CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216993Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	06/26/2023
Reviewer:	Orestis Panagiotou, MD, PhD Division of Epidemiology 1
Team Leader:	Fang Tian, PhD, MPH, MHS Division of Epidemiology 1
Associate Division Director:	Steven Bird, PhD, PharmD, MS Division of Epidemiology 1
OPE Deputy Director:	CAPT David Moeny, R.Ph., MPH, USPHS Office of Pharmacovigilance and Epidemiology (OPE)
OSE Sentinel Associate Director:	Patricia Bright, PhD Regulatory Science Staff
OSE Deputy Director:	Robert Ball, MD, MPH Office of Surveillance and Epidemiology (OSE)
Subject:	ARIA Sufficiency Memo
Drug Name(s):	Quizartinib
Application Type/Number:	NDA 216993
Applicant/sponsor:	Daiichi Sankyo Inc.
Nexus TTT #:	2023-3965

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Quizartinib is a kinase inhibitor under FDA review for use "in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) positive as detected by an FDA-approved test."

Quizartinib monotherapy was evaluated in a previous New Drug Application (NDA) submitted in September 2018 for the treatment of patients with relapsed or refractory FLT3-ITD positive AML based on results of the randomized, controlled, trial QuANTUM-R. That previous application was not approved due to several concerns, among which were serious risks including fatal cardiac events.

The Sponsor has submitted the results of QuANTUM-First to support its marketing application. Analyses of toxicity on QuANTUM-First demonstrated a greater incidence of QTc prolongation in the quizartinib arm. Quizartinib prolongs the QTc interval in a dose-dependent and concentration-dependent manner through the unique mechanism of inhibiting the slow potassium current (IKs). This mechanism differs from the mechanism by which essentially all other FDA-approved drugs prolong the QTc interval (i.e., blockade of the rapid outward delayed-rectifier potassium current, IKr). Since quizartinib inhibits IKs, its use with other QTc-prolonging agents risks inhibition of both IKs and IKr currents, leaving patients with reduced or no repolarization reserve.

In vitro studies of quizartinib and its major metabolite AC886 were conducted to assess their effects on major cardiac repolarization currents, IKs and IKr. Although inhibition of both currents was observed, results showed that the predominant effect on cardiac repolarization would be due to inhibition of IKs by quizartinib

1.2. Describe the Safety Concern

The FDA reviewed the ECGs of the one patient in the QuANTUM-First study with fatal cardiac arrest and the recorded ventricular fibrillation was consistent with Torsades de Pointes. For the one patient with grade 4 cardiac arrest, ECGs of the ventricular fibrillation were not available for review. There were no reported cases of cardiac arrest or Torsades de Pointes on the placebo arm.

The common features of the two cases of cardiac arrest include middle aged women recovering from induction chemotherapy, exposure to several QT prolonging medications, and severe hypokalemia. Avoiding QT prolonging mediations and severe hypokalemia appear to be two factors that can be addressed to mitigate the clinical risk of arrhythmias and cardiac arrest.

Because of these concerns, quizartinib will have boxed warnings for QTc prolongation and risks of torsades de pointes and cardiac arrest. In addition, the Applicant proposed a Communication Plan (CP) Risk Evaluation and Mitigation Strategy (REMS). Accordingly, it is recommended that ECGs are performed to monitor the QTc at baseline, weekly during induction and consolidation therapy, weekly for at least the first month of maintenance, and periodically thereafter. This includes (b) (4) a patient wallet card, and a REMS website.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The purpose of this ARIA memo is to evaluate whether ARIA is sufficient to characterize the safety of quizartinib regarding the incidence of severe and fatal arrhythmias and provide granular clinical data related to these adverse events, including their clinical features, severity, and risk factors. It is also of interest to understand the temporality of these elements. The regulatory goal is signal refinement in the post-marketing setting.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Because the interest is in assessing the rates of arrhythmias in patients treated with quizartinib in the real world in relation to those in the trials, this will be a single arm prospective study of patients treated with quizartinib. There is no comparator group against which quizartinib will be evaluated, and therefore no effect size has been specified.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The study population should include adult patients (18 years or older) with newly diagnosed AML that is FLT3-ITD positive as detected by an FDA-approved test.

2.2 Is ARIA sufficient to assess the intended population?

Yes, ARIA is sufficient to assess the intended population. Patients with newly diagnosed AML can be identified based on ICD-10 codes in claims data and electronic medical records. The use of an FDA-approved test to determine FLT3-ITD positivity can be captured Current Procedural Terminology (CPT) codes 81245 and 81246 which are available in claims data. Furthermore, because quizartinib has no other currently approved indication, initiation of treatment with quizartinib will imply a prior diagnosis of AML that is FLT3-ITD positive.

3 EXPOSURES

3.1 Treatment Exposure

The treatment exposure of interest is quizartinib, which is administered orally (tablets).

3.2 Comparator Exposure

There is no comparator exposure of interest.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes. ARIA is sufficient to capture exposure to quizartinib based on National Drug Codes that are available in ARIA's administrative claims and electronic health records. ARIA tools generate longitudinal records of outpatient pharmacy dispensings, which permit construction of patient-specific episodes of treatment with quizartinib.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes of interest are severe and fatal cardiac arrhythmias, including Torsade de Pointes, ventricular tachycardia, ventricular fibrillation, or sudden cardiac death/cardiac arrest. For ventricular tachycardia and ventricular arrhythmia, severity should be assessed with a particular focus on Grade 3-4 events. For all outcomes, granular information on clinical features is also needed, including ECG findings and laboratory findings (e.g., serum electrolyte levels) to characterize the clinical features of patients experiencing such an event. In addition, information on QTc length (in ms) is needed to characterize quizartinib safety.

Monitoring of the QTc is recommended as part of routine monitoring of quizartinib treated patients over the course of treatment. Longitudinal ECG readings are needed for accurate measurements of QTc length, to track changes over time during quizartinib exposure, and to assess temporal trends over time.

4.2 Is ARIA sufficient to assess the outcome of interest?

No. ARIA is insufficient because ECGs are required as part of this PMR to assess for arrhythmias and QTc monitoring while on treatment. Accurate measurement of QTc length is only feasible using ECG regardless of whether its length meets the diagnostic criteria of long QTc syndrome. While claims data and electronic medical records may capture diagnosis of the syndrome itself, they lack serial measurements of the QTc length, which is necessary to record for determining how it is affected by quizartinib. Although healthcare providers may monitor patients with ECGs during the course of treatment with quizartinib to document QTc length, the ECG results are not available in the ARIA system.

In addition, given the critical importance of fatal arrhythmias in the regulatory context of quizartinib, accurate ascertainment of the cause of death and its attribution to Torsade de Pointes, ventricular tachycardia or ventricular fibrillation is needed. This determination may

be possible for in-hospital deaths using ARIA, however, there is potential misclassification of cause of death for fatal events occurring outside the hospital setting.

5 COVARIATES

5.1 Covariates of Interest

5.2 The following covariates are necessary to account for in the design and/or analyses stages:

a. Demographics: age, sex, race/ethnicity

b. Clinical information: FLT3-ITD activating mutation in bone marrow, Eastern Cooperative Oncology Group (ECOG) performance score, renal function based on creatine clearance, hepatic function, QTcF

c. Concomitant medications: QTc-prolonging drugs, CYP3 inhibitors

d. Medical history: cardiac disease (e.g., myocardial infarction, other arrhythmias), long QTc syndrome, thyroid disorders

e. Laboratory values: levels of electrolytes in the serum (e.g., potassium), levels of liver enzymes (bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase)

Certain covariates from those listed above are also needed to assess potential risk factors associated with the risk of severe and fatal arrhythmia in patients treated with quizartinib.

5.3 Is ARIA sufficient to assess the covariates of interest?

No. ARIA is not sufficient to assess the covariates of interest. While demographics and comorbidities are available in Sentinel, other important covariates are not captured. These covariates include ECOG status, FLT3-ITD activating mutation in bone marrow, renal function, markers of liver function (bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase), and levels of serum electrolytes. Determining elevations of liver enzymes as well as electrolytes requires laboratory test results. Currently the results of laboratory tests are unavailable in most Sentinel data partners.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

A single arm cohort with incidence rates for study outcomes of interest and risk factors for these outcomes is needed.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes, ARIA's design and analytic tools are expected to be sufficient to assess the question of interest.

7 NEXT STEPS

DEPI-I has determined that the Sentinel ARIA system is insufficient to assess the risk of severe and fatal arrhythmias in patients treated with quizartinib for newly diagnosed FLT3-ITD positive AML. DEPI recommends that the Division of Malignant Hematology I issue a PMR for conducting a prospective observational clinical study to further characterize and assess these risks. The following PMR language is suggested:

"Conduct an observational study using electronic health records (EHR) to further assess the risk of severe (Grades 3-4) and fatal ventricular arrhythmia events in adult patients treated with quizartinib for the indication of acute myeloid leukemia (AML) that is FLT3-ITD positive as detected by an FDA-approved test. The selected EHR data source should contain access to clinical data elements including ECG results, laboratory results, concomitant medications, and clinical data to allow for outcome validation (i.e., via chart review). Evaluate the incidence of severe and fatal arrhythmia events and collect detailed clinical features of the adverse reactions, to investigate associations and temporal relationships between the incidence and severity of arrhythmia events and other potential associated risk factors. Specify case definitions, measurement, validation methods, and procedures for all study outcomes."

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/s/

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FANG TIAN
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STEVEN BIRD
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PATRICIA L BRIGHT
06/28/2023 12:52:34 PM

ROBERT BALL
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 4, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 216993
Product Name, Dosage Form, and Strength:	Vanflyta (quizartinib) tablets, 17.7 mg and 26.5 mg
Applicant/Sponsor Name:	Daiichi Sankyo, Inc.
TTT ID #:	2022-1092-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on May 1, 2023 for Vanflyta. We reviewed the revised container labels and carton labeling for Vanflyta (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

5 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[a] Iverson, N. Label and Labeling Review for Vanflyta (NDA 216993). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 NOV 29. TTT ID No.: 2022-1092.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 7, 2023

To: Sheila Ryan, Senior Regulatory Project Manager
Division of Hematologic Malignancies I (DHM1)

From: Valerie Guerrier, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for VANFLYTA® (quizartinib) tablets, for oral use

NDA: 216993

Background:

In response to DHM1's consult request dated August 29, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original NDA submission for VANFLYTA® (quizartinib) tablets, for oral use.

PI/Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on February 22, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on March 6, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on March 6, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Valerie Guerrier at (240) 402-2162 or Valerie.Guerrier@fda.hhs.gov.

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/s/

VALERIE GUERRIER
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 6, 2023
To:	Sheila Ryan, PharmD Senior Regulatory Project Manager **Division of Hematologic Malignancies 1 (DHM1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Valerie Guerrier, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	VANFLYTA (quizartinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 216993
Applicant:	Daiichi Sankyo, Inc.

1 INTRODUCTION

On May 6, 2022, Daiichi Sankyo, Inc. submitted for the Agency's review an original New Drug Application (NDA) 216996 for VANFLYTA (quizartinib) tablets, a New Molecular Entity (NME). The proposed indication for VANFLYTA (quizartinib) tablets, in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, is for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) positive as detected by an FDA-approved test.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies 1 (DHM1) on August 29, 2022 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VANFLYTA (quizartinib) tablets.

2 MATERIAL REVIEWED

- Draft VANFLYTA (quizartinib) tablets MG received on May 6, 2022, and received by DMPP and OPDP on February 22, 2023.
- Draft VANFLYTA (quizartinib) tablets Prescribing Information (PI) received on May 6, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 22, 2023.
- Approved XOSPATA (gilteritinib fumarate) tablets comparator labeling dated January 12, 2022.
- Approved RYDAPT (midostaurin) capsules comparator labeling dated November 15, 2021.
- Approved TIBSOVO (ivosidenib) tablets comparator labeling dated May 25, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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CLINICAL INSPECTION SUMMARY

Date	January 31, 2023
From	Anthony Orencia, M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., F.A.A.P., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Joseph Wynne, M.D., Ph.D., Medical Officer Kelly Norsworthy, M.D., Medical Team Leader R. Angelo de Claro, M.D., Division Director Sheila Ryan, Pharm.D., Senior Regulatory Health Project Manager Division of Hematology Malignancies 1 (DHM1) Office of Oncology Drugs
NDA	NDA 216993
Applicant	Daiichi Sankyo, Inc.
Drug	VANFLYTA™ (quizartinib)
NME	Yes
Division Classification	Inhibitor of tyrosine kinases
Proposed Indication	Treatment of adult patients with newly diagnosed FLT3-ITD (+) acute myeloid leukemia
Review Type	Priority Review
Consultation Request Date	October 4, 2022
Summary Goal Date	January 31, 2023. Extended: February 15, 2023
Action Goal Date	February 21, 2023
PDUFA Date	April 23, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study AC220-A-U-302 were submitted to the Agency in support of a New Drug Application (NDA) for the drug quizartinib, proposed as treatment in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and continuation monotherapy, for treatment of adult patients with newly diagnosed FLT3-ITD (+) acute myeloid leukemia. A single foreign clinical investigator site (Pau Montesinos, M.D., Spain) and the sponsor, Daiichi Sankyo, Inc. were inspected.

Based on the above inspection, the study data derived from this clinical investigator site are considered reliable. The sponsor's oversight and monitoring of Study AC220-A-U-302 appear adequate. The study data submitted to the Agency for assessment appear acceptable in support of the proposed indication.

II. BACKGROUND

Quizartinib is an orally available small molecule with potential antineoplastic activity. This new molecular entity inhibits class III receptor tyrosine kinases, including FMS-related tyrosine kinase 3 (FLT3/STK1), colony-stimulating factor 1 receptor (CSF1R/FMS), stem cell factor receptor (SCFR/KIT), and platelet derived growth factor receptors (PDGFRs), resulting in inhibition of ligand-independent leukemic cell proliferation and apoptosis.

Mutations in FLT3, resulting in constitutive activation, are the most frequent genetic alterations in acute myeloid leukemia (AML) and occur in approximately one-third of AML cases.

A single trial, AC220-A-U-302, was conducted to support the proposed indication for treatment for patients with FLT3-ITD acute myeloid leukemia. A single clinical site plus the applicant were selected for onsite FDA inspection.

Study AC220-A-U302

AC220-A-U302 was a Phase 3, randomized, double-blind, placebo-controlled, global study to compare the effect of quizartinib versus placebo in subjects with newly diagnosed acute myeloid leukemia with FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutations. The study design consisted of four consecutive phases (induction, consolidation, continuation, and long-term follow up).

The comparative treatment groups were: (a) quizartinib: round film-coated tablets; 20 mg (white) and 30 mg (yellow), and (b) placebo was supplied to the study site as tablets matching the appearance of quizartinib 20-mg tablets and 30-mg tablets.

The primary objective of this study was to compare the effect of quizartinib versus placebo (Subjects were administered treatment with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles) on the primary endpoint of overall survival in subjects with newly diagnosed AML with FLT3-ITD mutations.

The total duration of treatment with study drug was up to 42 cycles (inclusive of the induction, consolidation, and continuation phases) and until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurred first.

The primary efficacy endpoint was overall survival, with three stratification factors used for randomization: region (North America, Europe, other regions), age (less than 60 years, 60 years and above), and white blood cell count at the time of diagnosis of AML (less than 40×10^9/L, at least 40×10^9/L). Subjects without an overall survival event were censored at the last known alive date.

Subjects were enrolled and treated at 193 study sites. A total of 533 subjects were randomized. The first subject first visit date was: Aug 18, 2016. The data cut-off date was Aug 13, 2021.

III. RESULTS

1. Pau Avinguda Montesinos, M.D./Site 3402
Avenida de Fernando Abril Martorell
106 Valencia 46026
Spain

Inspection dates: December 12 to 16, 2022

This site in Valencia, Spain (Site 3402) was selected due to high subject enrollment with remarkable overall survival results. The clinical data from Site 3402 made a significant contribution to the overall results of the primary endpoint (overall survival) in the study.

A total of 74 subjects were screened; 12 subjects were enrolled at the site. Of the 12 study subjects who enrolled, six subjects were removed from the study due to disease progression, and three subjects were discontinued due to adverse events. One study subject withdrew consent. Only two study subjects completed treatment.

The inspection reviewed subject eligibility, protocol adherence, adverse event evaluation and reporting, safety assessments and drug accountability, approval letters and correspondence, informed consent forms, monitoring reports, financial disclosure reports, site signature and responsibility logs and site training documentation. Source records also comprised a review of study specific case report forms, electronic laboratory results, progress and nurse notes, imaging scan results both in paper and electronically, and study subject requisition forms.

The audited twelve subject records were maintained in electronic and paper format; these records contained required documentation such as medical histories and test results. Records appeared to be accurate and supported that protocol procedures were followed. Study subject data line listings were compared to source documents. No discrepancies were reported.

The primary efficacy endpoint (overall survival) was verifiable during the study site inspections. Records were also assessed for adverse events. No underreporting for adverse and serious adverse events were found.

At the close out discussion with the study site, FDA noted that the enrolled subjects had multiple required tests not conducted, such as ECG tests and laboratory blood draws. The clinical trial study monitor identified these deviations during site visits and as the study progressed, the site was brought into compliance regarding missing tests.

A Form FDA 483 (Inspectional Observations) was not issued at the end of the site inspection.

2. Daiichi Sankyo, Inc./Sponsor
211 Mt. Airy Road
Basking Ridge, NJ 07920

Inspection dates: November 17 to 30, 2022

FDA site audit reviewed contract agreement documents; vendor, site and investigator selection and qualifications; electronic Trial Master File (eTMF); study plans; clinical site monitoring; training records; Form FDA 1572, financial disclosures; quality assurance activities; safety reports and handling; monitoring boards; data collection; protocol deviations and investigational products.

As part of the electronic systems management, iMedidata RAVE was used as the electronic data capture/case report form (EDC/eCRF). Veeva Vault is currently the eTMF used by the sponsor to store all study related documents. CTMS (Clinical Trial Management System) by CRO (b) (4) tracked protocol deviations. FDA inspector reviewed procedures for protocol deviation reporting and randomly reviewed records for protocol deviations. For example, during review of adverse events reports, protocol deviations found by the study clinical research associates were compared to the to the data listings in the FDA background information and found to be unremarkable. Adverse events reported to the Agency appeared comprehensive.

RAVE contained the eCRFs deployed for query generation and coding. According to the Data Management Plan, an audit trail was activated at the point of data entry and integration. No deficiency with these electronic records were found.

At the close-out of the inspection site, FDA inspector raised the issue of lost drug kits at the following study sites and subjects noted in the site monitoring reports: (1)16 kits lost by Site 0705 in Russia, (2) 16 lost kits by study subjects in Site 3416 in Spain, (3) 8 kits lost by Site 3802 in Serbia, (4) 13 kits lost by Site 4203 in Czechoslovakia, (5) 10 kits lost by a study participant at Site 4203 in Czechoslovakia, and (6) 19 kits lost by a study participant at Site 8203 in South Korea. Reasons for lost kits across clinical study sites were derived from several factors: (a) used kits were not returned by the study subject; (b) study subjects did not bring in bottles when consumed, but bottles were thrown away inadvertently; (c) accountability was performed by the study site but the site lost the used kits, or (d) deviation practices in sponsor recording systems persisted, where investigational drug product used kits were arbitrarily marked “lost” in Almac Interactive Voice/Web Response System. Sponsor explained that the monitoring and program management plans were implemented (e.g., site subjects retrained, study subject counseled, trip reports captured information, lost investigational product documented).

The following supplementary measures shall be instituted prior to any changes to site supply strategy by study sponsor: (a) each study site will be reviewed by sponsor’s clinical operations group along with CRO on a case by case to assess drug demand, and (b) for ongoing and future studies with utilization of IXRS® interactive response technology system outputs, study teams will utilize risk-based quality monitoring processes, as outlined in the monitoring plan.

At the end of the sponsor inspection, no FDA Form 483 was issued. In general, the sponsor oversight and monitoring of this clinical study appear to be acceptable.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
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CONCURRENCE:

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Jenn Sellers, M.D., Ph.D., Branch Chief
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Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
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JENN W SELLERS
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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 9, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead Cardiac Safety IRT, DCN

To: Sheila Ryan
RPM, DHM1

Subject: QT Consult to NDA 216993 (SDN 002)

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

This is addendum to our memo dated 12/7/2022 responding to your consult to us dated 8/29/2022.

There was a dose error in Table 1 as well as in our recommendations to section 12.2 of the label. Our updated Table 1 and labeling section 12.2 are shown below for the corrected dose.

Table 1. Predicted ΔQTcF in newly diagnosed AML patients during the continuation phase

Dosing	Cmax,ss	ΔQTcF, msec	90% CI, msec
26.5 mg QD	293 ng/ml	18.4	16.3 to 20.5
53 mg QD	586 ng/ml	24.1	21.4 to 26.6

[Source: Applicant's analysis based on final model for QTcF]

12.2 Pharmacodynamics

Cardiac Electrophysiology

In vitro studies have shown that quizartinib is a predominant inhibitor of the slow delayed rectifier potassium current, IKs.

The exposure-response analysis predicted a concentration-dependent QTcF interval prolongation of 18 and 24 (b) (4) ms (upper bound of two-sided 90% CI of 21 and 27 (b) (4) ms) at the steady-state Cmax of quizartinib at the 26.5 and 53 mg dose levels during (b) (4) therapy.

***Reviewer's comment**: We recommend including both dose levels used during continuation therapy. At both doses, 20 ms QTc prolongation cannot be excluded.*

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOSE VICENTE RUIZ
12/09/2022 09:23:10 AM

CHRISTINE E GARNETT
12/09/2022 10:07:40 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 7, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead Cardiac Safety IRT, DCN

To: Sheila Ryan
RPM, DHM1

Subject: QT Consult to NDA 216993 (SDN 002)

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

This memo responds to your consult to us dated 8/29/2022 regarding the division's QT related question. We reviewed the following materials:

- Previous IRT review for NDA 212166 dated 01/16/2019 in DARRTS;
- Previous IRT review for IND 74552 dated 05/07/2021in DARRTS;
- Reviewer's guide (NDA 216993 / SDN 0002; link);
- Clinical Overview (NDA 216993 / SDN 002; link);
- Clinical study AC220-A-U302 protocol (NDA 216993 / SDN 002; link);
- Concentration-QT report of study AC220-A-U302 (NDA 216993 / SDN 0002; link);
- Statistical Analysis Plan of study AC220-A-U302 (NDA 216993 / SDN 0002; link);
- Clinical study report AC220-A-U302 (NDA 216993 / SDN 0002; link);
- Summary of clinical pharmacology studies (NDA 216993 / SDN 0002; link);
- Regulatory History (NDA 216936 / SDN 0001; link);
- Annotated label (NDA 216993 / SND 0002; link);
- Proposed label for previous indication (NDA 212166 / SDN 0002; link);
- Complete Response Letter for NDA 212166 dated 06/14/2019 in DARRTS (link);
- QT Evaluation Report Checklist (NDA 216993 / SDN 0003; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA 216993 / SDN 0003; link).

1 Summary of Findings

Quizartinib, a predominant IKs blocker, is associated with concentration-dependent QTc interval prolongation with a mean effect >20 ms with the 35.4 mg and 53 mg daily doses on continuation therapy.

In study AC220-A-U302, 2.3% of subjects had QTcF >500 msec and 10% of subjects had an increase >60 msec above baseline on centrally read ECGs. Adverse events associated with QTc prolongation/TdP (customized query of AEs) occurred in 18% of subjects in the quizartinib arm and 9% of subjects in the placebo arm. Any grade QTc prolongation adverse events occurred in 14% of subjects and 3% of subjects had grade ≥3 severity. QTc prolongation led to dose reduction (3.8% subjects), dose interruption (2.6% subjects) and discontinuation (0.8% subjects).

DCN's cardiologist, Dr. Rosalyn Adigun, reviewed the ECG waveforms and narratives for subjects with clinically significant cardiac events. Important findings are as follows:

- Two subjects ((b) (6) and (b) (6)) in the quizartinib arm experienced cardiac arrest with recorded ventricular fibrillation, one with a fatal outcome. Both subjects were taking concomitant QTc prolongation medications and had hypokalemia, and one subject had a medical history of congenital long QT syndrome per the narrative. ECGs from the implicated subjects ((b) (6) and (b) (6)) were reviewed. ECG tracings from subject (b) (6) on Day 79 ((b) (6)) appears consistent with polymorphic ventricular tachycardia with oscillatory changes in the amplitude of the QRS complex above and below the isoelectric line consistent with Torsades de Pointes (updated tracing). ECG tracings from subject (b) (6) reported as Ventricular fibrillation were not available for review.
- Subject ID (b) (6) had 2 events of loss of consciousness within 5 days of starting quizartinib. The local ECGs showed QTcF measurements >500 ms; however, digitized ECGs at the central laboratory indicated that QTc measurements on both days were not prolonged (<450 ms). Dr. Adigun's review of the ECG tracings showed:
    - The ECG tracing provided 1 day prior to the first event reveals a normal QRS axis with poor R wave progression and an underlying sinus tachycardia (rhythm) with a prolonged 537ms. QTc prolongation is consistent with local reads.
    - The ECG taken on the day of the second event showed normal axis with an underlying rhythm - sinus tachycardia and a QT interval of 400 ms (when assessed in multiple leads), after adjusting for the heart rate (121 bpm) the QTc is prolonged at 505 ms. QTc prolongation is consistent with the local reads.

The effect of quizartinib on cardiac repolarization was evaluated in a sub-study in AC220-A-U302 using exposure-response analysis as the primary analysis. The highest dose that was evaluated was 53 mg/day, which covers therapeutic exposure at the highest recommended dose for continuation therapy. The overall analysis results are shown by study in Table 1.

Table 1. Predicted ΔQTcF in newly diagnosed AML patients during the continuation phase

Dosing	Cmax,ss	ΔQTcF, msec	90% CI, msec
(b) (4)	293 ng/ml	18.4	16.3 to 20.5
53 mg QD	586 ng/ml	24.1	21.4 to 26.6

[Source: Applicant's analysis based on final model for QTcF]

Most subjects were on at least one QTc prolonging medication at some time during the study. Fluconazole, ondansetron, levofloxacin and ciprofloxacin were used in more than 10% of subjects. The Applicant investigated this pharmacodynamic drug interaction on the QTc interval in their population exposure-response analysis and concluded that concomitant use of QTc prolonging drugs with quizartinib did not further increase the QTc interval. These negative findings are not persuasive because the analysis has many limitations (e.g., applicant lump all QTc prolonging drugs together without accounting for potency and dosage) and the sensitivity to detect an interaction was not demonstrated. Therefore, the effects of coadministration of QTc prolongation drugs that are IKr blockers with quizartinib have not been characterized.

It's uncertain whether the risk of fatal arrhythmias with quizartinib treatment can be managed through QTc interval monitoring alone. In this relatively small study with intensive ECG and electrolyte monitoring and dose reduction/interruptions for QTc prolongation, two subjects experienced cardiac arrest (one fatal) with recorded ventricular arrhythmias, including torsades de pointes. The Applicant has not conducted the Division's requested ECG study to evaluate QTc effects and safety in the presence of heart rate increases with exertion as described in the Complete Response Letter for NDA 212166.

Note on the quality of digitized ECGs.

In AC220-A-U302, 32,233 ECG waveforms were collected from scheduled and unscheduled visits. Of these waveforms, 3,567 from 293 subjects (153 and 140 in quizartinib and placebo arms, respectively) were digitized from paper ECGs. The process of scanning and digitizing paper ECGs can increase the variance in the QT measurement (Stockbridge, N., J Electrocardiol 2005; 38, 319-20). In one subject, the difference between the local and digitized central QTc measurement was over 100 ms on 2 occasions. This raised concerns about bias in the digitized ECGs. We did not have access to the local QTc measurements because the Applicant did not enter these values into their database, and instead relied on central reads. We conducted an exploratory analysis on the central reads for the digital and digitized QTc measurements collected during the continuation phase where the highest doses were administered (section 6). Our exploratory analysis indicated that the distributions of QTc measurements were not the same, with the digitized QTc being slightly shorter than the digital QTc measurements at QTc >420 ms for quizartinib. Therefore, we cannot rule out the presence of bias in the digitized ECGs. However, we don't believe that any systematic bias in these measurements, if it exists, would greatly impact the overall interpretation of study findings because the number of digitized ECGs were small (11% of total) and the timing of the digitized ECGs was random.

2 Recommendations

2.1 Additional Studies

In our prior review for NDA 212166 dated 1/16/2019 in DARRTS, we provided the following recommendation:

> *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.*

We defer to the review division to decide if this recommendation also applies to the new indication in NDA 216993.

2.2 Product label

Our changes to the Product Label are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. We do not have edits to the box warning, dosing and administration (section 2.3), drug interaction (section 7) and patient counseling information (section 17). We defer final labeling decisions to the Division.

4 CONTRAINDICATIONS

VANFLYTA is contraindicated in patients with [redacted] long QT syndrome or in patients with a history of ventricular arrhythmias or torsades de pointes. [see Warnings and Precautions (5.1)].

***Reviewer's comment**: We propose to include an additional condition because not all subjects will have a genetic test for congenital long QT syndrome and medical history would also important.*

5.1 QT Prolongation, Torsades de Pointes and Cardiac Arrest

VANFLYTA [redacted] prolong the QT interval in a dose- and concentration-dependent manner [redacted]. Torsades de pointes, ventricular fibrillation, cardiac arrest and sudden death have occurred in patients treated with VANFLYTA. [redacted]

Perform ECGs and correct electrolyte abnormalities prior to initiation of treatment with VANFLYTA. Do not [redacted] treatment with VANFLYTA if the QTcF interval is greater than 450 ms.

During induction and consolidation, perform ECGs prior to initiation and then once weekly during VANFLYTA treatment or more frequently as clinically indicated.

During [redacted], perform ECGs prior to initiation [redacted] once weekly for [redacted] following dose initiation and escalation and thereafter as clinically indicated. Do not escalate the dose if QTcF is greater than 450 ms.

Permanently discontinue VANFLYTA in patients who develop QT interval prolongation with signs or symptoms of life-threatening arrhythmia [see Dosage and Administration (2.3)].

Perform ECG monitoring of the QT interval more frequently in patients who are at significant risk of developing QT interval prolongation and torsades de pointes.

Monitor and correct hypokalemia and hypomagnesemia prior to and during treatment with VANFLYTA.

Maintain electrolytes in the normal range. Monitor electrolytes and ECGs more frequently in patients who experience diarrhea or vomiting.

Monitor patients more frequently with ECGs if coadministration of VANFLYTA with drugs known to prolong the QT interval is required. (b) (4)

Reduce the VANFLYTA dose when used concomitantly with strong CYP3A inhibitors, as they may increase quizartinib exposure [see Dosage and Administration (2.3)].

Reviewer's comment: *We agree with proposed text and offer a few minor edits.* (b) (4)

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

• QT (b) (4) Prolongation, Torsades de Pointes and Cardiac Arrest [see Warnings and Precautions (5.1)]

6.1 Clinical Trials Experience

(b) (4)

(b) (4)

Reviewer's comment: *We verified the numbers included in this section.* (b) (4)

12.2 Pharmacodynamics

Cardiac Electrophysiology

In vitro studies have shown that quizartinib is a predominant inhibitor of the slow delayed rectifier potassium current, IKs.

The exposure-response analysis predicted a concentration-dependent QTcF interval prolongation of 18 and 24 (b) (4) ms (upper bound of two-sided 90% CI of 21 and 27 (b) (4) ms) at the steady-state Cmax of quizartinib at the (b) (4) and 53 mg dose levels during (b) (4) therapy.
***Reviewer's comment**: We recommend including both dose levels used during continuation therapy. At both doses, 20 ms QTc prolongation cannot be excluded.*

3 BACKGROUND

3.1 Product Information

Daiichi Sankyo is developing Vanflyta (quizartinib) tablets for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) positive as detected by an FDA-approved test. Quizartinib is a Class III receptor tyrosine kinase inhibitor, and a highly potent and selective FLT3 inhibitor.

In 2018, the Applicant submitted a marketing application for quizartinib for the treatment of adults with relapsed or refractory AML (NDA 212166). The Division issued a complete response letter (CRL) on 06/14/2019 stating that the risks with quizartinib did not outweigh the benefit of treatment. Specifically, the CRL stated the following:

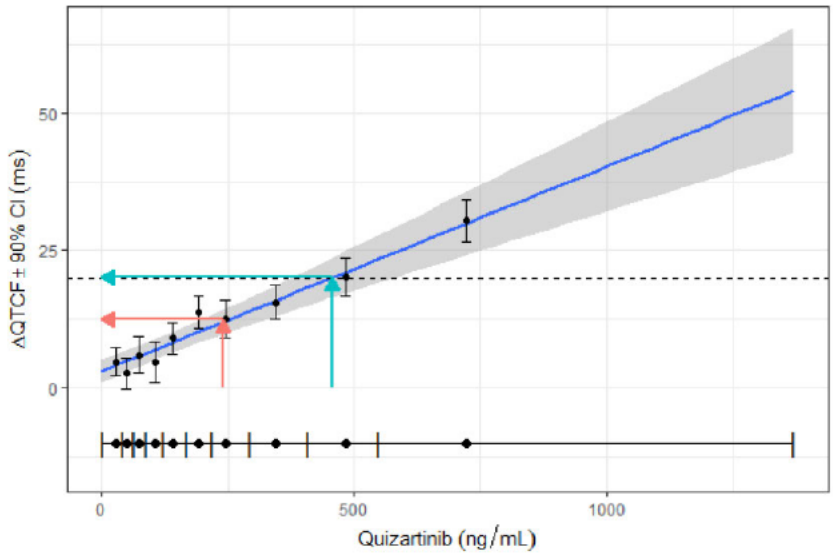
> "*The risks associated with quizartinib therapy as evidenced from the data submitted from the clinical development program are not outweighed by the benefit of quizartinib therapy. Specifically, the risk of fatal cardiac events that cannot be predicted consistently by QTcF measurements must be addressed, and strategies to mitigate this risk implemented. Conduct a Holter ECG study to evaluate the QTc effects and safety in the presence of heart rate increases, such as with exertion. Based on the results of the Holter study, provide a mitigation strategy to prevent fatal and life-threatening cardiac events in patients treated with quizartinib.*"

3.2 QTc Evaluation Under NDA 212166

We previously noted that (1) quizartinib is associated with concentration-dependent QTc prolongation via IKs inhibition (> 20 ms at the 60 mg/day dose in study 2689-CL-2004, Figure 1); (2) there was imbalance of serious cardiac adverse events in study AC220-007 as well as in the clinical development program, including 1 report of torsade de pointes and 1 report of cardiac arrest with QTc prolongation in subjects taking > 60 mg quizartinib; and (3) that the risk for the serious cardiac AEs might not reflect the cardiac safety of quizartinib because patients with increased torsade de pointes risk were excluded, and concomitant use of QT prolonging drugs was generally prohibited. 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].

We recommended that the Applicant conducts a Holter ECG study to evaluate the QTc effects and safety in the presence of heart rate increases with exertion, if quizartinib is further developed for other hematology/oncology diseases with longer survival times or tested at doses >60 mg/day. Refer to our prior review under NDA 212166 dated 01/16/2019 for details.

Figure 1: Quizartinib concentration-QTc relationship in Study 2689-CL-2004 (FDA analysis)



[*Source: IRT review for NDA 212166 dated 01/16/2019. Red and blue arrows point to the observed Cmax and the estimated ΔQTcF, 12.6 ms (90% CI: 10.3 ms to 14.9 ms) and 22.1 ms (18.0 ms to 26.1 ms), at 30 mg QD and 60 mg QD dose levels, respectively, in Study 2689-CL-2004.]*

3.3 Proposed QTc Assessment in PK-ECG Biomarker Substudy of the Phase 3 Study AC220-A-U-302 Protocol

We provided comments on the PK-ECG Biomarker Substudy in the Phase 3 study AC220-A-U-302 protocol (VERSION 6.0, 28 Oct 2020). (b) (4) Refer to our prior review under IND 74552 dated 05/07/2021 for details.

4 QTc and Cardiac Safety Assessment in Current Submission

4.1 QT assessments in Study AC220-A-U-302

The applicant submitted results of the PK-ECG Biomarker Substudy. Study AC220-A-U-302, was a Phase 3, randomized (1:1), double-blind, placebo-controlled study of quizartinib administered in combination with induction and consolidation chemotherapy, and administered as continuation therapy in subjects with newly diagnosed FLT3-ITD (+) acute myeloid leukemia (QuANTUM-First). The study dose is 40 mg QD during Induction and Consolidation phases, then 60 mg QD if QTcF $\leq$ 450 msec during the Continuation phase. Quizartinib was reduced by half if co-administered with strong CYP3A inhibitors but was reduced to no less than 20 mg (Figure 2). The study excluded patients with uncontrolled or significant cardiac disease, including those with baseline QTcF >450 msec, diagnosis of long QT syndrome, history of ventricular arrhythmias and those with other cardiovascular diseases. The study included guidelines for managing QTc prolongation through dose interruptions, reduction, discontinuation, and electrolyte monitoring.

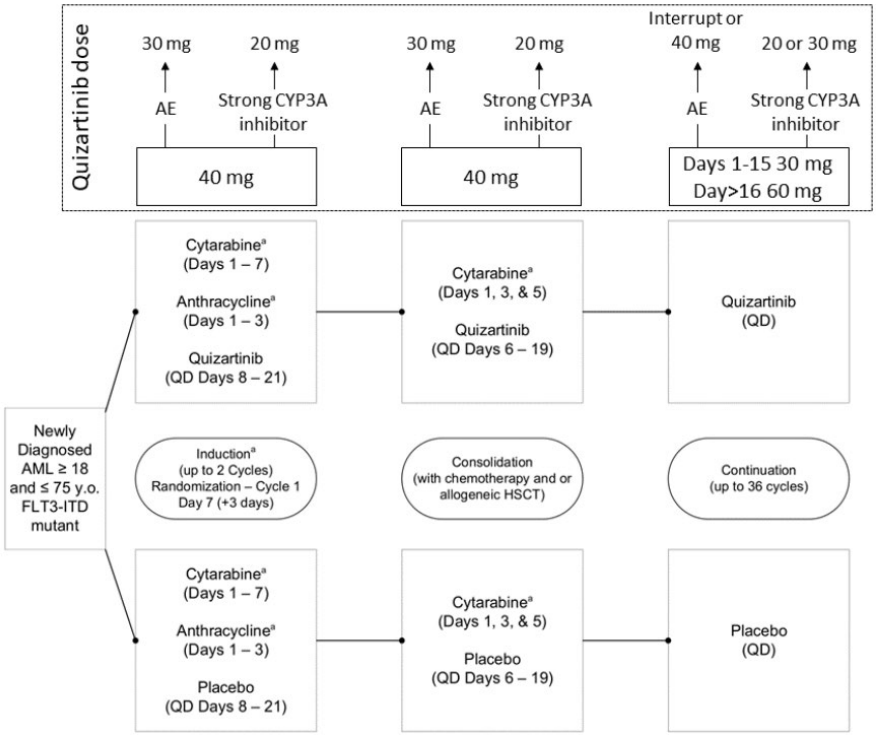
The study included local 12-lead ECG at Screening, central 12-lead ECG (mostly at 2–4 hours postdose) in all subjects every 6 or 7 days in the first 2 cycles the Induction Phase, on Days 6,

13, 19 in each cycle during the Consolidation Phase, on Days 1, 8, 15 in Cycle 1, Days 1, 15 in Cycle 2, Day 1 in Cycle 3 and every 3 cycles during the Continuation Phase. The Applicant collected triplicate ECGs with time-matched PK data (within 10 minutes after the ECG) for central reading at the time points listed below (see study protocol section 6.5 Study Assessments and referenced appendixes for details).

- Induction and Consolidation phases: -0.5 to 0 hours pre-dose, 2-4 hours post-dose.
- Continuation phase: 2-4 hours post-dose.
- For the PK-ECG-Biomarker substudy Induction phase cycle 1 only: -0.5 to 0 hours pre-dose, 1-, 2-, 4-, 6- and 24-hours post-dose.

***Reviewer's comment**: The inclusion of ECGs and time-matched PK data from the Consolidation and Continuation phases addresses our concerns* (b) (4) *that we raised in our prior review under IND 74552 dated 05/07/2021.*

Figure 2: AC220-A-U302 study design



[Source: Figure 1 in AC220-A-U302 concentration-QT study report (link)]

Table 2 shows the applicant's final Emax model predictions for ΔQTcF at 30 mg QD and 60 mg QD dose levels.

***Reviewer's comment**: The Applicant's results are similar to our results using a linear model for the prior Study 2689-CL-2004 (Figure 1) in our prior review for NDA 212166*

dated 01/16/2019 in DARRTS. Therefore, we did not conduct an independent analysis for exposure-response in the current submission.

Table 2: Predicted ΔQTcF at Cmax,ss in AC220-A-U302 During the Continuation Phase

	Predicted ΔQTcF (ms)		
	Lower Bound of 90% CI	**Median**	**Upper Bound of 90% CI**
30 mg ($C_{max,ss}$ = 293 ng/mL)			
Final model	16.3	18.4	20.5
Sensitivity analysis	16.0	18.2	20.6
60 mg ($C_{max,ss}$ = 586 ng/mL)			
Final model	21.4	24.1	26.6
Sensitivity analysis	21.8	24.9	27.8

CI = confidence interval; Cmax,ss = maximum observed plasma concentration at steady state; ΔQTcF = change from baseline QTcF; QT = time between the start of the Q wave and the end of the T wave; QTcF = QT interval corrected with Fridericia's formula
Note: The Cmax,ss is that of the typical subject in Study AC220-A-U302 (male, 70.3 kg, 56 years) and was derived based on the final population PK model for quizartinib. ΔQTcF predictions were obtained from simulations with uncertainty (n = 250).
Source: ER Report AC220-PMx010 Table 29

[Source: Table 3.2 in Summary of clinical pharmacology studies (link).]

To investigate if the QT interval appropriately shortens at high heart rates after quizartinib treatment, the Applicant performed a graphical exploration of the relationship between QT and the interval between two R waves on ECG. The applicant concludes that this QT-RR analysis did not show an increased risk for QT prolongation at higher HR or ΔHR with quizartinib treatment. However, the study report also notes that high heart rates were elevated at a relatively rested state and not elevated through exertion as well as that these elevations in heart rates cannot be considered sudden.

> ***Reviewer's comment****: The statistical analysis plan listed as Appendix 2 of the clinical study report of the PK-ECG substudy of AC220-AU302 list this analysis as Objective #6 as well as under the exploratory analysis (link). However, the data used in this analysis are not adequate to address the issue raised in the Complete Response Letter regarding evaluating the "QTc effects and safety in the presence of heart rate increases, such as with exertion" because, as noted by the applicant in the study report, the heart rates assessed cannot be considered sudden. Therefore, the safety of quizartinib in presence of sudden heart rate changes raised in the Complete Response Letter remains uncertain.*

The Applicant also performed a sensitivity analysis with and without data from subjects taking concomitant QT prolonging drugs. Results of this analysis showed that concomitant administration of QT-prolonging medications or beta-blockers were not found to be statistically significant covariates on baseline QTcF or Emax. Further evaluation of the concentration-QTcF relationships using data from subjects who had matched concentrations and ECG measurements during the time of concomitant administration of QT-prolonging medications and during the time when those same subjects were not taking QT-prolonging medications showed that the concomitant administration of QT-prolonging medications had no impact on the observed QTcF increases associated with quizartinib concentrations. While concomitant administration of QT-prolonging medications may potentially lead to increased incidence of QT prolongation with

quizartinib, the Applicant concluded that in Study AC220-A-U302, where a large proportion of subjects received QT prolonging medications concomitantly, the overall incidence of QTcF >500 ms was low, and the analysis QTcF while receiving QT-prolonging medications were not notably different from when these same subjects were not on concomitant QT-prolonging medications (Clinical Overview, page 82, link).

> ***Reviewer's comment****: This analysis did not show a difference on baseline QTcF or Emax based on concomitant QT prolongation status. This could be because of heterogeneity in QT prolongation covariate as it was a yes/no flag depending on the concomitant use of QT-prolonging per Arizona Center for Education and Research on Therapeutics (AZCERT) designation for QT-prolongation and torsade de pointes risk.*
>
> *The negative finding in the exploratory analysis is not persuasive that concomitant use of quizartinib with QTc prolonging drugs will not result in arrhythmias. The clinical study was not designed to detect such an interaction. Furthermore, the exposure-response analysis lumped all QTc prolonging drugs together and did not account for potency or dosage of the QTc prolonger; the time between initiating the QTc prolonging drug in relation to the timing of ECG sample was not considered; and the sample size needed to detect a 10-msec increase in QTc interval for such an analysis was not determined. Overall, the applicant did not demonstrate that this analysis has the sensitivity to detect an interaction. It therefore remains uncertain whether there is a synergistic interaction between quizartinib and other QTc prolongers via Ikr inhibition.*

4.2 Clinical Cardiac Safety

4.3 Sources of Data for Safety

The data from Study AC220-A-U302 was evaluated for cardiac safety as it relates to proarrhythmia and QTc prolongation.

The Clinical Reviewer performed a customized search for adverse events related to QTc prolongation/TdP. The customized search included the following MedDRA preferred terms: cardiac arrest, cardio-respiratory arrest, electrocardiogram QT prolonged, long QT syndrome, loss of consciousness, sudden death, syncope, torsade de pointes, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, ventricular tachycardia, sudden cardiac death, cardiac death, electrocardiogram repolarisation abnormality, electrocardiogram U wave abnormality, electrocardiogram U wave present, long qt syndrome congenital, cardiac fibrillation, electrocardiogram U wave inversion, electrocardiogram QT interval abnormal, ventricular tachyarrhythmia, presyncope, agonal rhythm, arrhythmia, cardiac flutter, paroxysmal arrhythmia, death, and seizure.

4.4 Safety Summary

4.4.1 Overview

There were 18% of subjects in the quizartinib arm and 9% of subjects in placebo arm who experienced adverse events associated with QT prolongation/TdP customized query (Table 3). This imbalance was mainly driven by the adverse event, ECG QT prolonged, but there were also two subjects with cardiac arrest and 1 subject with unexplained death in the quizartinib arm.

***Reviewer's comment**: A review of narratives showed that the two subjects with cardiac arrest also had ventricular fibrillation in the quizartinib arm ((b) (6) and (b) (6)). Brief narratives for these subjects are presented below.*

Table 3: Treatment Emergent Adverse Events Identified by FDA Custom Query for QT prolongation/TdP (FDA analysis)

Custom Query (Broad)[2] Preferred Term	**Quizartinib N=265 n (%)**	**Placebo N=268 n (%)**
Custom	48 (18.1%)	25 (9.3%)
Electrocardiogram QT prolonged	36 (13.6%)	11 (4.1%)
Syncope	7 (2.6%)	5 (1.9%)
Presyncope	4 (1.5%)	7 (2.6%)
Seizure	2 (0.8%)	1 (0.4%)
Cardiac arrest	2 (0.8%)	0 (0.0%)
Loss of consciousness	1 (0.4%)	1 (0.4%)
Ventricular tachycardia	1 (0.4%)	1 (0.4%)
Death	1 (0.4%)	0 (0.0%)
Electrocardiogram QT interval abnormal	1 (0.4%)	0 (0.0%)
Ventricular fibrillation[3]	1 (0.4%)	0 (0.0%)
Ventricular arrhythmia	0 (0.0%)	1 (0.4%)

Reviewer's results. Source: adsl, adae**; Software:** R

Abbreviations: N, number of patients in treatment arm; n, Number of patients with an event; CI, Confidence Interval; AE, Adverse Event

[1]Treatment-Emergent AEs occurred after the first dose of study drug or AEs that worsened in severity after the first dose of study drug and up to 30 days after the last dose of study drug

[2]Custom query included the following PTs: cardiac arrest, cardio-respiratory arrest, electrocardiogram qt prolonged, long qt syndrome, loss of consciousness, sudden death, syncope, torsade de pointes, ventricular arrhythmia, ventricular f brillation, ventricular flutter, ventricular tachycardia, sudden cardiac death, cardiac death, electrocardiogram repolarisation abnormality, electrocardiogram U wave abnormality, electrocardiogram U wave present, long qt syndrome congenital, cardiac fibrillation, electrocardiogram U wave inversion, electrocardiogram QT interval abnormal, ventricular tachyarrhythmia, presyncope, agonal rhythm, arrhythmia, cardiac flutter, paroxysmal arrhythmia, death, seizure

[3]There are two subjects in quizartin b arm with ventricular fibrillation: subjects (b) (6) and (b) (6).

There were more SAEs with fatal outcome and toxicity grade >3, and AEs leading to dose modification and discontinuation in the quizartinib arm (Table 4).

Table 4: Overview of Treatment Emergent Adverse Events Identified by FDA Custom Query for QT prolongation/TdP (FDA Analysis)

Event	Quizartinib N=265 n(%)	Placebo N=268 n(%)
SAE	4 (1.5%)	3 (1.1%)
Fatal outcome	2 (0.8%)	0 (0.0%)
Life-threatening	1 (0.4%)	0 (0.0%)
Requiring hospitalization	1 (0.4%)	2 (0.7%)
Persist or Signif Disability/Incapacity	0 (0.0%)	0 (0.0%)
Other	1 (0.4%)	1 (0.4%)
AE leading to permanent discontinuation	5 (1.9%)	0 (0.0%)
AE leading to dose modification of study drug	27 (10.2%)	8 (3.0%)
AE leading to interruption	7 (2.6%)	4 (1.5%)
AE leading to dose reduced	10 (3.8%)	1 (0.4%)
Any AE	48 (18.1%)	25 (9.3%)
Grade <3	39 (14.7%)	18 (6.7%)
Grade ≥ 3	19 (7.2%)	9 (3.4%)

Reviewer's results. Source: adsl, adae; **Software:** R

Abbreviations: N, number of patients in treatment arm; n, Number of patients with an event; CI, Confidence Interval; SAE, Serious Adverse Event

4.4.2 Deaths

Two subjects had fatal cardiac adverse events in the quizartinib arm; however, only one of the two subjects also had QTc prolongation prior to the fatal event.

Subject No. (b) (6) (SAE of cardiac arrest, 54 y/o female): The subject's QTcF interval at Baseline (Day 1 predose) was 421 ms on central reading. On (b) (6) (Day 71, Induction Phase, C2D8), the subject experienced an AE of Grade 3 hypokalemia (3.3 mmol/L) and an AE of Grade 2 ECG QT prolonged [average QTcF of 484 ms (>60 ms change from baseline)]. Quizartinib therapy was interrupted due to the AE of prolonged QTc. It is worth noting that concomitant medications around the time of the abnormal ECG (prolonged QTc 484 ms) included fluconazole and ondansetron (QT-prolonging medications). Repeat 12-lead ECG obtained about 24 hours later ((b) (6)), demonstrated persistently prolonged QTcF of 494 ms (> 60 ms change from baseline). Subject did not receive further therapy with quizartinib until (b) (6) (Day 73) when quizartinib was resumed at a reduced dose of 30 mg QD. This dosing regimen was maintained until (b) (6) (Day 78) when the subject experienced a SAE of Cardiac arrest. Last reported QTcF interval of 407 ms (normal) was reported from a centrally read 12 –lead ECG obtained on (b) (6), a day before the subject experienced the reported SAE.

A day prior to the reported SAE (Day 78), laboratory data showed Grade 3 hypokalemia for which the subject received intravenous potassium supplementation (no further laboratory data were available). Pertinent medications at the time of the SAE included ciprofloxacin and piperacillin/tazobactam (QT-prolonging medications).

On (b) (6) (Day 79), the subject was found unresponsive by hospital staff with ventricular fibrillation recorded on ECG (reported as a SAE of cardiac arrest). Resuscitation was attempted with IV adrenaline but unsuccessful, and the subject died; no autopsy was performed. The last dose of quizartinib 30 mg prior to the event was administered on the same day. Other concomitant medications ongoing at the time of the SAE (cardiac arrest) included acyclovir, potassium chloride, micafungin sodium, and ranitidine hydrochloride.

Reviewer's comment: *Applicant's cardiologist reviewed the ECG waveforms for the arrhythmia and noted "interpretation revised based on subject's history." It's not clear which part of subject's history would cause the change in interpretation from torsade de pointes to ventricular fibrillation.*

Cardiology comment*: The submitted ECG tracings from subject (b) (6) on Day 79 ((b) (6)) appears consistent with polymorphic ventricular tachycardia with oscillatory changes in the amplitude of the QRS complex above and below the isoelectric line consistent with Torsades de Pointes (see Figure 3 in section 5). On the day of the event, the subject received quizartinib 30 mg in addition to other QTc prolonging medications. The contribution of quizartinib to ventricular arrhythmia and subsequent cardiac arrest cannot be ruled out.*

Subject No. (b) (6) (SAE of death; 69 y/o male): The subject's medical history included diabetes and hypertension. On Day 104 (Consolidation Phase, 10 days after the last dose of quizartinib), the subject died in his sleep. The subject was last seen by the site staff on Day 95 and there were no AEs reported at that visit. The subject's QTcF interval at Baseline (Day 1 predose) was 400 ms, and the maximum average QTcF during the study was 458 ms (Day 8, Induction Phase). The exact cause of death was unknown as no autopsy was performed; the investigator assessed the event as secondary to AML disease. The subject did not experience any significant QT/QTc prolongation during the study and did not complain of any symptoms in the days prior to his death.

Reviewer's comment*: QTc interval prior to last dose of quizartinib on day 94 (10 days before death) was < 450 ms.*

4.4.3 Non-Fatal Serious Adverse Events

Subject (b) (6) had a treatment-emergent serious cardiac event and QTc prolongation.

Subject No. (b) (6) (SAEs of cardiac arrest and ventricular fibrillation; 63 y/o female): The subject's past medical history was significant for QTc prolongation (congenital), coronary artery disease, myocardial infarction, and CMV infection. The subject was randomized to the quizartinib arm on (b) (6), and quizartinib 20 mg QD was initiated the same day (Day 1). The starting dose of quizartinib was reduced due to concomitant use of strong CYP3A inhibitor posaconazole (also known as a QT-prolonging medication with conditional risk per AZCERT). The subject's predose average QTcF interval was 463 ms on central reading. The subject was treated with quizartinib for 5 days, after which it was discontinued due to the SAEs of cardiac arrest and ventricular fibrillation (described below). The total duration of quizartinib treatment was 5 days. On (b) (6) (Day 2), potassium was low at 2.8 mmol/L (NR: 3.3 to 4.8 mmol/L). The subject was receiving intravenous potassium supplementation and the subject's potassium returned within the normal range (3.4 mmol/L [NR: 3.3 to 4.8 mmol/L]) on the same day. On (b) (6) (Day 4), QTc was 496 ms and potassium was within normal range (3.4 mmol/L). On

Day 5, the subject experienced cardiac arrest due to ventricular fibrillation and had Grade 4 hypokalemia. The subject was successfully resuscitated with cardioversion and correction of hypokalemia. Study drug was discontinued, and the subject recovered. ECG data provided by the investigator showed that at 05:29 (immediately after the event), the subject's heart rate (HR) was 80 bpm and QTcF was 489 ms. Repeat ECG at 22:02 provided by investigator showed HR 67 bpm and QTcF 587 ms. QT-prolonging medications at the time of the event included ondansetron (known risk per AZCERT) and omeprazole, hydrochlorothiazide, posaconazole (also a strong CYP3A4 inhibitor), loperamide hydrochloride, and piperacillin sodium/tazobactam sodium (all conditional risk per AZCERT).

Reviewer's comment*: This subject had congenital long QT syndrome based on this narrative and should have been excluded from the study. On the day of the event (ventricular fibrillation), the subject had hypokalemia and was taking concomitant QTc prolonging drugs and a CYP3A4 inhibitor. The contribution of quizartinib to ventricular fibrillation and cardiac arrest cannot be ruled out. We cannot rule out if this event was a torsade de pointes case because the ECG waveform for this event, if recorded, was not submitted.*

Subject (b) (6) had a treatment emergent serious QTc prolongation but without associated clinical events.

Subject No. (b) (6) (SAEs of Electrocardiogram QT prolonged, Myelodysplastic syndrome; 71 y/o female): Medical conditions ongoing at screening included post-menopause state, osteoporosis, secondary hypothyroidism, deep vein thrombosis, unstable angina, hypertension, asthenia, hypokalemia, and insomnia. The subject was randomized to the quizartinib arm on (b) (6), and quizartinib 20 mg QD was initiated the same day (Day 1). The total duration of quizartinib treatment for the 4 cycles was 56 days. On (b) (6) (Day 178 [CONS Cycle 3, Day 21]), the subject experienced medically important SAEs of Grade 3 electrocardiogram QT prolonged and Grade 4 (life-threatening) SAE of myelodysplastic syndrome. Quizartinib was discontinued on the same day (Day 178) due to the event of myelodysplastic syndrome. Details surrounding a reported SAE of an abnormal electrocardiogram (ECG) demonstrating a QTc interval of 600 ms is not available for review. Correction formula was not specified, and no symptoms were reported. No treatment was reported for the events of electrocardiogram QT prolonged and myelodysplastic syndrome. Metoclopramide hydrochloride (a QT-prolonging medication of "conditional" risk per AZCERT) was ongoing at the onset of the events.

Reviewer's comment*: The subject was not taking other QTc prolonging medications at the time of QTc prolongation >500 msec. Metoclopramide is not labeled for QTc prolongation or ventricular arrhythmias.*

4.4.4 Nonserious Adverse Events with QTc Prolongation

Four subjects with TEAEs of ECG QT prolonged in the quizartinib arm had associated nonserious clinical events also identified by the QT Prolongation/TdP search:

Subject No. (b) (6) (ECG QT prolonged AESI and Loss of consciousness; 62 y/o female): 2 nonserious events of loss of consciousness. The first event occurred on (b) (6) and was associated with an average QTcF of 547 ms based on local ECG read (405 ms on central) 1 day prior to the event. The second event occurred on (b) (6) and the subject had an average QTcF of 532 ms on local read (407 ms on central ECG) at the time of the event. This second

event was associated with study drug discontinuation. The subject recovered from both events. The subject was taking ondansetron (QTc prolonging medication) at the time of clinical event. The average heart rate was 120 bpm at the time of second event of loss of consciousness.

Cardiology comment: *The scanned ECGs (Figure 4, Figure 5 and* Figure 6*) from the clinical site were reviewed. The post dose ECG (C1D8)on* (b) (6) *has a normal axis with poor R wave progression and an underlying sinus tachycardia (rhythm) with a prolonged QTc 537ms. The ECG tracing obtained at the time of the second event (loss of consciousness) on* (b) (6) *revealed a normal axis with an underlying rhythm - sinus tachycardia and a QT interval of 400 ms (when assessed in multiple leads), after adjusting for the heart rate (121 bpm) the QTc is prolonged at 505 ms. The ECG obtained on* (b) (6) *(resubmitted tracings) after discontinuing quizartinib on* (b) (6) *demonstrated a sinus rhythm with a heart rate of 94 bpm with a regular R-R interval and a QTc of 454ms.*

Subject No. (b) (6): nonserious event of presyncope on the same day as average QTcF of 454 ms based on central ECG from which the subject recovered with no action taken with study drug. QTc interval was <480 ms throughout study.

Reviewer's comment*: We agree with Applicant's assessment.*

Subject No. (b) (6) (ECG QT prolonged AESI): nonserious event of presyncope 1 day after an average QTcF of 502 ms based on central ECG read from which the subject recovered. Study drug had been interrupted 1 day prior due to the AESI. The QTc interval was not prolonged after Day 1.

Reviewer's comment*: We agree with Applicant's assessment.*

Subject No. (b) (6): nonserious event of syncope 12 days after the last dose of study drug in Induction Cycle 1. The average QTcF based on central ECG ranged from 434 to 457 ms while the subject was on treatment prior to the event; no ECG data were available at the time of the event.

Reviewer's comment*: We agree with Applicant's assessment.*

4.5 Categorical Outliers

Using the centrally read ECGs, 6 subjects had post-baseline QTcF >500 ms and 27 subjects had a change from baseline QTc >60 msec. Quizartinib did not affect other ECG intervals.

Reviewer's comments:

- *Subject No.* (b) (6) *had QTcF value of 502 ms (central ECG) during the consolation phase on study day 19 that was not listed as TEAE of ECG QT prolonged. The average QTcF based on central ECGs ranged from 421 to 487 ms during the continuation phase, and the Applicant reported 2 mild AEs of ECG QT prolonged. The subject did not experience a cardiac-related TEAE.*
- *The outlier table does not include Subject No.* (b) (6) *who had 2 episodes of QTcF>500 ms on local ECG leads but not on central ECG reads.*

Table 5: Notable ECG Results, Overall Study Period (Safety Analysis Set)

ECG Parameter Maximum Post-dose Value	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)
QTcF		
New >450 and ≤480 ms	73 (27.5)	43 (16.0)
New >480 and ≤500 ms	15 (5.7)	4 (1.5)
New >500 ms	6 (2.3)	2 (0.7)
Increase from Baseline >30 ms	146 (55.1)	87 (32.5)
Increase from Baseline >60 ms	27 (10.2)	13 (4.9)
PR interval		
Increase from Baseline >25% and PR >200 ms	5 (1.9)	9 (3.4)
QRS interval		
Increase from Baseline >25% and QRS >100 ms	0	1 (0.4)
Heart rate		
Decrease from Baseline >25% and heart rate <50 bpm	11 (4.2)	12 (4.5)
Increase from Baseline >25% and heart rate >100 bpm	36 (13.6)	49 (18.3)

bpm = beats per minute; ECG = electrocardiogram; QT = interval between the start of the Q wave and the end of the T wave; QTcF = QT interval corrected with Fridericia's formula
Notes: "New" implies a newly occurring ECG abnormality, which is defined as an abnormal ECG finding post Baseline that is not present at Baseline.
ECGs are collected in triplicates and analysis is based on the average of the triplicates (or multiple).
Unscheduled visits are included. Overall Baseline is defined as the last nonmissing value on or prior to the first dose date of study drug within the Induction/Consolidation/Continuation Phase.
Data cutoff date: 13 Aug 2021.
Source: Table 14.3.5.3.2

[Source: Table 10.20 Clinical study report AC220-A-U302 link; Values confirmed by IRT]

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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6 Exploratory analysis of digitized ECG waveforms

Eleven percent of the ECGs collected in the trial were paper ECGs that were sent to the corelab for digitization and central read measurement. 293 subjects (140 and 153 in placebo and quizartinib, respectively) had at least 1 paper ECG. The majority of these paper ECGs were collected at scheduled visits. We did not have access to the local QTc measurements for all the paper ECGs because the Applicant did not enter these values into their database, and instead relied on central reads after digitization.

During scheduled visits of the continuation phase when highest doses were administered, the collection of paper ECGs appears random (Figure 7). Therefore, the distribution of digitized paper and digital ECG measures should be the same if there is no bias in the digitization and measurement process. However, the distribution of QTc measures from digitized ECGs is left-shifted compared to the digital ECGs for quizartinib during the continuation phase (Figure 8). Therefore, bias in the digitization readings cannot be ruled out.

Figure 7: Digital vs. digitized collection during continuation phase

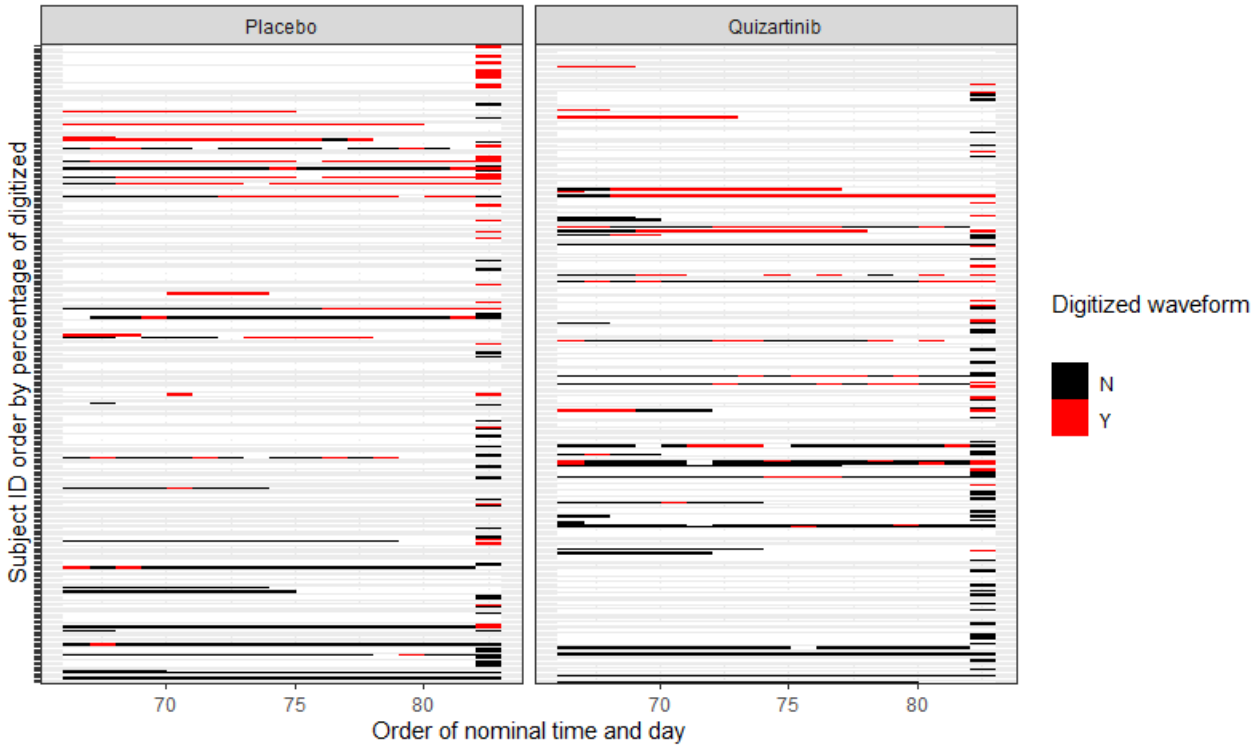
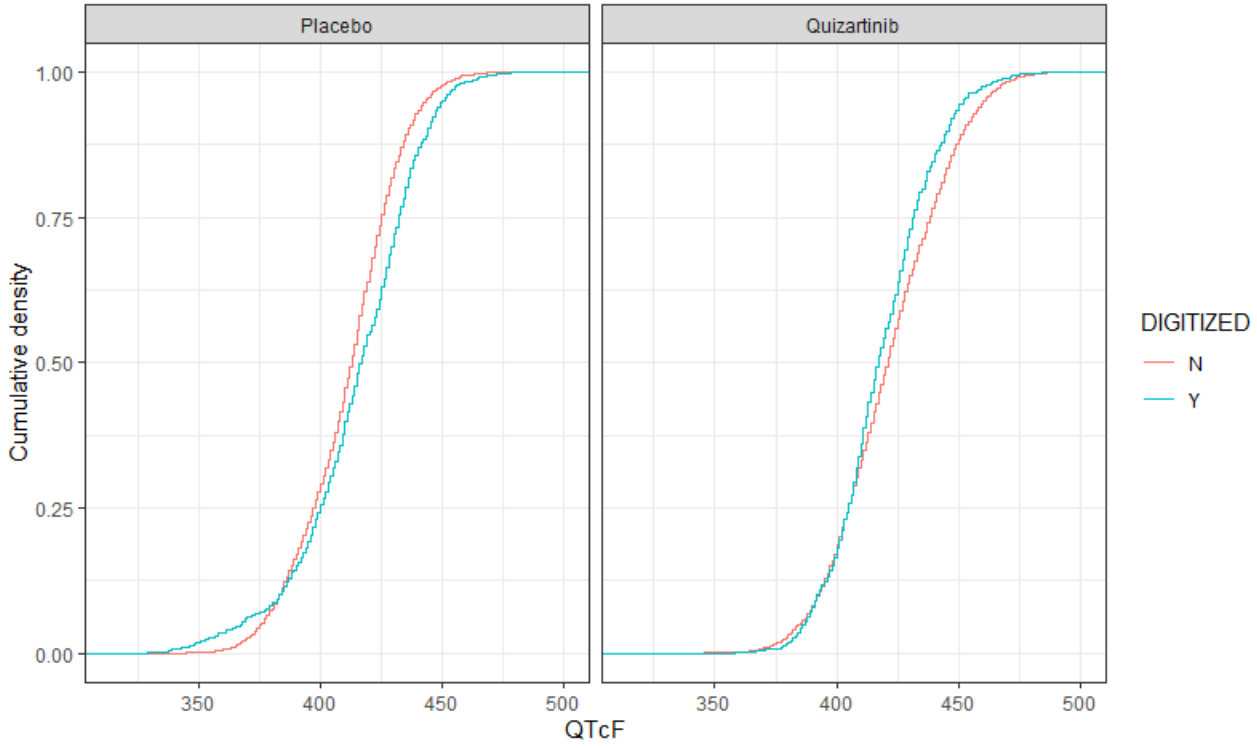


Figure 8: QTcF in digital vs. digitized ECG waveforms



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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 29, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 216993
Product Name, Dosage Form, and Strength:	Vanflyta (quizartinib) tablets, 17.7 mg and 26.5 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Daiichi Sankyo, Inc.
FDA Received Date:	August 24, 2022
TTT ID #:	2022-1092
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Vanflyta (quizartinib) tablets, we reviewed the proposed Vanflyta Prescribing Information (PI), Medication Guide, container labels and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Daiichi Sankyo submitted Vanflyta tablets for review under NDA 212166 on September 25, 2018; however, the application received a complete response letter on June 14, 2019 and was later withdrawn on March 9, 2022.

Subsequently, Daiichi Sankyo submitted, Vanflyta, tablets for review under NDA 216993 on August 24, 2022.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Daiichi Sankyo, Inc. submitted a 505(b)(1) application to obtain marketing approval of Vanflyta tablets. Vanflyta is proposed in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, for the treatment of adult patients with newly diagnosed

acute myeloid leukemia (AML) that is FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) positive as detected by an FDA approved test.

We performed a risk assessment of the proposed container labels, carton labeling, PI and Medication Guide for Vanflyta tablets to determine whether there are significant concerns in terms of safety related to preventable medication errors. We identified areas of the proposed container labels, carton labeling, PI, and Medication Guide that could be revised to improve clarity and readability of important information. For the Division, we note that the PI lacks clarity in the dosage instructions, administration instructions, and storage information. For the Applicant, we note terminology inconsistent with the PI, prominence of the Rx Only statement, and lack of clarity in the storage instructions. In addition, we note inadequate font color differentiation between the strength statement, proprietary name, and established name. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 for the Division and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We have identified areas in the proposed container label, carton labeling, PI and, that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Daiichi Sankyo, Inc. to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Highlights of Prescribing Information

1. (b) (4) therefore we recommend including the statement, "Take VANFLYTA tablets orally once daily with or without food at approximately the same time each day. (2.2)" as the first bullet in the Dosage and Administration Section of Highlights of Prescribing Information.
2. We recommend revising the statement, (b) (4) to "See Full Prescribing Information for recommended VANFLYTA dosage regimen and dose modifications. (2.2, 2.3)".

B. Prescribing Information

1. Dosage and Administration Section
    a. Section 2.2 Recommended Dosage

i. Vanflyta should not be split or cut. To prevent administration errors, consider including the statement, "Swallow tablets whole. Do not cut, crush, or chew the tablets."

b. 2.3 Section Monitoring and Dose Modifications

i. In table 3, [redacted] we recommend including the frequency of administration for all doses for added clarity.

2. How Supplied/Storage and Handling

a. We recommend revising the storage information as follows, "Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

3. Patient Counseling Information

a. [redacted]

C. Medication Guide

1. How should I take VANFLYTA

a. We recommend including the route of administration in the second bullet as follows, "Take VANFLYTA [redacted] one time a day at about the same time each day." for added clarity.

b. Vanflyta should not be split or cut. To prevent administration errors, consider including the statements as the third bullet, "Swallow VANFLYTA tablets whole. Do not cut, crush, or chew the tablets."

4.2 RECOMMENDATIONS FOR DAIICHI SANKYO, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The font color [redacted] of the 17.7 mg strength looks similar to the font color [redacted] used for the proprietary name. Additionally, the font color [redacted] of 26.5 mg strength overlaps with the font color [redacted] used for the established name. Lack of adequate differentiation may contribute to product selection errors. Color differentiation is most effective when the color used has no association

with a particular feature and there is no pattern in the application of the color scheme. Consider revising the font color of the 17.7 mg strength and 26.5 mg strength such that the strength, proprietary name, and established name appear in their own unique colors.

2. We recommend revising the statement, (b) (4) to "Dosage: See Prescribing Information." to ensure consistency with terminology in the Prescribing Information.
3. The Rx Only statement appears prominent on the principal display panel. We recommend decreasing the prominence by debolding the Rx Only statement.
4. We recommend revising the storage information as follows, "Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].
5. If space permits, consider adding the statements, "Swallow tablets whole. Do not cut, crush, or chew the tablets." on the principal display panel of the container labels. We recommend this revision to mitigate the risk of product administration errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vanflyta received on August 24, 2022 from Daiichi Sankyo, Inc..

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Vanflyta</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>quizartinib</td></tr>
<tr><td>Indication</td><td>In combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) positive as detected by an FDA approved test.</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dosage Form</td><td>tablets</td></tr>
<tr><td>Strength</td><td>17.7 mg and 26.5 mg</td></tr>
<tr><td>Dose and Frequency</td><td>Vanflyta should be administered in combination with standard chemotherapy at a dose of 35.4 mg once daily for two weeks in each cycle of induction. (b) (4) Vanflyta should be administered at 35.4 mg once daily for two weeks in each cycle of consolidation chemotherapy followed by Vanflyta continuation monotherapy initiated at 26.5 mg once daily. After two weeks the continuation dose should be increased to 53 mg once daily if the QT interval corrected by Fridericia's formula (QTcF) is less than or equal to 450 ms. Continuation therapy may be continued for up to 36 cycles.

Recommended Dose Modifications for Adverse Reactions
<table>
<tr><th>Adverse Reaction</th><th>Recommended Action</th></tr>
<tr><td>QTcF between 450 ms and 480 ms (Grade 1)</td><td>• Continue Vanflyta dose.</td></tr>
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</table>

	QTcF between 481 ms and 500 ms (Grade 2)	• Reduce the dose of Vanflyta without interruption. • Resume Vanflyta at the previous dose in the next cycle if QTcF has decreased to less than 450 ms. Monitor the patient closely for QT prolongation during the first cycle at the increased dose.
	QTcF greater than 500 ms (Grade 3)	• Interrupt Vanflyta. • Resume Vanflyta at a reduced dose when QTcF returns to less than 450 ms. • (b) (4) if QTcF greater than 500 ms was observed during induction and/or consolidation (b) (4) Maintain the 26.5 mg once daily dose.
	Recurrent QTcF greater than 500 ms (Grade 3)	• Permanently discontinue Vanflyta if QTcF greater than 500 ms recurs despite appropriate dose reduction and correction/elimination of other risk factors (e.g., serum electrolyte abnormalities, concomitant QT prolonging medications).
	Torsades de pointes, polymorphic ventricular tachycardia, signs/symptoms of life-threatening arrhythmia (Grade 4)	• Permanently discontinue Vanflyta.
	Grade 3 or 4 non-hematologic adverse reactions	• Interrupt Vanflyta. • Resume treatment at the previous dose if adverse reaction improves to Grade 1 or less. • Resume treatment at a reduced dose (see Table 3) if adverse reaction improves (b) (4) • Discontinue if Grade 3 or 4 adverse reaction persists beyond 28 days (b) (4)
	(b) (4) Grade 4 neutropenia or	• Reduce Vanflyta dose.

thrombocytopenia [redacted]	

Grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).

[redacted]

How Supplied

Tablet Strength	Tablet Description	Package Configuration	NDC
17.7 mg	White, film-coated, round, [redacted] tablet debossed with "DSC511"	28-count bottle	65597-504-28
		14-count bottle	65597-504-04
26.5 mg	Yellow, film-coated, round, [redacted] tablet debossed with "DSC512"	28-count bottle	65597-511-28
		14-count bottle	65597-511-04

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). (See USP Controlled Room Temperature.)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Vanflyta labels and labeling submitted by Daiichi Sankyo, Inc..

- Container labels received on August 24, 2022
- Carton labeling received on August 24, 2022
- Prescribing Information (Image not shown) received on August 24, 2022, available from \\CDSESUB1\EVSPROD\nda216993\0002\m1\us\114-labeling\draft\labeling\us-pi-clean.docx
- Medication Guide received on August 24, 2022, available from \\CDSESUB1\EVSPROD\nda216993\0002\m1\us\114-labeling\draft\labeling\us-medguide-clean.docx

G.2 Label and Labeling Images

Container labels

(b) (4)

[redacted]

5 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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