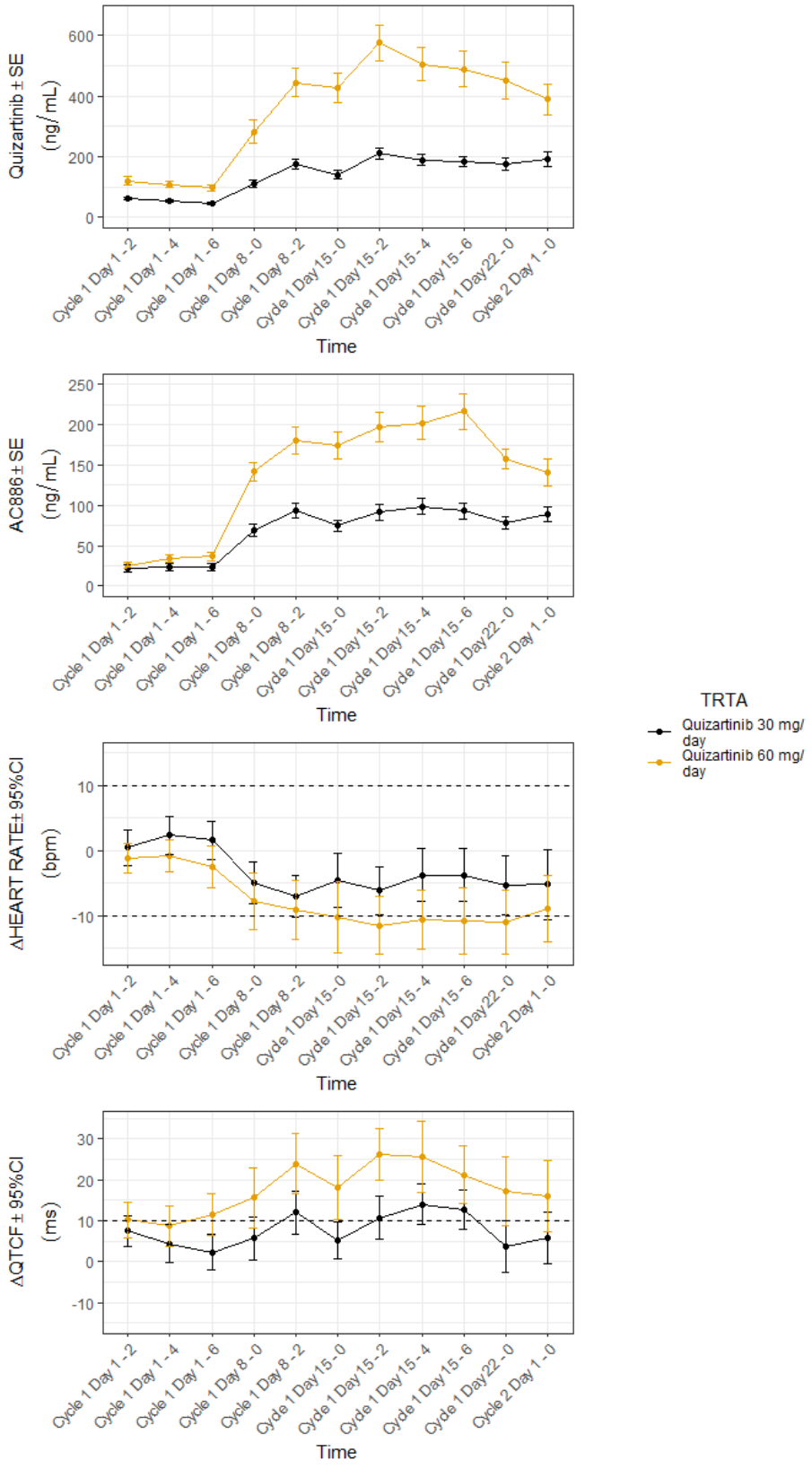
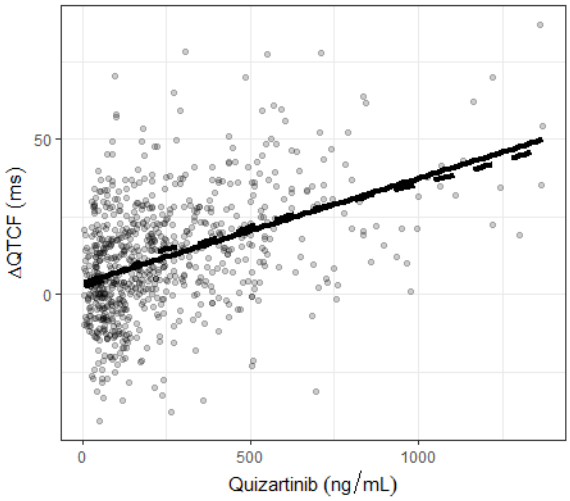


Figure 3: Assessment of linearity of concentration-QTc relationship for quizartinib.



The exposure-response relationship was evaluated using linear mixed effects model with ΔQTcF as dependent variable, quizartinib concentrations as a predictor, baseline adjustment as a fixed effect, and subject as a random effect on the intercept and slopes. There was a statistically significant positive slope ($p<0.05$) for exposure-response relationship for quizartinib. Goodness-of-fit plot is shown in Figure 4 and predictions from the concentration-QTc model are provided in Table 15. Following the administration of quizartinib 30 mg/day and 60 mg/day for 30 days with no dose adjustment and without strong CYP3A inhibitor use (hypothetical cases by population PK modeling), the QTcF model predicts a mean ΔQTcF of 12.6 ms (90% CI: 10.3, 14.9 ms) and 22.1 ms (90% CI: 18.0, 26.1 ms), respectively.

Figure 4: Goodness-of-fit plot with quizartinib concentration as the single exposure metric. Red and green arrows point to the observed Cmax and the estimated ΔQTcF at 60 mg QD and 30 mg QD dose levels in Study 2689-CL-2004.

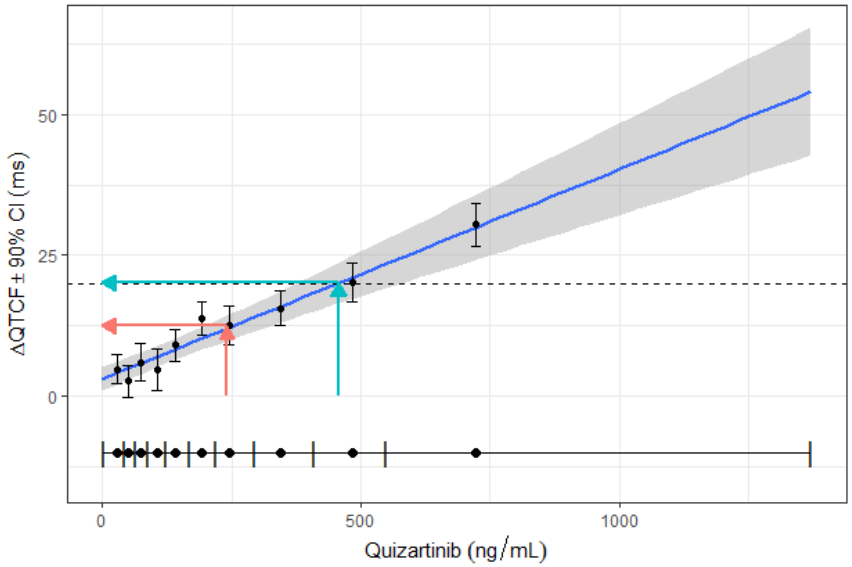


Table 15. The QTc Effects (Point Estimates and the 90% CI) at mean peak concentration of quizartinib (FDA Analysis)

Treatment	Quizartinib $C_{max,SS}$ (ng/mL)	ΔQTcF Mean (ms)	ΔQTcF 90% CI (ms)
30 mg/day (Study 2689-CL-2004)	241.2	12.0	9.8 - 14.2
60 mg/day (Study 2689-CL-2004)	457.3	20.1	16.4 - 23.7
30 mg/day (popPK prediction) *	256	12.6	10.3 - 14.9
60 mg/day (popPK prediction) *	512	22.1	18.0 – 26.1

* Predicted geometric mean of simulated quizartinib $C_{max,ss}$, from Table 33 in the exposure-response analysis report for Study AC220-007

4.6.1 Assay sensitivity

Not applicable.

4.7 SAFETY ASSESSMENTS

A description of the treatment emergent AEs related to the TdP/ QTc prolongation MedDRA SMQ is presented in section 3.3.3.

A MAED analysis was conducted in to evaluate whether there is an imbalance in adverse events associated with TdP/QT and Cardiac Arrhythmias in Study AC220-007. There is an imbalance in AEs (serious and nonserious) of QT prolongation, syncope and falls in the quizartinib arm as shown in the table below.

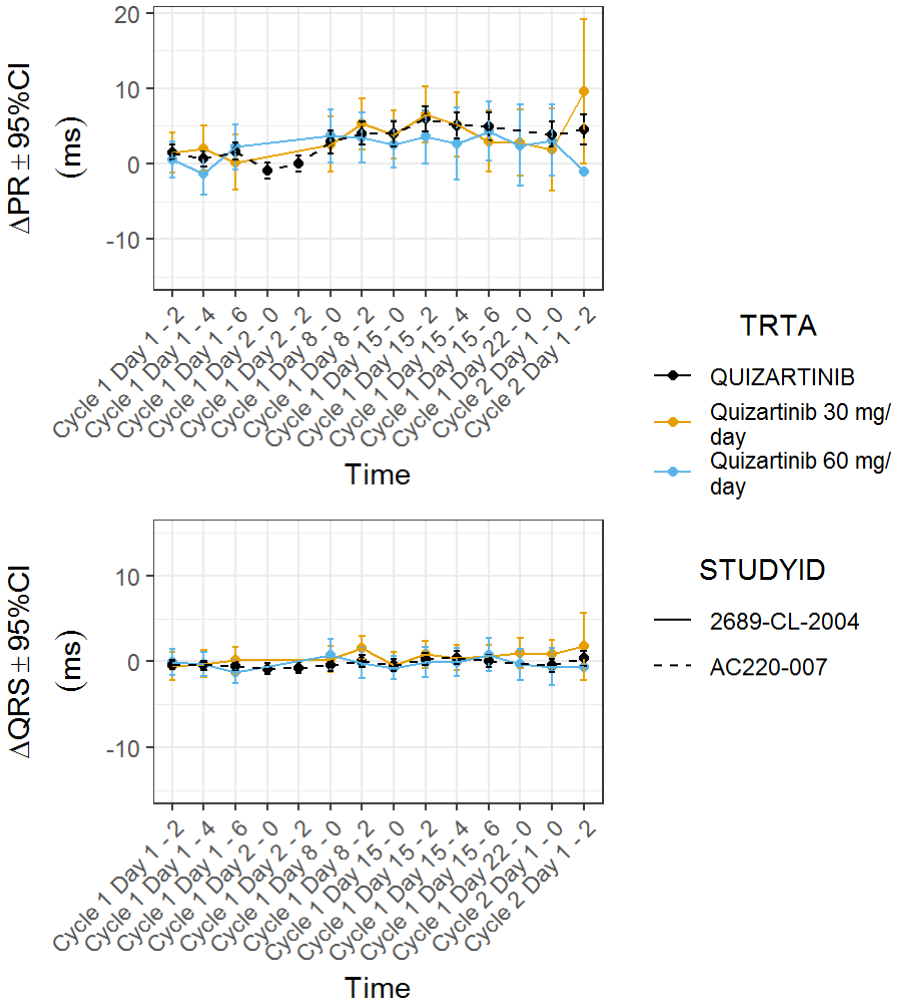
Customized Query for QT prolongation/arrhythmia events	Quizartinib 60 mg N=241	Salvage Chemotherapy N=94
Cardiac arrest	0	1 (1.1%)
Electrocardiogram QT prolonged	64 (26.6%)	2 (2.1%)
Fall	11 (4.6%)	2 (2.1%)
Syncope	12 (5.0%)	2 (2.1%)
Ventricular tachycardia	1 (0.4%)	3 (3.1%)

Within the cardiac arrhythmia SMQ, atrial fibrillation was the most frequently reported TEAE and was reported in 12 (5%) subjects in the quizartinib monotherapy group and 2 (2%) subjects in the salvage chemotherapy arm. Two of the atrial fibrillation events were serious.

4.8 OTHER ECG INTERVALS

Figure 5 shows the time course of ΔPR and ΔQRS in Studies 2689-CL-2004 and AC220-007. There is no consistent, dose-dependent change in ΔPR or ΔQRS. Considering the observed magnitude of changes, it is concluded that quizartinib does not have clinically significant effect in PR or QRS.

Figure 5: Time course of ΔPR and ΔQRS in Studies 2689-CL-2004 and AC220-007



5 IN VITRO ASSAY REVIEW BY THE DIVISION OF APPLIED REGULATORY SCIENCE

Executive summary.

Two nonclinical patch clamp studies that examined the direct effects of quizartinib (AC220) and its major metabolite AC886 on hERG current and one on $hK_VLQT1/minK$ current using heterologous expression systems were reviewed. For hERG channels, the estimated IC_{50} for quizartinib is 15.7 µM; for AC880, 22.7 µM. For $hK_VLQT1/minK$ channels, the estimated IC_{50} for quizartinib is 0.11 µM; for AC880, 23.0 µM. The free C_{max} values derived from humans administered with 60 mg of quizartinib are 8.7 nM for quizartinib and 3.3 nM for AC886. The safety margin (IC_{50}/free C_{max}) for hERG current for quizartinib is 1808X and for AC886 is 6879X; for **$hK_VLQT1/minK$ current for quizartinib is 12.7X** and for AC886 is 6970X. Quizartinib is thus considered a predominant $hK_VLQT1/minK$ channel blocker within the relevant therapeutic exposure levels.

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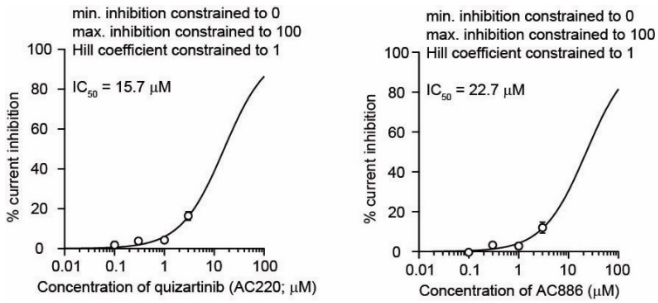
Clinical ECG data suggests that quizartinib (AC220) prolongs QT_C interval. Given that a case of torsade de pointes has been observed at a higher drug dose in the clinical development program, an FDA reviewer evaluated the nonclinical patch clamp study reports for cardiac repolarizing K^+ currents (hERG and hK_VLQT1/minK) associated with this NDA to understand the cellular basis for the observed repolarization abnormality.

HERG channels.

Non-clinical study report AN17-C0032-R01 (link) describes the potential effects of quizartinib (AC220) and its major metabolite AC886 on hERG current, a surrogate for I_{Kr} that mediate membrane potential repolarization in cardiac myocytes. The studies were conducted in accordance with GLP by Charles River Laboratory in October 2017.

Methods. Manual whole cell patch clamp experiments were performed at near physiological temperature (33-35°C, temperature measured with a thermistor probe in the recording chamber) on HEK293 cells that stably express cloned hERG channels (presumably hERG1a subunit only). From a holding potential of -80 mV, cells were depolarized to +20 mV for 1 s, then ramped down to -80 mV in 0.2 s (-0.5 V/s). The voltage protocol was repeated at 5 s intervals, and the peak current was measured during ramp down voltage step. Each recording ended with a supra-saturating concentration of E-4031 to eliminate hERG current completely, thereby allowing for offline subtracting of endogenous or leak current to isolate the hERG component. For pharmacology experiments, a steady state was maintained for at least 20 s (4 current traces) before applying test or positive control article. In the presence of test or positive control article, peak current was monitored until a new steady state emerged. One or more test article concentrations were applied sequentially in ascending concentration to each cell. Solution samples were collected from the outflow of the electrophysiology recording perfusion apparatus for concentration analysis. Either test article was tested up to 3 µM regardless of percentage of current inhibition due to solubility limit.

FDA reviewer's comments and study results. Sponsor's voltage protocol is quite similar to the recommended hERG current protocol by the FDA (http://cipaproject.org/wp-content/uploads/sites/24/2018/06/CiPA-protocol-100918.pdf). The reviewer did not expect protocol difference to impact hERG current pharmacology. Representative hERG current traces shown in figures 1 and 4 as well as the time course plots shown in figures 2 and 5 seem of reasonable quality. Due to low percentages of inhibition at the highest test article concentration examined (16.4% for quizartinib and 12% for AC886) the sponsor did not estimate IC_{50}s for either drug. However, IC_{50} values are useful for understanding of test articles' impacts on hERG channels at varying therapeutic exposure levels. The FDA reviewer thus fit the data using the Hill equation by constraining the maximal inhibition to 100%, minimal inhibition to 0%, and Hill coefficient to 1. These fits yielded an IC_{50} of 15.7 µM for quizartinib (AC220) and 22.7 µM for AC886 (see figure below).



C_{max} values in humans administered with 60 mg of quizartinib (53 mg free base) were 487 ng/mL for quizartinib and 192 ng/mL for its metabolite AC886. These values convert to 0.87 µM for quizartinib (based on MW of 560.7) and 0.33 µM for AC886 (based on MW of 576.7). Free C_{max} values, assuming >99% protein binding, are 8.7 nM for quizartinib and 3.3 nM for AC886. The safety margin (IC_{50}/free C_{max}) for hERG current for quizartinib is 1808X and for AC886 is 6879X.

Test article formulation analysis using solution collected at the outflow of the perfusion system showed good concordance between measured and nominal or target concentrations (<15% difference). Hence no adjustment was made to the concentrations used to report drug effect. Rundown assessment performed on 3 cells show marginal decrease in hERG current when recorded in control solution. These data gave reasonable assurance that percentages of current reduction in the presence of test articles were due to hERG current inhibition and not rundown process that occurs with prolonged whole cell recording.

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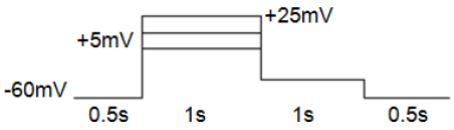
Non-clinical study report IPST study number 20100519-2 (link) also describes the potential effects of quizartinib (AC220) and its major metabolite AC886 on hERG current. The studies were conducted in accordance with GLP by IPS Therapeutique, Inc. in June 2010.

Methods. Manual whole cell patch clamp experiments were performed at 35±2°C on HEK293 cells that stably express cloned hERG channels (presumably hERG1a subunit only). The following set of voltage protocols was used:

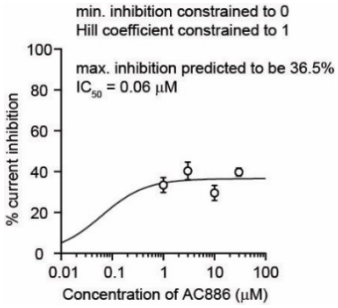


from a holding potential at -60 mV for 0.5 s, cells were depolarized from +5 to +25 mV for 1 s (at 10 mV increments), then back to -55 mV for 1 s, then finally back down to -60 mV for 0.5 s (see figure below). There was no mention of inter-trial interval in the study report. Given that recording was continuous, the voltage protocols (each with a different depolarizing voltage amplitude) were assumed to repeat at 3 s intervals.

This set of voltage protocols was repeated twice for each recorded cell in control solution, and then test articles were ***directly added*** to the recording chamber in increasing concentrations (1, 3, 10, and 30 µM). During test article application, solution flow was stopped, and test article was allowed to equilibrate for 5 min. HERG current run-down was evaluated in a set of cells that were exposed to vehicle/solvent only. This information was used to "correct" the effect of test articles on hERG current. Drug effects were analyzed using hERG tail current associated with the 15 mV depolarizing voltage step.

FDA reviewer's comments and study results. It is unclear why the sponsor used this set of voltage protocols to study drug effects on hERG current, given that only data from one voltage step was used to estimate drug effect. Concentrations of quizartinib and AC886 tested in this study were much higher than those in the preceding nonclinical study report by Charles River Laboratory, which stated that 3 µM was the solubility limit for both drugs (AN17-C0032-R01; link). It was concerning that the concentrations verified in dose formulation analysis differed substantially from the intended concentrations, ranging from 30 to 58.4% nominal concentration. The sponsor's stated that test articles degraded during storage for dose formulation analysis, that both articles were stable during the time frame for electrophysiology recordings. Therefore, no concentration adjustments were made in reporting drug effects. Examination of current traces shown in Appendix B raised concerns of data quality: in many cases hERG current activation by the depolarizing test pulses were slow for near physiological recordings, possibility due to inadequate temperature and/or voltage control. Odd hERG current profile also suggests possible over correction of leak current. For these reasons, the reviewer used the data from the first hERG current study (AN17-C0032-R01; link) and not this one to estimate safety margins for quizartinib and AC886. Nonetheless data from this study are shown below.

Results from IPST study number 20100519-2 showed that quizartinib at 1 to 30 µM did not significantly inhibit hERG current. AC886 inhibited hERG current by 30 to 40% at 1 to 30 µM, with all 4 concentrations achieving comparable inhibition. Based on these data, and assuming that the maximal efficacy of AC886 was ~40% hERG current inhibition, the IC_{50} for AC886 is estimated to be 0.062 µM (see figure on the right; data were fit with the Hill equation, with minimal inhibition constrained to 0 and Hill slope set to 1; here maximal inhibition is predicted to be ~37%).



The table below summarizes results from the two hERG channel studies:

	AN17-C0032-R01	IPST study number 20100519-2
AC220	15.7 µM	No effect
AC886	22.7 µM	0.06 µM (max. inhibition ~37%)

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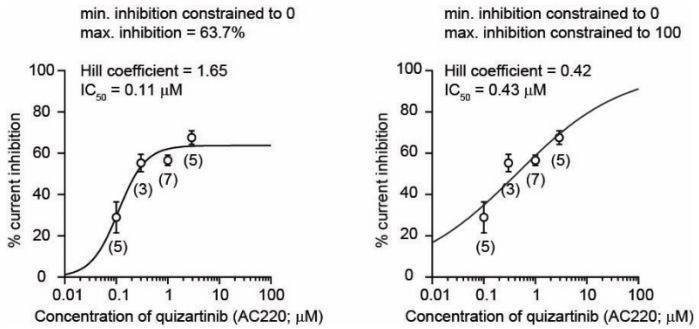
Non-clinical study report AN17-C0033-P01 (link) describes the potential effects of quizartinib (AC220) and its major metabolite AC886 on I_{Ks}, the slowly activating component of delayed rectifier K^+ current in cardiac myocytes. The studies were conducted in accordance with GLP by Charles River Laboratory, between Nov. and Dec. 2017.

Methods. Manual whole cell patch clamp experiments were performed at room temperature on HEK293 cells that stably express cloned hK_VLQT1/minK channels. From a holding potential of -80 mV, cells were first depolarized to +20 mV for 2 s, then repolarized to -40 mV for 0.5 s, and finally repolarized to -80 mV. The voltage protocol pulse pattern was repeated at 15 s intervals, and the peak current was measured during the

+20 mV step. A steady state was maintained for 45 s (3 current traces) before applying test article or positive control article. Peak current was monitored until a new steady state emerged. One or more test article concentrations were applied sequentially in ascending concentration to each cell. Solution samples were collected from the outflow of the electrophysiology recording perfusion apparatus for concentration analysis. Either test article was tested up to 3 µM regardless of percentage of current inhibition due to solubility limit.

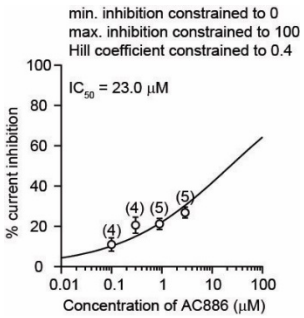
FDA reviewer's comments and study results. Examination of representative current traces in figures 1 and 4 of the study report showed that the +20 mV voltage step used to elicit $hK_VLQT1/minK$ current was too short: $hK_VLQT1/minK$ current recorded in control solution at room temperature was still rising at the end of the voltage step with no sign of reaching plateau. Extracting drug effect by comparing peak currents in control and drug solutions with this voltage protocol could lead to an underestimation of drug potency, particularly for particularly for drugs with faster kinetics as quizartinib is shown in figure 1, given that $hK_VLQT1/minK$ current was still growing in control solution. Future studies of $hK_VLQT1/minK$ current using this expression system should consider extending duration of this test voltage step by several seconds and also increase the test voltage amplitude to accelerate current activation (see K. Villatoro-Gomez et al., 2018, Fig. 1; https://www.ncbi.nlm.nih.gov/pubmed/29621539). The voltage protocol pulse frequency used in this study was low, at 0.067 Hz, raising a concern that drug potency would be underestimated if test article were to exhibit fast unbinding from $hK_VLQT1/minK$ channels during the unstimulated period. In this case, increasing test voltage duration would also help since longer time would be allowed for drugs to rebind following unbinding.

The figure below shows the effects of quizartinib on $hK_VLQT1/minK$ current. Given the likelihood of underestimating drug effect due to the voltage protocol used and the fact that 3 concentrations (0.3 to 3 µM) gave comparable percentages of inhibition, the FDA reviewer fit these data using the Hill equation without constraining maximal inhibition to 100 (left panel; minimal inhibition was set to 0). The fit yielded an IC_{50} of 0.11 µM and a Hill coefficient of 1.65 for quizartinib. For comparison, the panel on the right shows the results with maximal inhibition set to 100 (in this case, the Hill coefficient is shallow and IC_{50} is 0.43 µM).



The figure below shows the effects of AC886 on $hK_VLQT1/minK$ current. Because the maximal inhibition obtained in this study was only <27% (by 3 µM AC886), IC_{50} estimation was done by fitting the data with the Hill equation, with minimal and maximal

percentages of inhibition set to 0 and 100, and the Hill coefficient set to 0.4). The fit yielded an IC_{50} of 23.0 µM for this metabolite.



C_{max} values in humans administered with 60 mg of quizartinib (53 mg free base) were 487 ng/mL for quizartinib and 192 ng/mL for its metabolite AC886. These values convert to 0.87 µM for quizartinib (based on MW of 560.7) and 0.33 µM for AC886 (based on MW of 576.7). Free C_{max} values, assuming >99% protein binding, are 8.7 nM for quizartinib and 3.3 nM for AC886. The safety margin (IC_{50}/free C_{max}) for $hK_VLQT1/minK$ current for quizartinib is 12.7X and for AC886 is 6970X.

Rundown assessment performed on 3 cells show marginal decrease in $hK_VLQT1/minK$ current when recorded in control solution. These data gave reasonable assurance that percentages of current reduction in the presence of test articles were due to current inhibition and not rundown process that occurs with prolonged recording.

Summary. C_{max} values in humans administered with 60 mg of quizartinib (53 mg free base) were 487 ng/mL for quizartinib and 192 ng/mL for its metabolite AC886 (geometric C_{max} for 60 mg qd on cycle 1 – day 15 in 2689-CL-2004). These values convert to 0.87 µM for quizartinib (based on MW 560.7) and 0.33 µM for AC886 (based on MW 576.7). Free C_{max} values, assuming >99% protein binding, are 8.7 nM for quizartinib and 3.3 nM for AC886.

Sponsor's study reports show that quizartinib is a blocker for $hK_VLQT1/minK$ channels that mediate I_{Ks}, with a safety margin estimated to be 12.7X using IC_{50} of 0.11 µM. The hERG study reports differed on the effects of AC886. Given the concerns with drug concentrations tested as well as data quality mentioned for IPST study number 20100519-2, the FDA reviewer used data from AN17-C0032-R01 to calculate safety margin. The safety margin for hERG current for quizartinib is 1808X and for AC886 is 6879X. Thus, quizartinib is a predominant $hK_VLQT1/minK$ channel blocker within the therapeutic exposure levels.

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/s/

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Liang Li is the primary clinpharm reviewer for this report.

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