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APPLICATION NUMBER:

216993Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	216993
Priority or Standard	Priority
Submit Date(s)	August 24, 2022
Received Date(s)	August 24, 2022
PDUFA Goal Date	July 24, 2023
Division/Office	DHM1/OOD
Review Completion Date	July 19, 2023
Established Name	Quizartinib
(Proposed) Trade Name	Vanflyta
Pharmacologic Class	Kinase inhibitor
Code name	Quizartinib dihydrochloride [1-(5-tert-butyl-1,2-oxazol-3-yl)-3-(4-{7-[2-(morpholin-4-yl)ethoxy]imidazo[2,1-b][1,3]benzothiazol-2-yl}phenyl)urea dihydrochloride]
Applicant	Daiichi Sankyo, Inc.
Formulation(s)	Tablets
Dosing Regimen	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. See Section 6.2.2. General Dosing and Therapeutic Individualization for additional information.
Applicant Proposed Indication(s)/Population(s)	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 (<i>FLT3</i> -ITD) positive as detected by an FDA-approved test.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	In combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute

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	myeloid leukemia (AML) that is FLT3 internal tandem duplication (ITD)-positive as detected by an FDA-approved test.

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Reviewers of Multi-Disciplinary Review and Evaluation

[FDA will complete this section.]

Regulatory Project Manager	Sheila Ryan, PharmD, MPH, RAC
Pharmacology/Toxicology Reviewer(s)	Shwu-Luan Lee, PhD
Pharmacology/Toxicology Team Leader(s)	Brenda Gehrke, PhD
Office of Clinical Pharmacology Reviewer(s)	Ruby Leong, PharmD, Jeffrey Kraft, PhD, and Robyn Konicki, PharmD
Office of Clinical Pharmacology Team Leader(s)	Ruby Leong, PharmD, Sarah Dorff, PhD, and Jiang Liu, PhD
Clinical Reviewer	Joseph Wynne, MD, PhD
Clinical Team Leader	Kelly Norsworthy, MD
Safety Analyst (if applicable)	
Statistical Reviewers	Haiyan Chen, PhD
Statistical Team Leader	Jonathon Vallejo, PhD
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, RN, ACNP
Cross-Disciplinary Team Leader	Kelly Norsworthy, MD
Deputy Division Director (DHOT)	Haleh Saber, PhD
Division Director (OCP)	Brian Booth, PhD
Division Director (OB)	Yuan Li Shen, PhD
Division Director (OOD)	R. Angelo de Claro, MD
Office Director (or designated signatory authority)	Marc Theoret, MD

Additional Reviewers of Application

OPQ	Xiao Hong Chen, PhD (TL)/Dahlia Walters RBPM
Microbiology	N/A
OPDP	Valerie Guerrier, PharmD
OSI	Anthony Orenca
OSE/DEPI	Orestis Panagiotou, MD, PhD/Fan Tian, PhD, MPH (Team Leader)
OSE/DMEPA	Nicole Iverson, PharmD/Hina Mehta, PharmD (Team Leader)
OSE/DRM	Brad Moriyama, PharmD/Naomi Boston, PharmD (Team Leader)

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OSE/DMAMES	Wambui Kiruthi, PharmD, MPH/Barbara Bergquist, PharmD (Team Leader)
Other	Patient Labeling Team: Ruth Mayrosh, PharmD/Barbara Fuller (Team Leader)

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRM=Division of Risk Management

DMAMES=Division of Mitigation Assessment and Medication Error Surveillance

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADaM	analysis data model
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
Allo-HSCT	allogeneic hematopoietic stem cell transplantation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APDn	action potential duration at n% repolarization
APL	acute promyelocytic leukemia
AR	allelic ratio
Ara-C	cytarabine
AST	aspartate aminotransferase
AT	aminotransferase
AUC	area under the plasma concentration-time curve
AUC ₀₋₂₄	area under the plasma concentration-time curve up to 24 h
AUC _{0-t}	area under the plasma concentration-time curve up to the last quantifiable time (8 h or 24 h)
AUCinf	area under the plasma concentration-time curve from time zero extrapolated to infinity
AUCtau	area under the plasma concentration-time curve during a dosing interval
AUCss	area under the plasma concentration-time curve at steady state
AZCERT	Arizona Center for Education and Research on Therapeutics
BCRP	breast cancer resistance protein
BLA	biologics license application
BLQ	below the limit of quantification
BM	bone marrow
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	body surface area
BUN	blood urea nitrogen
C	cycle
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research

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CD	continuous dosing
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CEBPA	CCAAT enhancer-binding protein alpha
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CIR	cumulative incidence of relapse
C _{max}	maximum plasma concentration
C _{max,ss}	maximum plasma concentration at steady state
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CPZ	chlorpromazine
CR	complete remission
CR1	first complete remission
CR _c	composite complete remission (CR + CR _i)
CRF	case report form
CR _i	complete remission with incomplete neutrophil or platelet recovery
CRO	contract research organization
CR _p	complete remission with incomplete platelet recovery
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTA	clinical trial assay
CTCAE	Common Terminology Criteria for Adverse Events
C-QTcF	concentration-QT interval corrected with Fridericia's formula
CYP	cytochrome P450
DDI	drug-drug interaction
DIC	disseminated intravascular coagulation
DLT	dose-limiting toxicity
DS	differentiation syndrome
DSI	Daiichi Sankyo, Inc.
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
eCRF	electronic case report form
EDC	electronic data capture

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EEC	European Economic Community
EFS	event-free survival
ELN	European LeukemiaNet
Emax	maximum effect
EOP2	End of Phase 2
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer QLQ-C30
EQ-5D-5L	EuroQol 5 Dimension 5 Level
E-R	exposure-response
F	female
FAB	French-American-British classification of AML
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FLA	fludarabine and cytarabine
FLAG-IDA	fludarabine, cytarabine, and G-CSF with idarubicin
<i>FLT3</i>	FMS-like tyrosine kinase 3
<i>FLT3</i> -ITD	FMS-like tyrosine kinase 3-internal tandem duplication
<i>FLT3</i> -TKD	FMS-like tyrosine kinase 3-tyrosine kinase domain
<i>FLT3</i> -WT	FMS-like tyrosine kinase 3-wild type
FOB	functional observational battery
FWER	family-wise type I error rate
G-CSF	granulocyte-colony stimulating factor
GCP	good clinical practice
GD	gestation day
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GLP	good laboratory practice
GRMP	good review management practice
GVHD	graft-versus-host disease
h	hours
HCA	high-content analysis
HDAC	high-dose cytarabine
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
ICH	International Conference on Harmonisation
IHD	ischemic heart disease
I_{Ks}	slowly activating component of delayed rectifier potassium currents
IND	Investigational New Drug
INR	international normalized ratio
IP	Investigational Product
IRC	Independent Review Committee

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ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITD	internal tandem duplication
ITF	induction treatment failure
ITT	intent-to-treat
IV	intravenous(ly)
IVS	Invivoscribe, Inc.
K _d	dissociation constant
IXRS	Interactive Voice/Web Response System
LFT	liver function test
LoD	limit of detection
LoDAC	low-dose cytarabine
LQTS	long QT syndrome
LR	log-rank
LVEF	left ventricular ejection fraction
M	male
M:E	myeloid:erythroid
MATE1	multidrug and toxin extrusion 1
max	maximum
MCID	minimal clinically important difference
MDS	myelodysplastic syndrome
MEC	mitoxantrone, etoposide, and intermediate-dose cytarabine
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor and Welfare
min	minimum
mITT	modified intent-to-treat
MLFS	morphologic leukemia-free state
MMRM	mixed-effects model for repeated measures
MOE	margin of exposure
MPE	mean photo effect
MRD	measurable residual disease
MRHD	maximum recommended human dose
MRP2	multidrug resistance-associated protein 2
ms	millisecond(s)
MTD	maximum tolerated dose
M _w	molecular weight
N	total number of subjects
n	number of subjects in the category
NA	not applicable or not available
NCA	noncompartmental analysis
NCCN	National Comprehensive Cancer Network

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NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCI-ODWG	National Cancer Institute-Organ Dysfunction Working Group
n.d.	not determined
NDA	new drug application
NE	not estimable
NGS	next-generation sequencing
NME	new molecular entity
NOAEL	No observed adverse effect level
<i>NPM1</i>	nucleophosmin 1
<i>NPM1^{mut}</i>	mutant <i>NPM1</i>
<i>NPM1^{wt}</i>	wild-type <i>NPM1</i>
NR	not reported
OATP	organic anion transporting polypeptide
OAT2	organic anion transporter 2
OCT1	organic cation uptake transporter 1
OCS	Office of Computational Science
ODAC	Oncologic Drugs Advisory Committee
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBPK	physiological based pharmacokinetic modeling and simulation
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	polymerase chain reaction
PD	pharmacodynamics
P-gp	P-glycoprotein
PH	proportional hazards
PI	prescribing information
PK	pharmacokinetic(s)
PLLR	Pregnancy and Lactation Labeling Rule
PMC	postmarketing commitment
PMDA	Pharmaceuticals and Medical Devices Agency
PMR	postmarketing requirement
PND	postnatal day
PO	by mouth
pp	percentage point
PP	per protocol
PPS	Per-protocol Set
PPI	patient package insert
PPK	population PK

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PREA	Pediatric Research Equity Act
PS	performance status
PRO	patient-reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
QD	once daily
QoL	quality of life
QT	interval between the start of the Q wave and the end of the T wave
QTc	corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
RBC	red blood cell
REML	Restricted Maximum Likelihood
REMS	risk evaluation and mitigation strategy
RFS	relapse-free survival
RMST	restricted mean survival time
R/R	relapsed or refractory
RSE	relative standard error
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	standard deviation
SDTM	Study Data Tabulation Model
SEER	Surveillance, Epidemiology and End Results
SMQ	Standardized MedDRA Query
SN	sequence number
SGE	special government employee
SOC	system organ class
SPA	Special Protocol Assessment
TBL	total bilirubin
TdP	Torsade de Pointes
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TKD	tyrosine kinase domain
TLA	three-letter acronym
Tmax	time to reach maximum plasma concentration
TTE	time-to-event
UGT1A1	UDP glucuronosyltransferase family 1 member A1
UK	United Kingdom
ULN	upper limit of normal

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US	United States
UVA	ultraviolet A light
UVB	ultraviolet B light
VAF	variant allele frequency
VAS	visual analog scale
VPC	visual predictive check
WBC	white blood cell
WHO	World Health Organization
WT	wild type
y.o.	years old

1 Executive Summary

1.1. Product Introduction

Proposed Trade Name: Vanflyta
Established Name: Quizartinib
Therapeutic Class: Antineoplastic
Chemical Class: Small molecule
Pharmacologic Class: Kinase inhibitor
Dosage Forms: Oral tablet (17.7 mg and 26.5 mg)

Quizartinib is a new molecular entity, an orally administered, small molecule kinase inhibitor. Quizartinib was previously evaluated under NDA 212166 for the treatment of adults with relapsed or refractory acute myeloid leukemia (AML) which is FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) positive, as detected by an FDA-approved test. However, that application received a Complete Response on June 14, 2019, due to several concerns, including failure to demonstrate substantial evidence of effectiveness and serious risks including fatal cardiac events. The current NDA 216993 was submitted for a newly proposed indication 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 AML that is FLT3-ITD positive as detected by an FDA-approved test. The proposed dosage is 35.4 mg (40 mg salt) orally once daily on Days 8 to 21 of each cycle of induction (or Days 6 to 19 for Induction cycle 2) with cytarabine and anthracycline and on Days 6 to 19 of each cycle of consolidation with high-dose cytarabine. Following induction and consolidation, the proposed dosage of quizartinib as maintenance monotherapy is 26.5 mg (30 mg salt) once daily Days 1 through 14 of the 28-day cycle, and if the QT interval corrected by Fridericia's formula (QTcF) is less than or equal to 450 msec, the dosage is increased to 53 mg (60 mg salt) once daily for the remainder of the 28-day cycle; maintenance therapy may be continued until disease progression or unacceptable toxicity for up to thirty-six 28-day cycles.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval for quizartinib "in combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 internal tandem duplication (ITD)-positive as detected by an FDA-approved test." The recommendation is based on the findings of improved overall survival (OS) in Study AC220-A-U302 (QuANTUM-First). Supportive evidence

was also demonstrated with data on complete remission (CR) and CR with partial hematologic recovery (CRh) rates from Study AC220-007 (QuANTUM-R).

Quizartinib was evaluated in one randomized (1:1), double-blind, placebo-controlled Phase 3 study in adult patients ages 18 to 75 years with newly diagnosed AML with FLT3-ITD mutation. Patients were randomized to quizartinib (n=268) or placebo (n=271) in combination with standard induction and consolidation chemotherapy, followed by a maintenance monotherapy phase per the initial randomization for up to 36 months. Randomization was stratified by age, white blood count at diagnosis, and region. The demographic and disease characteristics of the randomized patients were balanced between arms.

The final analysis of QuANTUM-First included a prespecified assessment of the primary endpoint of OS, measured from the date of randomization until death from any cause. At the time of analysis, there was an OS advantage in patients who received quizartinib in addition to standard chemotherapy compared to those who received placebo in combination with standard chemotherapy with HR 0.78 (95% confidence interval [CI] 0.62, 0.98; p=0.0324).

The improvement in OS on the quizartinib + chemotherapy arm versus the placebo + chemotherapy arm was generally consistent across various disease subsets (e.g., intermediate cytogenetics HR 0.76, unfavorable cytogenetics HR 0.45, FLT3-ITD variant allelic frequency [VAF] ≥ 3 to $\leq 25\%$ HR 0.87, FLT3-ITD VAF $>25\%$ to $\leq 50\%$ HR 0.77, and FLT3-ITD VAF $>50\%$ HR 0.53). Patients with favorable cytogenetics and NPM1 wild-type patients, however, had HR 2.07 (95% CI 0.71-5.97) and HR 1.01 (95% CI 0.73-1.41), respectively. Given the small sample size for the favorable cytogenetic risk group (N=14 quizartinib + chemotherapy, N=19 placebo + chemotherapy) and the post-hoc nature of these analyses, no firm conclusions can be drawn.

Secondary endpoints on QuANTUM-First included event-free survival (EFS) and CR rate. EFS was defined as the time from randomization until the date of the earliest of refractory disease or treatment failure determined at the end of the Induction Phase (ITF), relapse, or death from any cause. ITF was defined as failure to achieve CR within 42 days of the start of the last cycle of induction. At the time of the final analysis, EFS was not significantly improved on the quizartinib + chemotherapy arm (HR 0.92, 95% CI 0.75-1.11; p-value 0.2371).

FDA-adjudicated CRs were achieved by 147 (55%) patients on the quizartinib + chemotherapy arm and 150 (55%) patients on the placebo + chemotherapy arm. The median duration of CR (DOCR) was 38.6 (95% CI, 21.9 - not evaluable) months on the quizartinib + chemotherapy arm and was 12.4 (95% CI, 8.8-22.7) months on the placebo + chemotherapy arm.

Following completion of consolidation therapy and/or hematopoietic stem cell transplantation (HSCT), maintenance therapy (termed "continuation" therapy in the protocol) was initiated by 39% of patients on QuANTUM-First. FDA guidance has been to rerandomize prior to

maintenance therapy to allow for isolation of the treatment effect of study drugs on maintenance (FDA's Guidance for Industry Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment, 2022). While rerandomization was not performed in QuANTUM-First and the contribution of treatment effects of quizartinib from different phases of therapy cannot be certain, the clinical data demonstrated a later separation in the survival curves and relatively compelling results on OS in patients *who received maintenance post-consolidation chemotherapy*, such that limiting the indication for quizartinib to induction and consolidation therapy may limit the efficacy of the regimen in this patient population (see Section 8.1).

The review team recommends a limitation of use that quizartinib “is not indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (HSCT); improvement in overall survival with [quizartinib] in this setting has not been demonstrated.” The applicant did not establish safety and effectiveness of quizartinib in patients *who received maintenance post-HSCT*, a biologically distinct subgroup of patients with different benefit-risk considerations. The post-HSCT population has received a known potentially curative therapy, which may preclude any further benefit from a prolonged maintenance regimen, and these patients are prone to additional risks, particularly infectious risks, that make the benefit-risk considerations distinct in this patient subgroup. Furthermore, the design and conduct of the trial was inadequate to support an evaluation of the benefit-risk in this subgroup given the relatively small sample size and post-hoc exploratory nature utilizing post-randomization subgroup comparisons. The limited data that are available from the QuANTUM-First trial in this patient population suggest that use of quizartinib in the maintenance setting may add toxicity without added benefit (see Sections 8.1 & 8.2). Recent results also showed lack of benefit of gilteritinib, another FLT3-inhibitor, that was studied in a large randomized, controlled maintenance therapy trial post-HSCT (Astellas and BMT CTN Announce Topline Results from Phase 3 MORPHO Trial of Gilteritinib, 2023).

Efficacy of quizartinib was supplemented by data from Study QuANTUM-R. QuANTUM-R was an open-label, randomized (2:1), controlled, multicenter clinical trial of quizartinib monotherapy versus choice of salvage chemotherapy in patients with relapsed or refractory (R/R) FLT3-ITD positive AML. The trial randomized 367 adult patients, including 245 patients on the quizartinib arm, with a target dose of 53 mg orally once daily. The primary endpoint was OS, and the study showed a statistically positive result with hazard ratio [HR] 0.77 (95% confidence interval [CI]: 0.59-0.99; $p = 0.019$; median OS 26.9 weeks vs 20.4 weeks). However, there was lack of internal consistency in other efficacy endpoints (event-free survival HR 0.90, CR rate 4% quizartinib versus 1% chemotherapy), an imbalance in use of HSCT favoring the quizartinib arm, and differences between arms in patients randomized and not treated and early censored that favored the quizartinib arm, leading to the lack of a robust analysis of OS. These uncertain efficacy results contributed to the Complete Response action on NDA 212166. However, the QuANTUM-R study demonstrated quantifiable single-agent activity of quizartinib compared to

the active control arm. On the quizartinib arm, the CR plus CRh rate was 11% and transfusion independence (TI) was achieved by 26% of patients for at least 56 days post-baseline. Thus, while the prior review concluded that QuANTUM-R was not an adequate and well-controlled trial to support a separate indication, the study provides supportive evidence of clinical benefit for quizartinib in patients with FLT3-ITD positive AML.

The FDA review team concludes that the overall survival benefit of quizartinib in combination with chemotherapy in patients with newly-diagnosed FLT3-ITD mutated AML, supported by CR+CRh rates with quizartinib monotherapy in patients with R/R FLT3-ITD positive AML constitute substantial evidence of effectiveness. However, based on inadequate evidence to establish a favorable benefit-risk profile for quizartinib maintenance therapy post HSCT, the indication will only specify use of maintenance quizartinib following consolidation chemotherapy and will include a limitation of use that “[quizartinib] is not indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (HSCT); (b) (4)

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Quizartinib is an oral Class III receptor tyrosine kinase (RTK) inhibitor that binds to FLT3 and several other Class III RTKs, with a proposed indication 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 AML that is FLT3-ITD positive as detected by an FDA-approved test. Quizartinib was previously evaluated under NDA 212166 for monotherapy treatment of adults with relapsed or refractory FLT3-ITD positive AML and received a Complete Response on June 14, 2019. This new NDA is seeking an indication for quizartinib in combination with standard chemotherapy in patients with newly-diagnosed FLT3-ITD positive AML.

FLT3-ITD positive AML is an aggressive form of AML associated with increased relapse rates and inferior survival. Standard of care for eligible patients with newly-diagnosed FLT3-ITD positive AML includes treatment with induction and consolidation chemotherapy in combination with the FDA-approved kinase inhibitor midostaurin. Midostaurin was approved based on a randomized, placebo-controlled trial comparing midostaurin plus chemotherapy versus placebo plus chemotherapy in patients with newly-diagnosed FLT3-mutated AML ages 18-60 years. Although the indication was not restricted to adults ≤ 60 years, the lack of enrollment of older patients on the pivotal study led to some uncertainty regarding treatment of older patients with chemotherapy plus midostaurin. Furthermore, long-term outcomes in patients with FLT3-ITD mutated AML continue to be suboptimal, leaving this patient population with a significant unmet medical need.

The recommendation for regular approval is based on the efficacy results from one randomized, controlled trial evaluating quizartinib in combination with standard chemotherapy in patients with newly-diagnosed FLT3-ITD positive AML, with supportive data from a randomized, controlled trial evaluating quizartinib monotherapy in patients with relapsed or refractory FLT3-ITD positive AML. Study QuANTUM-First was a randomized (1:1), double-blind, placebo-controlled trial of quizartinib in combination with chemotherapy (n=268) versus placebo in combination with chemotherapy (n=271). Randomization was stratified by age, white blood count at diagnosis, and region. Patients randomized to quizartinib plus chemotherapy had significantly longer survival compared to placebo plus chemotherapy (HR 0.78; 95% CI: 0.62 – 0.98; p-value = 0.032). The HR for EFS was 0.92 and CR rate was 55% on both arms. Median DOCR was 38.6 months (95% CI, 21.9 to not evaluable) and 12.4 months (95% CI, 8.8 to 22.7), respectively. Analysis of OS in patients treated with post-consolidation maintenance

suggested a benefit to maintenance monotherapy with quizartinib (HR 0.68), but this was driven by patients who received maintenance post-consolidation chemotherapy (HR 0.40), with no apparent benefit in patients post-HSCT (HR 1.62).

Study QuANTUM-R was an open-label, randomized (2:1), controlled, multicenter clinical trial of quizartinib monotherapy versus choice of salvage chemotherapy in patients with R/R FLT3-ITD positive AML. The trial served as the basis of the initial NDA 212166 submitted for quizartinib. The trial randomized 367 patients, including 245 on the quizartinib arm, with a target dose of 53 mg daily. OS was statistically positive with a HR 0.77 (95% CI 0.59, 0.99; $p=0.019$), but issues with the study's conduct called into question the robustness of the OS results. The CR+CRh rate for quizartinib was 11%, with TI achieved by 26% for at least 56 days post-baseline. Thus, quizartinib had measurable, albeit low, single agent activity in patients with R/R FLT3-ITD positive AML.

Safety of quizartinib was demonstrated on the QuANTUM-First study, as well as in the Applicant's Integrated Summary of Safety (ISS) AML population, which included the quizartinib arm of QuANTUM-R and several single-arm studies of quizartinib in combination with chemotherapy and as monotherapy in patients with AML. Common adverse reactions (> 30%) not related to a laboratory evaluation for the combination of quizartinib plus chemotherapy from Study QuANTUM-First were febrile neutropenia, diarrhea, mucositis, and nausea. Frequent serious adverse reactions (> 5%) included febrile neutropenia. QT interval prolongation occurred in 14% of patients on the quizartinib arm, with 3% being Grade 3-4 in severity. Of 1,081 patients in the ISS AML population, torsades de pointes occurred in 0.2%, cardiac arrest occurred in 0.6% (0.4% with a fatal outcome), and 0.1% experienced ventricular fibrillation. Adverse reactions were mitigated by electrocardiogram (ECG) monitoring, electrolyte monitoring and correction, anti-infectives, and transfusions as indicated. The seriousness of the QT prolongation and arrhythmia risk warrants a boxed warning and specific instructions to patients regarding the risks and optimal management. Furthermore, it was determined that a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) was necessary to educate prescribers of the unique and potentially fatal risk of arrhythmias, as well as the risk factors for, and strategies to mitigate QT prolongation, torsades de pointe, and fatal cardiac arrest.

In terms of safety in the maintenance phase on QuANTUM-First, common adverse reactions in quizartinib-treated patients during maintenance included neutropenia, gastrointestinal toxicity (diarrhea, nausea, abdominal pain, vomiting, decreased appetite), thrombocytopenia, upper respiratory infections, herpesvirus infections, mucositis, hypertransaminasemia, QTc prolonged, musculoskeletal pain, cough, and headache. Most of the reported adverse reactions during this phase occurred during the first year of maintenance treatment. Notably, patients who received maintenance therapy post-HSCT had a higher rate of adverse reactions to quizartinib (on average 8% higher) than for patients who received quizartinib maintenance post-consolidation chemotherapy without HSCT. Thus, the safety of extended maintenance therapy with

quizartinib for 3 years post-HSCT was deemed unacceptable in the face of the possible OS detriment in this subgroup and lack of benefit of gilteritinib, another FLT3 inhibitor, in a properly conducted randomized, controlled trial in the post-HSCT maintenance setting (Astellas and BMT CTN Announce Topline Results from Phase 3 MORPHO Trial of Gilteritinib, 2023).

In conclusion, the primary endpoint used to assess efficacy in the pivotal QuANTUM-First trial was OS. The median OS was 31.9 months (95% CI 21.8, not evaluable) on the quizartinib + chemotherapy arm compared to 15.1 months (95% CI 13.2, 26.8) on the placebo + chemotherapy arm with HR 0.78 (95% CI 0.62, 0.98); $p = 0.0324$. Analyses to discern the impact of the maintenance phase of quizartinib monotherapy on the OS results suggested a positive effect overall (HR 0.68), but there was inadequate evidence to establish a favorable benefit-risk profile in the subgroup of patients who received maintenance post-HSCT (HR 1.62 and added toxicity), leading to inclusion of only post-consolidation chemotherapy maintenance in the indication statement and a limitation of use for maintenance monotherapy post-HSCT. These findings were supported by external information from the results of the dedicated post-HSCT randomized placebo-controlled maintenance clinical trial of gilteritinib. Results of QuANTUM-R showing HR for OS 0.77 for quizartinib monotherapy versus choice of salvage chemotherapy, CR+CRh rate of 11%, and transfusion independence 26% support the effectiveness of quizartinib in patients with FLT3-ITD positive AML.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• FLT3-ITD positive AML is a fatal disease • Long-term prognosis with available therapy remains suboptimal	AML is a fatal disease. Patients have poor long-term outcomes despite available therapies.
Current Treatment Options	• Patients with newly-diagnosed AML with positive FLT3-ITD who are eligible for treatment with intensive chemotherapy may use midostaurin in combination with chemotherapy with reported CR rates of 59%. The median OS was approximately 75 months. Of note, the pivotal study for midostaurin only enrolled patients ages 18-60 years.	There is a need for effective therapies for patients with newly-diagnosed FLT3-ITD positive AML who are eligible for intensive induction chemotherapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	• QuANTUM-First was a randomized (1:1), placebo-controlled trial that randomized 268 patients ages 18-75 years to quizartinib in combination with induction and consolidation chemotherapy, followed by quizartinib maintenance, and 271 patients to placebo in combination with induction and consolidation chemotherapy, followed by placebo maintenance. • Median OS on QuANTUM-First was significantly longer on the quizartinib versus the placebo arm (HR 0.78; 95% CI: 0.62 – 0.98; p-value = 0.032). EFS was not significantly improved (HR 0.92; p-value = 0.23) and CR rate was 55% on both arms. DOCR was 38.6 months for quizartinib and 12.4 months for placebo. • QuANTUM-First was not designed to determine the benefit of quizartinib maintenance therapy. Of the subpopulation of patients who received maintenance, the HR for OS was 0.68; however, HR 1.62 in patients who received maintenance post-HSCT. Patients who received maintenance post-consolidation chemotherapy had HR for OS 0.40. • QuANTUM-R was an open-label, randomized (2:1) trial that randomized 245 patients with R/R FLT3-ITD positive AML to quizartinib monotherapy and 122 patients to salvage chemotherapy. Median OS was statistically greater on the quizartinib arm (HR 0.77; 95% CI: 0.59 – 0.99; p-value = 0.019). However, results of the OS analysis were not robust. CR+CRh rate for quizartinib was 11% and TI as achieved by 26% of patients for at least 56 days.	Quizartinib is effective for the treatment of patients with newly-diagnosed FLT3-ITD positive AML when combined with induction and consolidation chemotherapy followed by maintenance therapy. However, the efficacy of quizartinib maintenance post-HSCT was not established. The OS results for quizartinib monotherapy versus salvage chemotherapy in patients with R/R FLT3-ITD positive AML are uncertain. However, the low CR+CRh rate of 11% and 26% TI rate indicate some monotherapy activity of quizartinib in patients with FLT3-ITD positive AML.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Common adverse reactions (> 30%) not related to a laboratory evaluation for quizartinib + chemotherapy were febrile neutropenia, diarrhea, mucositis, and nausea. • Frequent serious adverse reactions (> 5%) for quizartinib + chemotherapy included febrile neutropenia. • QT interval prolongation, torsades de pointes, and cardiac arrest that were life-threatening or fatal occurred. Frequent ECG monitoring and electrolyte repletion are needed to prevent treatment-related mortality. • Common adverse reactions in the maintenance phase included cytopenias, gastrointestinal toxicities, and infections. Patients who received maintenance post-HSCT had a higher rate of adverse reactions to quizartinib. • The optimal dosage of quizartinib monotherapy during maintenance has not been established. • The arrhythmia risks of quizartinib during heart rate increases has not been established. • The protocol included monitoring for risks and instructions for intervention. With this in place, serious arrhythmias could be avoided.	The overall safety profile for quizartinib in combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy is acceptable for patients with newly-diagnosed FLT3-ITD positive AML, in light of the demonstrated survival benefit. However, the safety risks are not justified for maintenance therapy post-HSCT. Safety information for quizartinib monotherapy at different dose levels during maintenance therapy, information on the arrhythmia risk with heart rate increases, and better characterization of the arrhythmia risk in the post-marketing setting is needed. A patient medication guide is required to inform and educate patients of the risk of arrhythmias and when to seek immediate medical attention. Labeling should include a boxed warning for the serious risk of arrhythmias, instructions for monitoring, and dose modifications for toxicities. A REMS with ETASU will be needed to inform prescribers of the unique risks of QTc interval prolongation, including risk factors (e.g.,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		hypokalemia, concomitant QTc prolonging medications), and mitigation strategies (e.g., strict QTc interval and electrolyte monitoring, dose modifications).

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☒	☐ Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
	☒ Patient-reported outcome (PRO)	Section 8.1.2 Study Results
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	

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☐	Patient experience data that was not submitted in the application, but was considered in this review.

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Acute myeloid leukemia (AML) is the most common acute leukemia in adults ([Siegel, 2022](#); [De Kouchkovsky, 2016](#)). The United States (US) Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute (NCI) estimated that 20,240 people in the US would be diagnosed with AML in the year 2021, and 11,400 of these patients would die from the disease (accounting for 1.9% of all cancer deaths; [SEER, 2021](#)).

The incidence of AML increases with age, ranging from 1.8 cases per 100,000 people aged <65 years to 17.6 cases per 100,000 people aged >65 years. More than half of the patients with newly diagnosed AML in developed countries are over 65 years of age, with a median age at diagnosis of 67 years ([Heuser, 2020](#)).

Overall, the outcome of patients with AML is poor, with a 5-year survival rate of 40%, which rapidly declines with increasing age at diagnosis ([Thein, 2013](#)). Outcome is influenced by multiple factors, both disease-specific factors (cytogenetic and/or molecular genetic alterations, including FMS-like tyrosine kinase 3 [*FLT3*], nucleophosmin 1 [*NPM1*], and others) and patient-specific factors, such as age, performance status (PS), organ function, and other comorbidities ([Döhner, 2017](#)). Age is the most prominent patient-specific risk factor, while chromosomal aberrations/genetic mutations have been considered the strongest disease-specific risk factors ([Kottaridis, 2001](#)). The assessment of genetic mutations, including *FLT3*, as prognostic factors has become increasingly important for risk assessment and in the treatment of AML as recommended by both the European LeukemiaNet (ELN) and the National Comprehensive Cancer Network (NCCN) guidelines ([Döhner, 2017](#); [Pollyea, 2021](#)).

Overexpression of the *FLT3* receptor occurs in nearly all cases of AML, and mutations in *FLT3* represent one of the most common genetic alterations occurring in approximately 30% of adult patients with newly diagnosed AML (Papaemmanuil, 2016; [Kennedy, 2020](#)).

There are 2 types of *FLT3* mutations: internal tandem duplication (ITD) mutations in the juxta-membrane domain (*FLT3*-ITD) and point mutations or deletion in the tyrosine kinase domain (*FLT3*-TKD). The *FLT3*-ITD mutation is more common than the TKD mutation, and these are found in 20% to 25% and 7% to 10% of all AML cases, respectively. Two methods are used to define *FLT3*-ITD positivity: the allelic ratio (AR), which calculates the ratio of the area under the plasma concentration-time curve (AUC) of mutant to wild-type (WT) alleles (*FLT3*-ITD/*FLT3*-WT), and variant allele frequency (VAF), which is defined as the number of mutant alleles divided by the number of total alleles, reported as a percentage (*FLT3*-

ITD/*FLT3*-WT + *FLT3*-ITD). Patients harboring a *FLT3*-ITD mutation, particularly those with a high AR defined as a *FLT3*-ITD to *FLT3*-WT ratio of ≥ 0.5 , show increased relapse rates and inferior survival (Papaemmanuil, 2016; Patel, 2012; Thiede, 2002; Kottaridis, 2001). *FLT3*-ITD mutations are associated with a higher leukemic burden with marked leukocytosis and higher blast percentage. Females are affected more frequently and there is evidence that the incidence of *FLT3*-ITD mutations decreases with age, with an incidence of up to 35% in patients between 20 and 59 years compared with 16% to 20% in patients older than 60 years (Konig, 2015). In contrast, *FLT3*-TKD mutations have not been associated with a consistent prognostic impact (Mead, 2007).

The FDA's Assessment:

FDA agrees with the Applicant's assessment that AML is a serious disease that still presents therapeutic challenges since 5-year survival remains poor. FDA also agrees that *FLT3*-ITD is one of the most common genetic subtypes of AML.

2.2. Analysis of Current Treatment Options for Newly Diagnosed *FLT3*-ITD (+) AML

For subjects who are eligible to receive chemotherapy, standard chemotherapy is the mainstay of treatment for newly diagnosed AML, and cytarabine in combination with an anthracycline remains the standard induction therapy, regardless of cytogenetic or molecular abnormalities, with complete remission (CR) achieved in 60% to 85% of adults ≤ 60 years of age and 40% to 60% in adults > 60 years of age (Döhner, 2015). For subjects who achieve a CR, the current guidelines recommend that patients must be offered post-induction therapy to eradicate residual disease and prevent relapse. Available options for consolidation include chemotherapy and/or allogeneic hematopoietic stem cell transplantation (allo-HSCT) depending on the risk group. Allo-HSCT has improved the prognosis of patients with AML, but relapse remains high and non-relapse mortality associated with allo-HSCT is as high as 20% (Styczynski, 2020). Overall, cure rates following chemotherapy with or without HSCT are only 35% to 40% in patients under age 60 and 5% to 15% in patients over age 60 (Döhner, 2015).

Per NCCN and ELN guidelines (Pollyea, 2021; Döhner, 2017), for AML patients with *FLT3* mutations (ITD or TKD) < 60 years of age, midostaurin should be added to standard chemotherapy as part of frontline treatment. This recommendation is based on the results of the RATIFY study in newly diagnosed AML subjects with *FLT3* mutations (ITD and/or TKD) < 60 years of age (Stone, 2017). For AML patients with *FLT3* mutations ≥ 60 years benefiting from intensive cytarabine-based induction therapy, the NCCN recommends also that midostaurin be added to standard chemotherapy (Pollyea, 2021). For those who are not candidates for intensive chemotherapy, low-intensive regimens including venetoclax with hypomethylating agents such as azacitidine or decitabine are recommended (Pollyea, 2021;

[Döhner, 2017](#)).

Further, the safety and efficacy of midostaurin were evaluated in a single-arm Phase 2 study, AMLSG 16-10, in which midostaurin was added to intensive chemotherapy followed by allo-HSCT and single-agent midostaurin maintenance therapy in adult patients with *FLT3*-ITD (+) AML (Schlenk, 2019). In this study, the authors reported that while older patients (61 to 70 years old) may benefit from midostaurin, outcomes were inferior to those observed in younger patients (18 to 60 years old) in terms of total CR rate (including CR with incomplete neutrophil or platelet recovery [CRi]), event-free survival (EFS), and 2-year OS. Less than 50% of patients finished the 1-year intended maintenance therapy, and the median time of maintenance therapy was 9 months after allo-HSCT and 10.5 months after high-dose cytarabine (HDAC) with premature termination mainly a result of causes other than relapse (gastrointestinal toxicity and infections).

Table 1 – FDA-approved Treatments for *FLT3*-ITD (+) Newly Diagnosed AML Eligible for Standard Chemotherapy

Product(s) Name	Approved Indication	Approval Year, Type	Dosing/ Administra tion	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA-approved treatments for <i>FLT3</i>-ITD (+) newly diagnosed AML eligible for standard chemotherapy						
Midostaurin	Newly diagnosed AML that is <i>FLT3</i> mutation positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation	2017, Regular	50 mg orally twice daily with food Administered on Days 8 to 21 of each cycle of induction with cytarabine and daunorubicin and on Days 8 to 21 of each cycle of consolidation with HDAC	Phase 3 Study CALGB 10603 (RATIFY) of RYDAPT versus placebo plus standard chemotherapy Primary endpoint: OS (HR: 0.77; 95% CI: 0.63, 0.95; 2-sided p = 0.016)	Embryo-fetal toxicity Pulmonary toxicity: Interstitial lung disease or pneumonitis. Fatal cases have occurred. Most common adverse reactions (≥20%): Febrile neutropenia, nausea, mucositis, vomiting, headache, petechiae, musculoskeletal pain, epistaxis, device-related infection, hyperglycemia, ECG QT prolonged, and upper respiratory tract infection. The most frequent Grade 3/4 (≥10%) AEs are febrile neutropenia, device-related infection, and mucositis.	The RATIFY study included subjects with newly diagnosed <i>FLT3</i> -TKD (+) or <i>FLT3</i> -ITD (+) AML aged 18 to 59 years. Midostaurin combined with standard chemotherapy showed a differential benefit in OS for TKD and ITD AR high/low subjects (HRs of 0.65 and 0.80-0.81, respectively)

Source: [Stone, 2017](#)

The Applicant's Position:

In the newly diagnosed *FLT3*-mutated AML treatment setting, midostaurin, a multitargeted kinase inhibitor, is the only drug that has been approved thus far based on the RATIFY study results. Given the poor prognosis of patients with *FLT3*-ITD (+) AML and the high risk of relapse, the unmet medical need remains high and new treatment options are urgently needed.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that midostaurin added to induction and consolidation chemotherapy is the only treatment specifically approved for newly diagnosed *FLT3*-mutated AML. We also agree that despite improvement in overall survival seen with the addition of midostaurin to induction and consolidation chemotherapy, that long-term overall survival remains guarded and represents continued unmet medical need.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Quizartinib is not currently registered or approved in the US. In September 2018, a new drug application (NDA 212166) for quizartinib was submitted for the treatment of patients with relapsed/refractory (R/R) *FLT3*-ITD (+) AML based on Study AC220-007 (QuANTUM-R). The application was the subject of an Oncologic Drug Advisory Committee (ODAC) meeting in May 2019, and the FDA subsequently issued a Complete Response Letter in June 2019.

Quizartinib was approved by the Ministry of Health, Labor and Welfare (MHLW) in Japan in Jun 2019 for the treatment of R/R *FLT3*-ITD (+) AML and is currently marketed in Japan under the trade name VANFLYTA®.

The FDA's Assessment:

FDA agrees with Applicant's position. Please refer to the FDA May 2019 ODAC materials (<https://public4.pagefreezer.com/browse/FDA/04-03-2022T19:30/https://www.fda.gov/advisory-committees/advisory-committee-calendar/may-14-2019-meeting-oncologic-drugs-advisory-committee-meeting-announcement-05142019-05142019>)

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Based on input from FDA, several key aspects of the design of Study AC220-A-U302 were revised: (1) selected overall survival (OS) as the sole primary endpoint, (2) revised the definition of EFS based on the FDA guidance published during the conduct of the study, (3) revised the definition of induction treatment failure (ITF), (4) revised the statistical hierarchy for testing of secondary endpoints, and (5) included measurable residual disease (MRD) as a secondary endpoint. The key interactions with FDA are summarized in [Table 2](#).

Table 2 – Key FDA Interactions

Interaction	Date	Description
IND submission	27 Sep 2006	Original IND 074552 Application submitted
Orphan Drug Designation	18 May 2009	Quizartinib granted Orphan Drug Designation #09-2771 for the treatment of AML
Type B EOP2	11 Aug 2009	Discussion of clinical pharmacology and toxicology package to support an NDA
Type C	10 May 2011	Discussion of the study design and endpoints for Study AC220-007 (QuANTUM-R) in R/R <i>FLT3</i> -ITD (+) AML
Type C CMC	18 Oct 2011	Discussion of the CMC program and the adequacy of the CMC package to support an NDA submission
Type C	31 Oct 2011	Discussion of contents of a complete nonclinical ADME, pharmacology, safety pharmacology, and toxicology package to support an NDA
Type C	04 Feb 2013	Discussion on limiting enrollment to <i>FLT3</i> -ITD (+) subjects in the planned Phase 3 study and clinical pharmacology package for an NDA
Type B EOP2	07 Jul 2015	Discussion of the design and endpoints for Study AC220-A-U302 (QuANTUM-First) in newly diagnosed <i>FLT3</i> -ITD (+) AML
Type C	26 Oct 2015	Discussion of PRO measures and instruments for Study AC220-A-U302
Type B pre-NDA CMC	11 Apr 2018	Agreement reached on the quality components of the planned NDA 212166 in R/R <i>FLT3</i> -ITD (+) AML
Type B pre-NDA	10 Jul 2018	Agreement reached that Study AC220-007 supports NDA submission for R/R <i>FLT3</i> -ITD (+) AML and on contents of a complete NDA
NDA submission	24 Sep 2018	NDA 212166 application submitted for R/R <i>FLT3</i> -ITD (+)

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Interaction	Date	Description
		AML
ODAC	14 May 2019	ODAC was convened to discuss robustness of efficacy results from Study AC220-007 and risk management strategies to reduce the risk of life-threatening and fatal cardiac events resulting from I _{Ks} blockade if quizartinib is marketed
Complete Response Letter	14 Jun 2019	Complete response letter issued based on the FDA assessment that substantial evidence of effectiveness was not demonstrated since Study AC220-007 does not represent an adequate and well-controlled trial
Type C	18 May 2021	Agreement reached regarding the content and format of the planned NDA submission in newly diagnosed <i>FLT3</i> -ITD (+) AML, the timing of the primary analysis, and the hierarchical testing order for secondary endpoints The FDA reiterated the request to revise the definition of EFS using the 42-day window for ITF assessment and to adjust the statistical hierarchy.
Type B Pre-NDA	24 Mar 2022	Agreement reached that results from Study AC220-A-U302 support the NDA submission and on the contents of the NDA
Fast-track Designation Granted	30 Mar 2022	The FDA granted fast-track designation for treatment of adult patients with newly diagnosed <i>FLT3</i> -ITD (+) AML, in combination with standard cytarabine and anthracycline induction and cytarabine consolidation
NDA submission	24 Aug 2022	Submission of NDA 216993 for newly diagnosed <i>FLT3</i> -ITD (+) AML

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted inspections for QuANTUM-First at a clinical site in Valencia, Spain (Site 3402). This site was selected given high subject enrollment with remarkable OS results. Inspection review of the site led to a classification of No Action Indicated. The Applicant (Daiichi Sankyo, Inc.) was also audited. The classification for the Applicant inspection was also No Action Indicated. Based on these inspection results, the study data derived from the inspected clinical site was considered reliable in support of the requested indication.

4.2. Product Quality

Quizartinib drug product (Vanflyta) is presented as round, film-coated tablets for oral use containing 17.7 or 26.5 mg quizartinib. The capsules are debossed with “DSC511” and “DSC512,” respectively. Inactive ingredients include hydroxypropyl betadex, microcrystalline cellulose, and magnesium stearate. The tablet coating contains hypromellose, talc, triacetin and titanium dioxide. All excipients, except for (b) (4) are comprised of compendial components, but the (b) (4) are comprised of compendial components. The CMC reviewer noted that the quantity of each excipient used in the manufacture of quizartinib tablets is below the “maximum potency” for oral administration as reported in the FDA Inactive Ingredient Database. Individual unspecified impurities are proposed to be controlled at a limit consistent with ICH Q3B (R2). The drug product is supplied in bottles of 14 or 28 tablets with an expiry of 60 months when stored at USP controlled room temperature.

There were no outstanding safety issues identified for the manufacturing process or from the facilities inspections. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment and the claim was accepted. Approval of the NDA was recommended by the Product Quality review team.

Lastly, there are no impurity issues from a Pharmacology/Toxicology perspective. The proposed specifications for impurities in the drug substance and drug product that exceed the ICH qualification thresholds are justified. The Applicant conducted a 28-day impurity qualification toxicology study in rats to justify the higher limits.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

The Applicant is seeking an indication for patients with newly-diagnosed AML limited to those who have a FLT3-ITD mutation, which is the target of quizartinib. In Study QuANTUM-First, patients were selected based on detection of a FLT3-ITD mutation with a clinical trial assay, and the results were confirmed retrospectively using the companion diagnostic LeukoStrat® CDx FLT3 Mutation Assay. It was determined that a device to select patients for therapy would be required for safe use of quizartinib when marketed. The Applicant cross-referenced PMA P160040 for the LeukoStrat® CDx FLT3 Mutation Assay, which identifies the FLT3-ITD mutation. The Center for Devices and Radiological Health (CDRH) reviewed the LeukoStrat® CDx FLT3 Mutation Assay for its intended use as a companion diagnostic to identify AML patients with a FLT3-ITD mutation for treatment with quizartinib under P160040/S011 (MDUFA date 4/12/2023). Following review, CDRH decided that the information provided was acceptable and the sPMA is approvable pending approval of quizartinib.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Quizartinib (AC220) is a receptor tyrosine kinase (RTK) inhibitor that binds to Fms Related Receptor Tyrosine Kinase 3 (FLT3) and several other RTKs. Kinase inhibition is mediated through competition with the adenosine triphosphate (ATP) binding pocket of the kinase. Quizartinib binding is relatively specific for FLT3 ($K_d = 1.3$ nM) and KIT ($K_d = 4.9$ nM), as is the active metabolite AC886, with K_d values of 0.54 nM for FLT3 and 0.97 nM for KIT. In binding assays, quizartinib and AC886 showed approximately 10-fold lower affinity towards the FLT3 internal tandem duplication (FLT3-ITD) mutation ($K_d = 9.4$ nM and 5.8 nM for quizartinib and AC886, respectively) compared to FLT3 ($K_d = 1.3$ nM and 0.54 nM for quizartinib and AC886, respectively).

Quizartinib pharmacology was characterized in vitro and/or in vivo in MV4-11 cells and RS4;11 cells. MV4-11 cells are a human leukemia cell line that expresses FLT3 with an internal tandem duplication (ITD) activating mutation. The RS4;11 cell line is a leukemia cell line that expresses wild-type FLT3 and is not dependent on FLT3 activity for proliferation. Western blot analysis showed quizartinib induces concentration-dependent inhibition of autophosphorylation of FLT protein in MV4-11 cells in vitro. Quizartinib inhibited proliferation of cultured MV4-11 cells with an IC_{50} of 0.3 nM, whereas it had more than 1000-fold weaker activity against the RS4;11 control cell line ($IC_{50} = 990$ nM). Using the MV4-11 cell line, quizartinib also displayed in vivo anti-tumor activity in a mouse tumor xenograft model and increased the lifespan of animals.

Quizartinib was tested for inhibitory activity against a panel of 118 non-kinase enzymes, receptors, channels, and transporters. Quizartinib produced greater than 50% inhibition in five of the 118 targets, but was more than 1000-fold less potent against those targets than for FLT3.

Standalone in vitro and in vivo safety pharmacology studies were conducted to assess the cardiovascular risks of quizartinib and AC886, whereas endpoints to assess the effects of quizartinib on the central nervous and respiratory systems were incorporated into repeat-dose general toxicology studies. To assess the cardiovascular risks, in vitro studies examined the effects of quizartinib and its active metabolite on cloned human ether-a-go-go-related gene (hERG) potassium, L-type calcium, hKvLQT1/mink potassium, and early and late sodium channels. Additionally, ex vivo studies were conducted using isolated rabbit hearts and ventricular tissues and in dispersed canine cardiomyocytes, while in vivo cardiovascular data was collected in the repeat-dose toxicology studies in dogs and monkeys, as well as in a

dedicated study in telemetered monkeys. Overall, these studies demonstrated quizartinib exposure was associated with inhibition of potassium channel currents, prolongation of QT intervals, and transient increases in blood pressure.

The pharmacokinetics of quizartinib were characterized in the mouse, rat, dog, and monkey. Following oral administration of quizartinib, the plasma exposures were approximately dose proportional in the range of doses tested in nonclinical species. Female exposures were 1.4- to 2-fold higher than males in rats and dogs. Bioavailability was lower in monkeys than in rats and dogs (15% versus 30% to 40%). Both quizartinib and AC886 are highly bound to plasma proteins ($\geq 99\%$) in animals and humans. Quizartinib is well distributed in all species. Following oral administration of radioactive quizartinib in rats, the highest levels of radioactivity observed at T_{max} were found in the GI tract, pancreas, kidney, liver, lymphoid tissues (spleen, thymus, and lymph nodes), adrenal gland, pituitary, thyroid gland, adipose tissues, myocardium, lung, bone marrow, and male and female reproductive organs (such as prostate and ovary). The lowest levels were in the central nervous system and bone. In animals, the excretion was primarily hepatobiliary, with low levels excreted in the urine.

Repeat-dose toxicology studies were conducted in Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys given quizartinib dihydrochloride for up to 13 weeks. All dose levels employed were adequately justified. Hematologic and lymphoid toxicities were common and attributable to exaggerated pharmacology. Target organs of toxicity included the bone marrow (rats, dogs, and monkeys), liver (dogs and monkeys), kidney (rats and dogs), thymus (rats, dogs, and monkeys), ovary, vagina, and testes (rats and monkeys). Toxicologically significant microscopic findings included bone marrow hypocellularity, extramedullary hematopoiesis, liver crystals, single cell necrosis of the renal tubule and renal tubular basophilia and crystals, and thymic lymphoid atrophy/necrosis. When quizartinib was administered to juvenile rats, the toxicities were similar to those in adult rats. A 28-day repeat-dose toxicology study conducted in rats supports the proposed related substance impurity specifications, which are higher than ICH qualification thresholds.

In an embryo-fetal development (EFD) study in rats, quizartinib at doses resulting in exposures approximately 3 times the exposure at the maximum recommended human dose (MRHD) was associated with adverse developmental outcomes including structural abnormalities (anasarca and edema) and alterations to growth (lower fetal weights and effects on skeletal ossification). The embryofetal toxicities occurred in the absence of maternal toxicities. Because of the potential for serious adverse reactions in a breastfed child, patients will be advised that breastfeeding is not recommended during treatment and for 1 month after the last dose; the recommendation takes into consideration the elimination half-life of quizartinib and the active metabolite, AC886. Based on the EFD study and genotoxicity findings, female patients of reproductive potential will be advised to use effective contraception during treatment and for

at least 7 months after the last dose, and male patients with female partners of reproductive potential will be advised to use effective contraception during treatment and for at least 4 months after the last dose.

In genotoxicity studies, quizartinib was mutagenic in a bacterial reverse mutation assay. Quizartinib was not genotoxic in the following assays: mouse lymphoma thymidine kinase mutation assay, chromosome aberration assay in human peripheral blood lymphocytes, and rat bone marrow micronucleus assay (tested to the maximum tolerated dose, MTD). Of note, an equivocal result (positive genotoxicity but within the range of historical control data) at a dose approximating the MTD was obtained in the micronucleus assessment in a 28-day rat toxicology study. An additional genotoxicity study was conducted in transgenic F344 homozygous Big Blue rats, and the results were negative. No carcinogenicity studies were conducted or are required to support the marketing of quizartinib for the current indication.

Fertility studies in animals have not been conducted with quizartinib; however, adverse findings in male and female reproductive systems were observed in repeat-dose toxicity studies in rats and monkeys. In female rats, ovarian cysts and vaginal mucification modifications were observed at an exposure comparable to the MRHD based on area under the curve (AUC). Findings in female monkeys included atrophy of the uterus, ovary, and vagina at approximately 0.2 times the MRHD. In male rats, testicular seminiferous tubular degeneration and failure of sperm release were observed at approximately 6 times the MRHD. Findings in male monkeys included germ cell depletion in the testes at approximately 0.4 times the MRHD. Findings were reversible after a recovery period of about one month, except the vaginal mucosal modifications in the female rats.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of quizartinib for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for quizartinib.

The FDA's Assessment:

FDA concurs with the Applicant's statement.

5.3. Pharmacology

Primary pharmacology

Table 3 – In Vitro Pharmacology of Quizartinib

Type of Study	Test System	Method of Administration	Noteworthy Findings
Competition binding assay of quizartinib	T7 phage strains prepared in an E. coli host (BL21 strain) or in HEK-293 cells for 441 kinases	In vitro	Quizartinib binds with the highest affinity to FLT3 (Kd = 1.3 nM).
Competition binding assay of AC886	T7 phage strains prepared in an E. coli host (BL21 strain) or in HEK-293 cells for 391 kinases	In vitro	AC886 binds with the highest affinity to FLT3 (Kd = 0.54 nM).
Inhibition of kinase activity of quizartinib	MV4-11 cells with FLT3-ITD activating mutation	In vitro	Quizartinib is a highly potent intracellular inhibitor of FLT3-ITD catalytic activity in the leukemia cell line. The western blot clearly showed inhibition of FLT3 phosphorylation at concentrations of quizartinib from 0.8 to 20 nM.
Inhibition of cell proliferation of quizartinib	MV4-11 cells with FLT3-ITD activating mutation; RS4;11 cell line (control)	In vitro	Quizartinib inhibited proliferation of the MV4-11 cell line with the IC ₅₀ of 0.3 nM. Quizartinib is a highly potent inhibitor of FLT3-dependent proliferation.

Source: eCTD M4.2.1.1 Studies NR0006, NR0007, NR0118, and NR0119

The FDA's Assessment:

FDA acknowledges the tabulated information above. The following provides a more detailed review of the in vitro and in vivo studies.

Research has identified molecular targets for treating AML. Among molecular abnormalities, FLT3 mutations are frequent and well characterized actionable mutations in AML. FLT3 encodes a receptor tyrosine kinase expressed on normal hematopoietic stem/progenitor cells. FLT3 dimerizes and autophosphorylates upon the binding of the FLT3 ligand (FLT3L), activating the intracellular tyrosine kinase domain (TKD), which causes phosphorylation of downstream molecules and activation of signaling cascades that promote the transcription of genes

regulating survival, proliferation and differentiation. Mutations of FLT3 resulting in constitutive signaling are common in AML, including internal tandem duplications in the juxtamembrane domain (FLT3-ITD) and point mutations. Patients with AML with FLT3-ITDs may have a poor prognosis.

Using an array of in vitro and in vivo studies, the binding affinity and kinetics of quizartinib and its metabolite AC886 have been characterized, as well as the inhibition of FLT3 activity and anti-proliferative effects in leukemia cells.

In Vitro Studies

Binding assay (cell-free studies)

The binding affinity and kinetics of quizartinib and AC886 were evaluated for RTKs. KinomeScan technology was used to determine the biochemical potency and selectivity of quizartinib and AC886 against panels of 441 and 391 kinases, respectively (Study #NR0119 and #NR0118). The assay measured the ability of the test article to compete with the interaction between the target kinase and a known ATP site binding ligand. Quizartinib and AC886 displayed high binding affinity to RTKs (with K_d values <100 nM) with similar characteristics and bound to a few closely related RTKs with comparable K_d values.

Quizartinib had lower affinity towards the FLT3 internal tandem duplication, FLT3-ITD ($K_d= 9.4$ nM), compared to FLT3 ($K_d= 1.3$ nM). This trend was also noted for the AC886 metabolite ($K_d= 5.8$ nM for FLT3-ITD and 0.54 nM for FLT3).

Table 4: Binding Affinity (K_d) of Quizartinib and AC886 in a Panel of Kinases

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Kinase target	Quizartinib (nM)	AC886 (nM)
Class III RTK		
FLT3	1.3	0.54
FLT3[K663Q]	2.2	0.7
FLT3[N841I]	4.4	0.77
FLT[R834Q]	5.1	-----
FLT3[D835H]	3.9	1.9
FLT3[D835Y]	8.3	5.5
FLT3[ITD]	9.4	5.8
KIT	4.9	0.97
KIT[A829P]	3.6	----
KIT[L576P]	6.4	0.96
KIT[V559D]	5.2	1
KIT[V559D/T670I]	5.9	1.8
KIT[V559D/V654A]	42	10
PDGFRA	14	3.6
PDGFRB	8.4	1.8
CSFIR	9.6	8.6
Non-Class III RTKs		
RET	7.1	14
RET[M918T]	3	19
RET[V804L]	14	50
RET[V804M]	9.1	20
DDR1	81	-----
FLT1	44	-----
FLT4	49	-----

Binding affinity to ATP-binding site; --- not reported

Source: reviewer's summary based on Applicant's study #NR0119 and Study #NR0118 (Module 4.2.1.1)

The total (bound + unbound) C_{max} values of quizartinib and AC886 are 0.94 μ M and 0.45 μ M, respectively, in subjects taking an oral dose of 53 mg quizartinib (free base; Study No. 2689-CL-2004).

Intracellular inhibition of FLT3 activity

The MV4-11 cell line is derived from human leukemia that expresses the FLT3-ITD activating mutation that results in constitutive activation of FLT3 (Yee et al., Blood, 100: 2941-2949, 2002). Quizartinib appears to bind within the catalytic domain of the FLT3 protein, competing with ATP, thereby inhibiting the ability of the enzyme to phosphorylate proteins. Quizartinib induced concentration-dependent inhibition of FLT protein autophosphorylation (Study #NR0006).

The effect of quizartinib on the proliferation of MV4-11 cells was also evaluated. In study #NR0007, the RS4;11 cell line served as the negative control. The RS4;11 cell line expresses wild-type FLT3 and is not dependent on FLT3 activity for proliferation. The leukemia cells were

incubated with quizartinib (0.169 nM to 3 μ M) for 72 h (MV4-11 cells) or 48 h (RS4;11 cells). Quizartinib inhibited FLT3-dependent cell proliferation in the MV4-11 cell line (IC_{50} = 0.3 nM), while it exerted 1000-fold weaker activity against FLT3-independent proliferation of the RS4;11 cells (IC_{50} = 990 nM).

In Vivo Studies

Pharmacodynamic analysis: temporal effect of FLT3 inhibition

The inhibitory effect of quizartinib on the phosphorylation of FLT3 was assessed in vivo (Study #NR0112). MV4-11 tumor bearing female C.B-17-SCID mice were treated with a single oral dose of either vehicle (^(b)(4)% 2-hydroxypropyl- β -cyclodextrin [HBCD]) or quizartinib (10 mg/kg, n = 4 mice per timepoint) and tumors were collected at 0.25, 1, 2, 6, 16, 24, 48, and 96 hours after dosing. The tumors were harvested for FLT3 analysis, and plasma samples were collected for pharmacokinetic (PK) analysis of quizartinib and AC886. Phosphorylated FLT3 (p-FLT3) and total FLT3 protein were measured in tumor lysates with Meso Scale Discovery (MSD) analysis. A normalized percent p-FLT3 to total FLT3 ratio was calculated using the values for the vehicle at the 0.25-hour timepoint.

A time-dependent reduction of p-FLT3 was observed following a single dose of 10 mg/kg quizartinib. The maximal effect was observed at 1-, 2-, and 6-hours post-dose with a percent p-FLT3 value of 6%, 4%, and 7%, respectively. The p-FLT3 leveled off, i.e., ~60%, at 48-96 hours post-dose for quizartinib treatment, while vehicle treated animals remained stable over time and p-FLT3 ranged from 70%-126%. The results demonstrated that quizartinib treatment induced a temporal effect on the inhibition of auto-phosphorylation of FLT3. Exposure levels of both quizartinib and AC886 in the tumor and plasma samples over 48 h were comparable.

Anti-tumor activity in xenograft models

MV4-11 cells were implanted subcutaneously (SC) in mice to form localized tumors or injected intravenously (IV) to produce disseminated disease. In the latter case (Study #NR0116), the leukemia cells infiltrated the bone marrow. Quizartinib (0.1 to 10 mg/kg) was administered orally in mice after disease was established. In the SC tumor model (Study #NR0009), the anti-tumor activity of quizartinib treatment was both dose-dependent and treatment duration-dependent. In the disseminated graft model (Study #NR0116), quizartinib treatment prolonged the lifespan of animals in a dose-dependent fashion. Treatment with 1 mg/kg quizartinib once daily for 31 days produced an increased lifespan of 55%.

Secondary Pharmacology

The Applicant's Position:

Quizartinib was screened against a diverse panel of 118 nonkinase enzymes, receptors, channels, and

transporters in biochemical assays. Six assays showed >50% inhibition in the primary screen, and the IC₅₀ for quizartinib was subsequently determined for those six primary screen hits as summarized in Table 5. Quizartinib displayed no activity with an IC₅₀ below 2 µM against any of the targets tested, and quizartinib activity with an IC₅₀ below 10 µM was observed in only 5 of the 118 nonkinase assays (Study NR0011, eCTD 4.2.1.2).

Table 5 – Notable Off-target Activity for Quizartinib

Assay	% Inhibition (10 µM)	IC ₅₀ (µM) ^a
Lipoxygenase 15-LO	68	5.12
Peptidase; renin	67	10.3
Prostanoid EP4	70	5.55
Sigma σ1	57	7.16
Sigma σ2	62	5.04
Sodium channel, site 2	81	2.71

^a IC₅₀ was determined at 5 concentrations in the follow-up assay.

The FDA's Assessment:

FDA concurs with the Applicant's summary of Study #NR0011. In addition to the 5 targets described above, biochemical binding assays revealed that quizartinib binds 6 RTK's (ABL315I, MAP4K5, MKNK2, MUSK, TRKB, and TRKC) of 227 kinases tested, but with less than 1000 nM affinity (Study #NR0005).

Safety Pharmacology

Non-cardiovascular Safety Pharmacology:

Stand-alone CNS and respiratory system safety pharmacology studies were not conducted. However, there was no indication of CNS or pulmonary effects in the rat, dog, or monkey general toxicology studies of up to 13 week duration.

Cardiovascular Safety Pharmacology

In Vitro Ion Channel Currents:

Study Source: eCTD M4.2.1.3		GLP Compliance: Yes
Methods		
Test Systems:	Study Numbers:	Concentrations:
Cloned hERG/HEK 293 cells (hERG currents)	170504.EBH	Quizartinib 0.1-30 mM; AC886 0.1-30 mM
Beagle dog cloned hKvLQT1/mink-CHO cells (I_{Na} , I_{Ks} , I_{Ca-L} currents)	170506.EBH	Quizartinib/AC886 0.1-3 mM
Cloned hNav1.5-HEK293 cells (I_{Na} currents)	170507.EBH	Quizartinib/AC886 0.1-3 mM
Cloned late hNav1.5-HEK293 cells (I_{Na-L} currents)	170508.EBH	Quizartinib/AC886 0.1-3 mM
Cloned hVav 1,2-CHO cells (I_{Ca-L} currents)	170505.EBH	Quizartinib/AC886 0.1-3 mM
Key Drug-related Adverse Findings:		
- Quizartinib (parent compound) inhibited the I_{Ks} channel by approximately 30% at clinically relevant physiologic concentrations (approximately 7 nM) based on free drug concentration - Quizartinib and AC886 did not inhibit hERG, I_{Na}, I_{Na-L}, or I_{Ca-L} currents at clinically relevant concentrations. Inhibition of hERG currents by quizartinib and AC886 were minor as well as inhibition of I_{Ks} by AC886		

Table 6 – Ion Channel Inhibitory Activity of Quizartinib and Metabolite AC886

Quizartinib		
Ion Channel	IC₅₀ (mM)	Safety Margins^a
hERG	>3.0 ^c	>447
I_{Ks}	<0.3 ^b	<45
I_{Ca-L}	>2.3	>343
I_{Na}	>3.0	>447
I_{Na-L}	>3.0	>447
AC886		
Ion Channel	IC₅₀ (mM)	Safety Margins^a
hERG	>3.0 ^c	>824
I_{Ks}	>2.9	>797
I_{Ca-L}	>3.0	>824
I_{Na}	>3.0	>824
I_{Na-L}	>2.5	>687

^a Safety Margins based on IC₅₀ and 1% free concentration of quizartinib or AC886; protein binding ≥99% for both; at 60 mg quizartinib, free C_{max} 6.71nM (3.76 ng/mL), AC886 C_{max} 3.64 nM (2.1 ng/mL)

^b IC₅₀ could not be calculated therefore % inhibition at lowest concentration tested was reported; at 0.1 uM, quizartinib inhibition of I_{Ks} was 28.9%

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^c Maximum inhibition of hERG at 3.0 mM was 16.4% for quizartinib and 12.0% for AC886

Ex Vivo Assays: Cardiac Action Potential/Langendorff Assay

Study Source: listed below, eCTD 4.2.1.3		GLP Compliance: Yes	
Methods			
Test Systems: Cardiac action potential – Rabbit/NZW (ventricular tissues) Langendorff Assay – Rabbit/NZW (whole heart)		Study Numbers: 20100519-3 20100519-1	Concentrations: Quizartinib/AC886 1-30 mM Quizartinib/AC886 1-30 mM
Key Drug-related Adverse Findings: - AC886 induced statistically significant prolongation in action potential duration at 90% (APD₉₀) - QTc prolongation observed in isolated heart (Langendorff) assay at high concentrations of quizartinib (≥3 mM) or AC886 (≥10 mM) - At 3-30 μM (free concentration), prolongation ranged from 48-72 ms for quizartinib and 30-64 ms for AC886			

Conc (mM)	Quizartinib				AC886			
	Ventricular tissue APD prolongation (%)			Langendorff QTc prolongation (%)	Ventricular tissue APD prolongation (%)			Langendorff QTc prolongation (%)
	APD ₃₀	APD ₆₀	APD ₉₀		APD ₃₀	APD ₆₀ *	APD ₉₀	
1	-1.9	7.6	9.8	2.5	9.0	17.1	11.3	4.1
3	-5.0	3.7	2.8	19.3	3.6	18.6	15.6	12.4
10	-1.0	5.0	4.6	29.5	2.5	21.0	18.1	22.5
30	-1.9	0.6	7.0	24.7	-4.0	17.6	14.6	26.2

* Statistically significant increase in APD₆₀

Report Title: A Cardiovascular Telemetry Study in the Unrestrained Conscious Non-Naïve Cynomolgus Monkey	
Study Number: 692985 (eCTD 4.2.1.3)	GLP Compliance: Yes
Methods	
Species/Strain: Monkey/Cynomolgus	Route of administration: oral
Number/Sex/Group: 4 males	Method of administration: gavage
Initial Age: 4-5 years	Vehicle/Formulation: (b)(4)% HPβCD/Suspension
Study Design: Phase 1: Latin square crossover – doses 0, 30, 100, 200 mg/kg Phase 2: Modified escalating dose – doses 0, 3, 10, 30 mg/kg	

Report Title: A Cardiovascular Telemetry Study in the Unrestrained Conscious Non-Naïve Cynomolgus Monkey

Key Drug-related Adverse Findings:

- Dose-dependent ↑ QTc at ≥10 mg/kg which were observed 1 hr postdose and lasting to 24 hr postdose; mean peak changes were 33 to 135 ms (13% - 53%) vs baseline
- There were no changes in heart rate at any dose
- Dose-dependent ↑ systemic BP at ≥100 mg/kg (1 - 8 hr postdose) primarily due to transient elevations in systolic pressure.

In summary, quizartinib showed I_{Ks} current inhibition at clinically relevant physiologic concentrations based on free drug concentration. However, quizartinib and the major metabolite AC886 did not inhibit hERG, I_{Na} , I_{Na-L} , or I_{Ca-L} currents at clinically relevant concentrations. In vivo, a single dose of quizartinib administered to monkeys induced a dose-dependent increase in corrected QT interval (QTc) with sustained prolongation over 24 hours.

The FDA's Assessment:

Overall, the FDA concurs with the Applicant's cardiovascular safety pharmacology assessment for quizartinib and the metabolite AC886.

The Applicant's assessment contains typographical errors consisting mainly of mM to be corrected to microM (μ M) in the summary table of In Vitro Ion Channel Currents, Table 5 and the summary of ex vivo assays.

5.4. ADME/PK

The Applicant's Position:

Type of Study	Major Findings
Absorption	
Pharmacokinetics and Dose Proportionality of Quizartinib After a Single Dose in Rats (Study NR0016)	In male rats, quizartinib levels were approximately proportional to dose. Quizartinib has good bioavailability (F) in male and female rats (36% to 46% in male and 41% to 47% in female rats over dose range of 3 to 30 mg/kg). In fed rats (male) the bioavailability increased to approximately 100%, indicating that the presence of food enhanced the absorption of quizartinib.
Pharmacokinetics and Dose Proportionality of Quizartinib After a Single Dose in Dogs (Study NR0014)	In male dogs, PK characteristics after oral dosing appeared to be relatively dose proportional over the dose range of 1 to 10 mg/kg. Oral bioavailability was good at approximately 30% to 40%.

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Pharmacokinetics of Quizartinib After a Single Dose in Monkeys (Study NR0015)	Clearance after IV administration was high (approximately 30 mL/min/kg; similar to hepatic blood flow) and bioavailability after PO dosing was low (13% to 15%).
Distribution	
Tissue Distribution and Quantitative Whole Body Autoradiography (QWBA) Study of [¹⁴ C] Quizartinib in Rats (Study 021390-1)	The high concentrations of radioactivity observed in tissues at plasma Tmax were found in the stomach, small intestine, adrenal gland, liver, kidney medulla, pituitary gland, kidney cortex, pancreas, spleen, thyroid gland, brown adipose, mandibular salivary gland, stomach wall, myocardium, ovary, large intestine, lung, thymus, white adipose, bone marrow, lymph nodes, uterus wall, and prostate gland. The lowest radioactivity in tissues at Tmax was in the central nervous system and bone.
Plasma Protein Binding of Quizartinib: Mouse, Rat, Dog, Monkey, Human (Study PBC315-607)	Quizartinib and AC886 exhibited greater than or equal to 99% plasma protein binding in all of the species examined.
Metabolism	
Metabolite Profiling of [¹⁴ C]Quizartinib in Rats (Study 021390-1)	Metabolite profiling in plasma and feces from rats given [¹⁴ C]quizartinib dihydrochloride revealed that AC886 was the major metabolite in rat plasma. No other circulating metabolite was present at a fraction greater than 6.1% at any time point (2, 4, or 24 h).
Metabolite Profiling of [¹⁴ C]Quizartinib in Dogs (Study 021391-1)	AC886 was the major circulating metabolite at later time points, but another major metabolite at a fraction greater than 15%, identified as a morpholino oxidation product, was also found. This metabolite was not detected as a major plasma component in rats or humans, indicating species differences in oxidation of the morpholino side chain. No other circulating metabolite was present at a fraction greater than 8.2% at any time point (2, 4, or 24 h).
Excretion	
Mass Balance Study in Rats (Study 021390-1)	Recovery of the administered dose in SD rats Urine: 1.53% (male), 1.68% (female) Feces: 90.03% (male), 92.96% (female)
Mass Balance Study in Dogs (Study 021391-1)	Recovery of administered dose in dogs Urine: 0.52% (male), 0.70% (female) Feces: 91.86% (male), 87.26 (female)
Summary of PK parameters from pharmacokinetic studies	

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Pharmacokinetics and Dose Proportionality of Quizartinib After a Single Dose in Rats (Study NR0016)	Male rat, 3 - 300 mg/kg, PO C _{max} (μM): 0.58 - 27.11 AUC _{inf} (μM·h): 4.62 - 1037.27 F (%): 36 – 80 Male rat, 1 - 10 mg/kg, IV CL (mL/min/kg): 7.11 - 7.65 T _{1/2} (h): 4.7 - 5.5
Pharmacokinetics and Dose Proportionality of Quizartinib After a Single Dose in Dogs (Study NR0014)	Male dog, 1 - 10 mg/kg, PO C _{max} (μM): 0.23 - 2.77 AUC _{inf} (μM·h): 1.33 - 17.11 F (%): 28 – 65 Male dog, 1 mg/kg, IV CL (mL/min/kg): 6.6 T _{1/2} (h): 5.9
Pharmacokinetics of Quizartinib After a Single Dose in Monkeys (Study NR0015)	Male monkey, 3 mg/kg, PO C _{max} (μM): 0.16 AUC _{inf} (μM·h): 0.49 F (%): 15 Male monkey, 1 mg/kg, IV CL (mL/min/kg): 28.4 T _{1/2} (h): 2.1
Tabulation of any exposure margins used in proposed labeling.	
Not applicable	
TK data from general toxicology studies	
4-week and 13-week repeat-dose toxicology studies in: rats (Study 70040 and 802411); dogs (Study 60024 and 802412); monkeys (Study 1008-2493 and 803726)	
In rats, plasma exposure (AUC) to quizartinib increased greater than dose increment with oral doses up to 60 mg/kg/day. After 3 months repeated dosing, exposures were greater than on day 1 by approximately 3-fold. No apparent sex difference was observed. In dogs, C_{max} and AUC increased greater than dose increment at doses up to 150 mg/kg/day after 4 weeks, and almost with dose increment up to 15 mg/kg/day after 3 months. After 3 months repeated dosing, there were decreases in C_{max} at all doses up to 15 mg/kg/day and decreases in AUC at 15 mg/kg/day only. Gender effects were not observed after 4 weeks of dosing, however, at 15 mg/kg/day over 3 months, C_{max} and AUC were lower in males than females. In monkeys, systemic exposure to quizartinib was generally with dose increment up to 3 months dosing and at doses up to 60 mg/kg/day. Plasma exposures for quizartinib and the major metabolite, AC886, following repeated quizartinib dosing were higher than Day 1 exposures. Quizartinib and AC886 displayed no consistent gender effects in monkeys.	
TK data from reproductive toxicology studies	
Definitive oral (gavage) study for effects on embryo-fetal development in the rat (Study 901985)	
Exposure to quizartinib was greater than dose increment, whereas exposure to AC886 increased with dose increment. There was no relevant accumulation of either analyte after 12 days of administration, except for a slight increase in exposure of quizartinib at 6 mg/kg/day. AUC _{0-t} values of AC886 relative to quizartinib were 42% to 83% on Gestation Day (GD) 6 and 32% to 75% on GD 17	

from 0.6 to 6 mg/kg/day. Similarly, C_{max} values of AC886 relative to quizartinib were 41% to 78% on Gestation Day (GD) 6 and 31% to 77% on GD 17 from 0.6 to 6 mg/kg/day.

Source: eCTD M4.2.2.2: NR0016, NR0014, NR0015; M4.2.2.3: PBC315-607; M4.2.2.4: 021390-1, 021391-1; M4.2.3.2: 802411, 802412, 803726, 70040, 60024, 1008-2493; M4.2.3.5.2: 901985.

The FDA's Assessment:

FDA concurs with the Applicant's position.

Also see the toxicokinetic data under toxicology studies in Section 5.5

5.5. Toxicology

5.5.1. General Toxicology

Single-dose and repeated-dose toxicity studies for up to 13 weeks of daily quizartinib administration have been conducted in rats, dogs, and monkeys. At the early phase of development, the dog was used to characterize the toxicity of quizartinib as a nonrodent species. However, the dog showed a unique major circulating metabolite (morpholino oxidation product) that has not been detected in human, rat, and monkey, despite achieving higher exposure of those species than the dog to quizartinib, and may possibly contribute to a dog-specific liver toxicity due to birefringent crystal deposition. Based on pharmacokinetic (PK) and toxicology data, the cynomolgus monkey was selected as a potential alternate nonrodent model for evaluating the toxicity profile of quizartinib to predict human safety risk.

In all animal species studied, the principal target organs of toxicity were the bone marrow and lymphoid organs. In addition, toxicological effects were observed in the kidney, liver, ovary, vagina, and testis. Target-organ toxicity appeared to be dose and time dependent, and most toxicological findings were reversible following a 28-day or 30-day recovery period; however, slight decreases in red blood cell (RBC) and white blood cell (WBC) parameters, minimal bone marrow hypocellularity, and liver crystal deposition (only in dogs) persisted through the post recovery period. In 13-week studies, toxicological findings were present among rats and dogs at 10 mg/kg/day and 15 mg/kg/day, respectively, and these findings included decreases in hematology parameters, increased liver enzymes, and microscopic changes in bone marrow and lymphoid organs. In a 13-week study in monkeys, mortality and adverse clinical signs were reported at 10/6 mg/kg/day, with the findings consistent with those reported in the other species. NOAELs in the 13-week repeated dose toxicity studies were 3 mg/kg/day in rats, 5 mg/kg/day in dogs, and 3 mg/kg/day in monkeys.

Rat 28-day Repeat-dose Toxicity Study

Report Title: AC010220: A 28-Day Oral Toxicity Study in Sprague-Dawley Rats	
Study Number: 70040 (eCTD 4.2.3.2)	GLP Compliance: Yes
Key Drug-related Adverse Findings: - All animals in the 60/30 mg/kg/day dose group were found dead or prematurely euthanized from Study Days 3 to 15. Cause of death/moribundity was considered to be due to multi-organ toxicity related to deteriorated condition. Gross and microscopic histopathologic changes were noted in the kidneys, bone marrow, thymus, spleen, mandibular and mesenteric lymph nodes, liver, adrenals, testes, epididymides, heart, pancreas, stomach, and small and large intestines (data tables not shown). - Once daily dosing at 5 and 15 mg/kg/day for 28 days was well tolerated with target organ toxicities noted in bone marrow, kidney and thymus.	
Methods	
Species/Strain: Rat/Crl:CD(SD)	Route and method of administration: oral gavage
Number/Sex/Group: 10M, 10F	Dose: 5, 15, 60/30 mg/kg, once daily
Initial Age: 9-10 Weeks at start of dosing	Vehicle/Formulation: (b)(4)% HPβCD/Suspension
Satellite groups: recovery: 10M, 10F for each quizartinib-treated group – same animals used for toxicokinetic evaluation	

Toxicokinetics

C_{max} and AUC up to the last quantifiable time (AUC_{0-t}) increased more than dose increment in both male and female rats. No apparent sex difference was observed. Upon repeated dosing at 5 and 15 mg/kg/day for 28 days, no accumulation was evident.

Dose (mg/kg/day)	Sex	C _{max} (ng/mL)		T _{max} (h)		AUC _{0-t} (ng×h/mL)	
		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
5	M	487	615	4	4	7300	7920
	F	594	591	4	2	8170	8340

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Dose (mg/kg/day)	Sex	Cmax (ng/mL)		Tmax (h)		AUC _{0-t} (ng×h/mL)	
		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
15	M	2420	2340	4	4	30,000	39,600
	F	2210	2870	4	4	29,500	43,000
60/30 ^a	M	6710	NA	6	NA	123,000	NA
	F	8620	NA	6	NA	165,000	NA

^a A dose of 60 mg/kg/day was administered for 3 to 5 days. Due to observed toxicity, the highest dose was reduced to 30 mg/kg/day from Days 5 to 7 following a 1-day observation period.

Observations and Results: Changes From Control

Parameters	Major findings
Mortality	All rats in the 60/30 mg/kg/day dose group were either found dead or prematurely euthanized by Day 15 or earlier
Clinical signs	60/30 mg/kg/day: blood in urine (red liquid in tray), dark/loose/liquid feces, lacrimation, decreased physical activity, thinness, pallor skin color, cold to touch and eyes partially closed
Body weights	60/30 mg/kg/day: body-weight loss
Food consumption	60/30 mg/kg/day: reduced food consumption
Ophthalmoscopy	£15 mg/kg/day: no treatment-related changes
Hematology	≥15 mg/kg/day: decreases in absolute reticulocytes, microcytosis, macrocytosis, anisocytosis and polychromasia observed 60/30 mg/kg/day (M only) and £15 mg/kg/day: decreases in RBC, hemoglobin, hematocrit, neutrophil, monocyte and eosinophil counts; increases in MCV, MCH
Clinical chemistry	£60/30 mg/kg/day: increases in AST, ALT, ALP; increases were transient at 5 mg/kg/day
Urinalysis	No treatment-related changes
Micronucleus Test	See Section 5.5.3
Gross Pathology	No treatment-related changes
Organ weights	£15 mg/kg/day: decreased ovaries, testes, spleen

	15 mg/kg/day: decreased thymus

Histopathology Findings

Daily Dose (mg/kg/day)	0 (vehicle)		5		15		60/30 ^a	
Number of Animals	M: 8	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Histopathology: Scheduled Sacrifice (n, severity of finding)								
Adrenal, cortical mineralization	0	0	0	0	0	1+	NA	NA
Epididymis, ductal cell debris	0	NA	0	NA	1+	NA		
Epididymis, perivascular cell infiltrate	0	NA	3+	NA	0	NA		
Femoral bone marrow, hypocellularity	0	0	4+	1+	2+/6++/2+++	4+/5++/1+++		
Femoral bone marrow, hypercellularity	0	1+	0	0	0	0		
Heart, focal inflammation	2+	1+	1+/1++	0	5+	1+		
Kidney, calculus	0	0	1+++	0	0	1++		
Kidney, tubular basophilia	1+	0	2+	1+	5+	0		
Kidney, papillary mineralization	0	0	0	0	2+	1+		
Kidney, corticomedullary mineralization	0	6+	0	3+	0	3+		
Kidney, pyelitis	1++	0	1++++	0	0	0		
Kidney, pyelonephritis	0	1++++	0	0	0	1+++		
Kidney, tubular cell vacuolation	1+	1+	1+	0	6+/2++	0		
Kidney, granular cast	0	0	0	0	2+	0		
Kidney, interstitial cell infiltrate	1+	0	0	0	0	0		
Kidney, pelvic infiltrate	1+	0	0	1++	0	0		
Kidney, pelvic dilatation	1+/1++	1++/1+++	1+++	0	1++	1+++		
Kidney, pelvic mineralization	0	1+	1+	0	1+	1+		
Kidney, brown crystal deposition	0	0	0	0	1+	0		
Kidney, urothelial hyperplasia	0	0	0	1+	0	0		
Liver, focal necrosis	0	0	0	0	1+	0		

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Liver, extramedullary hematopoiesis	2+	0	0	0	0	0		
Liver, microgranuloma	3+	3+	0	2+	0	0		
Lymph node, lymphoid hyperplasia ^b	NA	1++	1++	NA	NA	1+		
Mandibular lymph node, agonal congestion/hemorrhage	1+	1+	0	0	2+	1+		
Mandibular lymph node, sinus erythrocytosis	0	0	1+	0	0	0		
Pancreas, interstitial cell infiltrate	0	0	0	1+	0	0		
Pancreas, acinar cell focal atrophy	1+	0	0	0	2+	0		
Sternal bone marrow, hypocellularity	0	0	8+	7+	5++/5+++	4+/5++/1+++		
Sternal bone marrow, hypercellularity	0	1+	0	0	0	0		
Stomach, mucosal erosion/ulcer	1+	1+	1+	0	0	0		
Thymus, atrophy	0	0	0	0	3+	3+		
Thymus, agonal congestion/hemorrhage	2+	2+	0	1+	0	1+		
Recovery								
At the end of the 28-day recovery period, all findings in surviving animals reversed except for the decreases in peripheral neutrophils at 5 and 15 mg/kg/day.								

+: Minimal; ++: Mild; +++: Moderate; ++++: Severe

^a Due to morbidity and mortality in the 60 mg/kg/day group, all surviving females received their last dose on Study Days 3 to 5 and were euthanized; all surviving males were not dosed on Study Day 4 but had their dose reduced to 30 mg/kg/day from Study Days 5 to 7 onward.

^b One female in the control group, 1 male in the 5 mg/kg/day group, and 1 female in the 15 mg/kg/day group were examined for lymphoid hyperplasia.

13-week Repeat-dose Toxicity Study in Rats

Report Title: A 90 Day Oral Gavage Toxicity Study of AC220 (With a 30-Day Recovery) in the Albino Rat	
Study Number: 802411 (eCTD 4.2.3.2)	GLP Compliance: Yes
Key Drug-related Adverse Findings:	
- No treatment-related mortalities occurred - Hematologic changes in RBC and WBC parameters were observed at ≥ 3 mg/kg/day - Target organs included bone marrow, kidney, spleen, thymus, testes, epididymis, ovary, and vagina.	

Report Title: A 90 Day Oral Gavage Toxicity Study of AC220 (With a 30-Day Recovery) in the Albino Rat	
Methods	
Species/Strain: Rat/Crl:CD(SD)	Route and method of administration: oral gavage
Number/Sex/Group: 10M, 10F • Recovery: 5M, 5F, [vehicle and high-dose groups]	Dose: 1, 3, 10 mg/kg, once daily
Initial Age: 9-10 Weeks	Vehicle/Formulation (b)(4)% HPβCD/Suspension
Satellite groups: toxicokinetic evaluation groups (9M, 9F for all doses)	

Toxicokinetics

C_{max} and AUC up to 24 h (AUC₀₋₂₄) increased greater than dose increment for both male and female rats on Days 1 and 86. TK values on Day 86 were higher than those on Day 1, suggesting evidence for accumulation with repeated daily dosing. No apparent sex difference was noted.

Dose (mg/kg/day)	Sex	C _{max} (ng/mL)		T _{max} (h)		AUC ₀₋₂₄ (ng×h/mL)	
		Day 1	Day 86	Day 1	Day 86	Day 1	Day 86
1	M	73.3	179	6	2	1090	2840
	F	116	236	4	4	1490	3140
3	M	296	730	4	2	4360	11,700
	F	374	908	2	2	4830	12,500
10	M	1360	3650	6	4	20,700	65,400
	F	1780	4610	6	4	25,500	85,800

Observations and Results: Changes From Control

Parameters	Major findings
Mortality	No treatment-related mortality
Clinical signs	No treatment-related clinical signs
Body weight	No treatment-related effects on body weight and body-weight gain
Food consumption	No treatment-related effects
Ophthalmoscopy	No treatment-related changes

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Hematology	≥3 mg/kg/day: decreases in WBC and all subpopulations; decreases in RBC, hemoglobin, hematocrit, platelets, absolute reticulocytes; increases in MCV, MCH, RDW and MPV
Clinical chemistry	10 mg/kg: increases in AST, ALT, ALP, glucose 10 mg/kg/day: increases in blood urea nitrogen (BUN) and creatinine; none of these increases were considered adverse effects
Urinalysis	No treatment-related changes
Gross pathology	10 mg/kg/day: small thymus (M/F), testes and epididymides
Organ weights	≥1 mg/kg/day: decreased thymus (F only) ≥3 mg/kg/day: decreased spleen 10 mg/kg/day: decreased thymus (M only) testes and uterus

Histopathology

Daily Dose (mg/kg/day)	0 (vehicle)		1		3		10	
Number of Animals	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10
Histopathology (n, severity of finding)								
Bone marrow								
Hypocellularity: hematopoietic	-	-	-	-	2+/8++	2+/7++	1+++/5++++ /4+++++	3++/2+++ /5++++
Kidney								
Tubular basophilia	2+	-	2+	-	2+	-	1+/3++/5+++ /1++++	3+/1++
Tubular crystal formation	-	-	-	-	-	-	4+/4++/1+++	-
Renal tubular vacuolation	-	-	-	-	1+	-	1+/1++	-
Tubular dilatation	-	-	1+	-	2+	-	1+/5++	-
Mononuclear cell infiltrates	-	1+	1+	1+	1+	-	5+	1+
Spleen								
Extramedullary hematopoiesis	-	-	-	1+	-	-	6+/3++	2+
Increased pigment deposition	-	1++	2++	4+/3++	1+/4++	2+/5++	1+/3++/6+++	2+/1++/5+++

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Thymus								
Lymphoid atrophy/necrosis	-	1+	-	3+	4+/3++	9+	3+/4++/2+++ /1++++	1+/5++/3+++
Testis								
Degeneration/atrophy of seminiferous epithelium	-	NA	-	NA	-	NA	2+/1++/2+++ /1++++	NA
Epididymis								
Oligo/aspermia	-	NA	-	NA	-	NA	2+++/1++++	NA
Cellular debris intratubular	-	NA	-	NA	-	NA	1+/1++	NA
Ovary								
Cysts	NA	-	NA	-	NA	1+/4++	NA	1+/5++/2+++
Vagina								
Abnormal/increased epithelial mucification of the mucosa	NA	-	NA	1++	NA	1+++	NA	2+/4++
Recovery: All findings in this study recovered or showed partial recovery except for the following: some RBC and WBC parameters at 10 mg/kg; spleen and thymus weights at 10 mg/kg. Histopathologic changes in the kidney (tubular basophilia, crystal formation, pigment deposits and tubular dilatation), spleen (pigment deposition), vagina (epithelial mucification) and bone marrow (hematopoietic hypocellularity), showed partial reversibility.								

-: No toxicologically significant findings; +: Minimal; ++: Slight; +++: Moderate; ++++: Marked; +++++: Severe

28-day Repeat-dose Toxicity Study in Dogs

Report Title: AC220: A 28-Day Oral Toxicity and Toxicokinetics Study in Beagle Dogs	
Study Number: 60024 (eCTD 4.2.3.2)	GLP Compliance: Yes
Key Drug-related Adverse Findings: - A male given 150 mg/kg/day was prematurely euthanized on Day 8 in moribund condition. Due to severe adverse effects in surviving animals administered 50 or 150 mg/kg/day, all dose levels were reduced from 10, 50 and 150 mg/kg/day to 5, 25 and 40 mg/kg/day, respectively. - Most treatment-related adverse effects occurred at doses ≥ 25 mg/kg/day. Target organ toxicities included bone marrow, kidney, liver, spleen and thymus.	
Methods	
Species/Strain: Dog/Beagle	Route and Method of administration: oral gavage
Number/Sex/Group: 3M, 3F	Dose: 10/5, 50/25, 150/40 mg/kg, once daily
Initial Age: 5-7 months	Vehicle/Formulation: (b)(4)% HP β CD/Suspension

Toxicokinetics

Both C_{max} and AUC_{0-t} increased greater than dose proportional. No consistent gender effects were noted.

Dose (mg/kg/day) ^a	Sex	C _{max} (ng/mL)		T _{max} (h)		AUC _{0-t} (ng×h/mL)	
		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
10	M	229	NA	2	NA	1740	NA
	F	439	NA	1	NA	2700	NA
5	M	NA	95.7	NA	2	NA	574
	F	NA	159	NA	1	NA	699
50	M	1890	NA	1	NA	18,600	NA
	F	1620	NA	4	NA	16,700	NA
25	M	NA	774	NA	1	NA	4580
	F	NA	805	NA	1	NA	3590
150	M	5480	NA	11	NA	83,600	NA
	F	5630	NA	1	NA	62,500	NA
40	M	NA	1950	NA	1	NA	9990

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Dose (mg/kg/day) ^a	Sex	Cmax (ng/mL)		Tmax (h)		AUC _{0-t} (ng×h/mL)	
		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
	F	NA	2760	NA	2	NA	18,100

^a Due to severe adverse effects observed in the 50 and 150 mg/kg/day group for up to Day 9, the dose levels of 10, 50, or 150 mg/kg/day reduced to 5, 25, or 40 mg/kg/day, respectively following at least 2 days observation period without dosing for most animals in the high-dose group. The reduced dose levels were used on Days 7 to 10 until on Day 28.

Observations and Results: Changes From Control

Parameters	Major findings
Mortality	50 mg/kg/day: Severe adverse effects in some animals 150 mg/kg/day: 1M prematurely euthanized on Day 8. Severe adverse effects in surviving animals Dose levels reduced from 10, 50 and 150 mg/kg/day to 5, 25 and 40 mg/kg/day, respectively. Most animals at 150 mg/kg/day were not dosed for 2 days prior to dose reduction.
Clinical signs	Surviving animals: ≥10/5 mg/kg/day: slight thinness ≥50/25 mg/kg/day: thinness, red liquid on cage tray, no feces 150/40 mg/kg/day: loose or no feces, decreased activity, yellow coloration on whole body, hunched back, cold to touch, excessive salivation, slow skin turgor
Body weight	≥50/25 mg/kg/day: reduced body weight
Food consumption	≥40 mg/kg/day: reduced food consumption
Ophthalmoscopy	No treatment-related changes
Electrocardiography	No treatment-related changes
Hematology	≥25mg/kg/day: decreases in RBC, hemoglobin, hematocrit, reticulocytes, WBC and most subpopulations 150 mg/kg: large platelet/platelet clumps, macrocytosis, anisocytosis
Clinical chemistry	≥25 mg/kg/day: dose-related increases in AST, ALT, ALP, TBL
Urinalysis	No treatment-related changes
Gross pathology	≥25 mg/kg/day: pale/discoloration of liver; small thymus
Organ weights	≥25 mg/kg/day: decreased thymus

Histopathology

Dose (mg/kg/day)	0 (vehicle)		10/5 ^a		50/25 ^a		150/40 ^a	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 2	F: 3
Histopathology, severity (n, severity of finding)								
Adrenal								
Cortical hypertrophy	-	-	-	-	2+/1++	1++	1+/1++	1++
Femur and marrow								
Hypocellular marrow	-	-	-	-	2+/1++	-	1+/1++	1+
Kidney								
Tubular dilatation	-	-	-	-	1+	-	-	-
Tubular basophilia	-	-	-	-	1+	-	1+	2+/1++
Tubular pigment	-	-	-	-	-	-	-	1+
Focal fibrosis	-	-	-	-	-	-	-	1+
Single cell necrosis	-	-	-	-	2+	-	1+	1+
Liver								
Crystal deposition	-	-	-	-	1+++/2++++	3+++	2++++	3++++
Hepatocellular vacuolation	-	-	-	-	1++	2+/1++	1++	1+/2++
Spleen								
Lymphoid atrophy	-	-	-	-	1++	2+	2++	1+/2++
Sternum and marrow								
Hypocellular marrow	-	-	-	-	2+/1++	-	1+/1++	1+
Thymus								
Lymphoid atrophy	-	-	-	-	1+++/1++++	2+/1++	1++/1+++	2+++

:- No noteworthy findings; +: minimal; ++: mild (slight); +++: moderate; ++++: severe.

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^a As a result of severe adverse effects observed in animals dosed with quizartinib 50 and 150 mg/kg/day for up to 9 days, dose levels of animals treated with quizartinib 10, 50 and 150 mg/kg/day were reduced to 5, 25 and 40 mg/kg/day, respectively. In addition, most animals that were in the 150 mg/kg/day dose group were not dosed for at least 2 days.

13-week Repeat-dose Toxicity Study in Dogs

Report Title: A 90 Day Oral Gavage Toxicity Study of AC220 (With a 30 Day Recovery) in the Beagle Dog	
Study Number: 802412 (eCTD 4.3.2.3)	GLP Compliance: Yes
Key Drug-related Adverse Findings: - No treatment-related mortalities occurred - Treatment-related changes were limited to the 15 mg/kg/day dose and included skin pallor, reductions in body weight, hematologic changes in RBC and WBC parameters, increases in liver chemistry-related parameters - Target organs included liver, kidney, spleen and thymus	
Methods	
Species/Strain: Dog/Beagle	Route and Method of administration: oral gavage
Number/Sex/Group: 4	Dose: 1, 5, 15 mg/kg, once daily
Initial Age: 7 to 8 months	Vehicle/Formulation: (b) (4)% HPβCD/Suspension
Satellite groups: recovery: 2M, 2F, [vehicle and high dose]	

Toxicokinetics

C_{max} and AUC₀₋₂₄ generally increased with dose increment. Between Days 1 and 90, there were decreases in C_{max} and increases in time to reach maximum plasma concentrations (T_{max}). In the high-dose group, mean AUC₀₋₂₄ was decreased between Days 1 and 90, and C_{max} and AUC₀₋₂₄ were lower for males than females.

Dose (mg/kg/day)	Sex	C _{max} (ng/mL)		T _{max} (h)		AUC ₀₋₂₄ (ng×h/mL)	
		Day 1	Day 90	Day 1	Day 90	Day 1	Day 90
1	M	97.3	86.4	1	2	697	769
	F	104	69.0	1	3	801	834
5	M	569	453	1	2	4520	4480
	F	546	387	1	2	3850	3380
15	M	2440	807	2	4	17,300	9470

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Dose (mg/kg/day)	Sex	Cmax (ng/mL)		Tmax (h)		AUC ₀₋₂₄ (ng×h/mL)	
		Day 1	Day 90	Day 1	Day 90	Day 1	Day 90
	F	2370	1240	2	5	17,700	13,200

Observations and Results: Changes From Control

Parameters	Major findings
Mortality	No treatment-related mortality
Clinical signs	15 mg/kg/day: skin pallor
Body weight	≥5 mg/kg/day: decreased body weight in males
Food consumption	No treatment-related effects
Ophthalmoscopy	No treatment-related changes
Electrocardiography	No treatment-related effects
Hematology	15 mg/kg/day: decreases in WBC and all subpopulations; decreases in RBC, hemoglobin, hematocrit ≥5 mg/kg/day: decreases in reticulocytes
Clinical chemistry	15 mg/kg: increases in AST, ALT, ALP, total and conjugated bilirubin; triglycerides (F only)
Urinalysis	No treatment-related changes
Gross pathology	15 mg/kg/day: small thymus (M only) 1 mg/kg/day: small thymus in one male
Organ weights	15 mg/kg/day: increased liver (M only); decreased thymus 5 mg/kg/day: decreased thymus (F only)

Histopathology

Dose (mg/kg/day)	0 (vehicle)		1		5		15	
Number of Animals	M: 4	F:4	M:4	F:4	M:4	F:4	M:4	F:4
Histopathology (n, severity of finding)								
Kidney								
Basophilia: tubular	1+	1+	2+	0	2+/1++	1+	2+	1+
Deposits pigment: tubular	0	0	0	0	0	0	2+/2++	0
Necrosis: single cell	0	0	0	0	1+	0	0	0

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Dose (mg/kg/day)	0 (vehicle)		1		5		15	
Number of Animals	M: 4	F:4	M:4	F:4	M:4	F:4	M:4	F:4
Liver								
Deposits: pigment	0	0	0	0	2+	0	1+++/3++++	4+++
Reactive sinusoidal lining cells	0	0	0	0	2+	0	4+++	1++/3+++
Fibrosis	0	0	0	0	0	0	1+/3++	1+
Inflammation	0	0	0	0	0	0	4+	2+/2++
Hematopoiesis: extramedullary	0	0	0	0	0	0	3+	2+
Hyperplasia: bile duct	0	0	0	0	0	1+	0	3+/1++
Vacuolation: hepatocellular	0	0	0	0	0	0	0	2+
Necrosis: single cell	0	0	0	0	0	0	4+	0
Spleen								
Deposits: pigment	0	0	0	0	0	2+	1+	2+
Hematopoiesis/extramedullary: increased	0	0	0	0	0	0	1+	0
Thymus								
Atrophy/necrosis: lymphoid	0	1++	1++/1+++	0	2++	1++	2++/1+++	1++
Recovery: Findings in this study recovered except for the following: decreased thymus weights at 15 mg/kg/day (M only); histopathologic changes including renal tubular basophilia and pigment deposits in 1 female, and pigment deposition, reactive sinusoidal lining cells and inflammation in the livers of all recovery animals.								

-: No toxicologically significant findings; +: Minimal; ++: Slight; +++: Moderate; ++++: Marked; +++++: Severe

28-day Repeat-dose Toxicity Study in Monkeys

Report Title: AC220: A 28-Day Oral Gavage Toxicity Study with a 28-day Recovery Period in the Cynomolgus Monkey	
Study Number: 1008-2493 (eCTD 4.2.3.2)	GLP Compliance: Yes
Key Drug-related Adverse Findings: - Oral administration of quizartinib was generally well tolerated up to 30 mg/kg/day; several monkeys in the 100/60 mg/kg/day dose group died prematurely due to moribundity - Treatment-related adverse effects were observed at doses ≥ 30 mg/kg/day and included reductions in body weight, clinical signs and changes in clinical pathology parameters - Target organs included bone marrow, lymphoid tissue, kidney, and GI tract	
Methods	
Species/Strain: Cynomolgus Monkey	Route and Method of administration:
Number/Sex/Group: 3	Dose: 10, 30, 100/60 mg/kg, once daily
Initial Age: 2-3 years	Vehicle/Formulation: (b)(4)% HP β CD/Suspension
Satellite groups: recovery: 2M, 2F	

Toxicokinetics

Systemic exposure to quizartinib increased less than the dose increment on Day 1 and generally with dose increment at steady-state (Day 28). There was no apparent sex difference in the systemic exposure to either quizartinib or AC886. After multiple dosing, there was a potential for plasma accumulation of quizartinib and AC886.

Dose (mg/kg/day)	Sex	Cmax (ng/mL)		Tmax (h)		AUC ₀₋₂₄ (ng×h/mL)	
Quizartinib							
		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
10	M	182	402	3	2	1420	2870
	F	180	365	2	2	1130	2600
30	M	490	811	3	4	3790	9210
	F	469	885	3	2	4330	8880
100 ^a	M	819	NA	3	NA	7470	NA
	F	1030	NA	3	NA	9810	NA
60 ^a	M	NA	1420	NA	4	NA	19,000

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	F	NA	1660	NA	5	NA	21,400
AC886							
		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
10	M	763	853	4	4	9040	11,400
	F	843	809	5	4	9000	10,300
30	M	1550	1510	5	5	18,000	23,200
	F	1990	1800	6	5	26,200	27,400
100 ^a	M	1950	NA	4	NA	24,400	NA
	F	3060	NA	4	NA	38,500	NA
60 ^a	M	NA	2140	NA	7	NA	40,000
	F	NA	2450	NA	6	NA	44,800

^a Due to adverse clinical signs on Days 11 and 16, dosing was interrupted for a period of 5 days and the dose level was subsequently lowered from 100 mg/kg/day to 60 mg/kg/day.

Observations and Results: Changes From Control

Parameters	Major findings
Mortality	100 mg/kg/day: 1 male and 1 female were found dead on Days 11 and 16 respectively due to body-weight loss related to quizartinib treatment. Dose was reduced to 60 mg/kg/day. 60 mg/kg/day: 1 female was euthanized on Day 33 due to moribund condition related to quizartinib treatment.
Clinical Signs	≥30 mg/kg/day: hunched posture, dehydration (slow skin turgor), thinness 100/60 mg/kg/day: in addition to clinical signs noted above, decreased activity, partly closed eyes
Body Weights	≥30 mg/kg/day: slight decreases in body weight
Ophthalmoscopy	No treatment-related changes
Electrocardiography	No treatment-related effects
Hematology	10 mg/kg/day: decreases in monocytes ≥10 mg/kg/day: decreases in lymphocytes, basophils (M only); decreases in RBC, hemoglobin and hematocrit ≥30 mg/kg/day: transient decreases in WBC; decreases in lymphocytes, basophils, and reticulocytes; increases in neutrophils; slight decreases in RBC, hemoglobin and hematocrit; microcytosis, macrocytosis and hyperchromia present

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Clinical Chemistry	≥30 mg/kg/day: increases in ALT, decreases in total protein, albumin, globulin, calcium, and phosphorus, ALP and cholesterol 100/60 mg/kg/day: in addition to changes above, increases in AST, creatinine and BUN
Urinalysis	No treatment-related changes
Gross Pathology	No treatment-related findings
Organ Weights	10 mg/kg/day: decreased spleen, (F only) ≥30 mg/kg/day: decreased spleen, thymus

Histopathology

Daily Dose (mg/kg/day)	0 (control)		10		30		100/60	
Number of Animals	M: 5	F:5	M:5	F:5	M:5	F:5	M:5	F:5
Histopathology (n, severity of finding)								
Kidney								
Acute tubular degeneration (Degeneration, tubular, medullary)	-	-	-	-	-	-	3+	-
Femur								
Hematopoietic hypocellularity	-	-	2++	1++	1+++/2++++	2++/ 1+++	3+++/1++++	2+++/2++++
Sternum								
Hematopoietic hypocellularity	-	-	1+/1++	1+	1++/1+++	1+/1+++	3++/1+++	1++/2+++/ 1++++
Spleen								
Atrophy/necrosis: lymphoid	-	-	-	1+	1+	1++/1+++	1+/1+++/ 1++++	1+/2++/1+++
Thymus								
Atrophy/necrosis: lymphoid	-	-	2+	1+	1+/1++/1+++	1+/2+++	2+++/2++++	2++/1+++/ 1++++
Mandibular lymph node								

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Atrophy/necrosis: lymphoid	-	-	2+	-	2++/1+++	1+/1+++	1++/2+++/ 1++++	1+++/2++++
Mesenteric lymph node								
Atrophy/necrosis: lymphoid	-	-	2+	-	1+/1+++	1++/1+++	1+/2++/ 1++++	1++/2+++/ 1++++
Jejunum, GALT								
Atrophy/necrosis: lymphoid	-	-	-	-	1+	1+	1++	1+
Ileum, GALT								
Atrophy/necrosis: lymphoid	-	-	-	-	1+	1+/1++	1++	3+/1++
Cecum, GALT								
Atrophy/necrosis: lymphoid	-	-	1++	-	1+/2++	1+/1++	1++/1++++	3+++/1++++
Colon, GALT								
Atrophy/necrosis: lymphoid	-	-	-	-	1+/2++	1++	1+/1++/2++++	1++/1+++/ 2++++
Rectum, GALT								
Atrophy/necrosis: lymphoid	-	-	1++	-	1+/2++	1+/1++	1+/1++/1+++	1++/2+++/ 1++++
Heart								
Edema	-	-	-	-	-	-	-	1++
Myocardial degeneration	-	-	-	-	-	-	-	1+
Necrosis of epicardial fat	-	-	-	-	-	-	-	1+
Kidney								
Acute tubular degeneration	-	-	-	-	-	-	3+	-
Stomach								
Erosion/ulceration of glandular mucosa	-	-	-	-	-	-	1+++	-

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Acute inflammation of glandular mucosa in pylorus	2++/ 3+++	4++	2+/ 1++	1+/2++/ 2+++	2+/2++/ 1+++	2++/2+++/1+++ +	2+/2+++	1+/1++/3+++
Cecum, GALT								
Atrophy/necrosis: lymphoid	-	-	1++	-	1+/2++	1+/1++	1++/1++++	3+++/1++++
Additional Examinations								
Bone Marrow Smears								
Erythroid hypoplasia	0	0	0	0	1+++	1+++	1+++/2++++	1+++/2++++
Granulocytic hyperplasia	0	0	0	0	0	0	3+++	3+++
Myeloid/erythroid ratio	0.9	0.9	1.4	0.8	1.7	1.1	8.7	5.1
Recovery: All findings in this study recovered except for slightly decreased reticulocytes in the surviving male from the 100/60 mg/kg/day group.								

:- no noteworthy findings; (n): indicates the number of animals affected; +: minimal; ++: slight/mild; +++: moderate; ++++: marked/severe.

13-week GLP Toxicology Study in Cynomolgus Monkeys

Report Title: A 13-Week Oral Gavage Toxicity Study of AC220 in the Cynomolgus Monkey With a 4 Week Recovery Period	
Study Number: 803726 (eCTD 4.2.3.2)	GLP Compliance: Yes
Key Drug-related Adverse Findings: - All monkeys in the 30 mg/kg/day group were prematurely euthanized due to moribundity; doses for mid and high doses were reduced - Treatment-related changes were observed at all doses with adverse and generally severe effects observed at doses ≥ 6 mg/kg - Target organs included lymphoid and hematopoietic systems, GI tract, liver, kidney, and male and female reproductive organs	
Methods	
Species/Strain: Cynomolgus Monkey	Route and Method of administration: oral gavage
Number/Sex/Group: 4	Dose: 3, 10/6, 30/12 mg/kg, once daily
Initial Age: 4.5-5 years	Vehicle/Formulation: (b)(4)%HP β CD/Suspension
Satellite groups: recovery group 2M, 2F	

Toxicokinetics

C_{max} and AUC₀₋₂₄ of quizartinib and AC886 increased as a function of quizartinib dose in both sexes. The plasma exposures for both analytes following repeated quizartinib dosing were higher than Day 1 exposures. Quizartinib and AC886 displayed no consistent gender effects in monkeys.

Dose (mg/kg/day)	Sex	Cmax (ng/mL)		Tmax (h)		AUC ₀₋₂₄ (ng×h/mL)	
Quizartinib							
		Day 1	Day 91	Day 1	Day 91	Day 1	Day 91
3	M	40.8	102	1	2	278	836
	F	71.8	123	1	2	332	618
10	M	191	NA	1	NA	1660	NA
	F	220	NA	1	NA	1570	NA
6	M	58.3	305	2	4	628	4060
	F	43.5	296	2	2	364	2440
30	M	274	NA	18	NA	4630	NA
	F	291	NA	2	NA	3650	NA
12	M	131	340	2	4	1580	4280
	F	158	618	2	4	1600	8140
AC886							
		Day 1	Day 91	Day 1	Day 91	Day 1	Day 91
3	M	177	347	4	4	2290	5010
	F	334	386	4	2	3540	4950
10	M	659	NA	4	NA	10,700	NA
	F	794	NA	4	NA	10,800	NA
6	M	331	656	4	4	4580	11,300
	F	219	657	4	4	3150	10,100
30	M	1410	NA	18	NA	25,900	NA
	F	1530	NA	5	NA	25,200	NA
12	M	610	1260	6	6	9510	24,000
	F	808	1320	4	6	11,000	25,400

Observations and Results: Changes From Control

Parameters	Major findings
Mortality	5 animals found dead or prematurely euthanized between Days 6 and 36, including 2F/1M at 30/12 mg/kg/day and 2F at 10/6 mg/kg/day. Two deaths were due to anemia, one was likely secondary to marked bone marrow hypocellularity. A cause of death could not be determined for the others.
Clinical Signs	≥6 mg/kg/day: reduced appetite, emesis, prominent backbone, decreased activity ≥10 mg/kg/day: severe dehydration, hunched posture, decreased respiratory rate, labored breathing, partly closed eyes, severe dehydration, soft/liquid feces, severe emesis ≥12 mg/kg/day: moderate to severe lack of coordination, severe dehydration; dosing discontinued on Study Days 61 (M) and 60 (F) and all animals prematurely euthanized ≥30 mg/kg/day: dosing suspended for 10 days due to moribundity/premature death in 1M/2F and severity of clinical signs in all animals. Dosing resumed at a reduced dose of 12 mg/kg/day until dosing discontinued as noted above.
Body Weights	≥6 mg/kg/day: decreased body weight
Ophthalmoscopy	No treatment-related changes
Electrocardiography	No treatment-related effects
Hematology	≥3 mg/kg/day: decreases in RBC, hemoglobin, hematocrit 10/6 mg/kg/day: decreases in reticulocytes; increases in platelets, MCV, RDW 30/12 mg/kg/day: increases in neutrophils; decreases in lymphocytes and eosinophils
Clinical Chemistry	3 mg/kg/day: decreases in total protein and globulin (M only) 10/6 mg/kg/day: increases in AST, ALT, BUN (M only); decreases in total protein, albumin, globulin and phosphorus 30/12 mg/kg/day: increases in AST, ALT, TBL (M only), BUN, creatinine, glucose (M only), triglycerides; decreases in total protein, albumin, globulin, phosphorus, sodium, potassium and chloride (M only)
Urinalysis	No treatment-related changes
Gross Pathology	10/6 mg/kg/day: small thymus (F only) 30/12 mg/kg/day: small thymus (M only); enlarged adrenals; small spleen in 1 female
Organ Weights	≥3 mg/kg/day: decreased uterus, ovaries, spleen ≥10/6 mg/kg/day: increased liver, adrenals; decreased thymus (F only) 30/12 mg/kg/day: decreased thymus

Histopathology

Scheduled euthanasia								
Dose (mg/kg/day)	0 (control)		3		10/6		30/12	
Number of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 2	M: 5	F: 5
Histopathology (n, severity of finding)								
Bone marrow								
Hypocellularity: hematopoietic	-	-	-	4+	2+/1+++	1+/1+++	2+/1++/ 1+++	3+/2++
Thymus								
Atrophy: lymphoid	1+/ 1++	2+	2+	1+	1+/1+++	1+/1++	3++/1+++	1++/2+++/2+++ +
Lymph node: mesenteric								
Atrophy: lymphoid	-	-	-	1++	1+/1++/1++ +	2+++	3+/2++	3++/1+++
Lymph node: mandibular								
Atrophy: lymphoid	-	-	-	-	2+/1++	1++	5+	1+++
Spleen								
Atrophy: lymphoid	-	-	-	1++	-	1+	1+	2+
Testis								
Depletion: germ cell	-	NA	-	NA	1+/3++	NA	1++/4+++	NA
Epididymis								
Oligo/Aspermial	-	NA	-	NA	-	NA	5+++++	NA
Uterus								
Atrophy	NA	-	NA	-	NA	1+	NA	5+++
Ovary								
Atrophy	NA	-	NA	-	NA	1++	NA	3++
Vagina								
Atrophy	NA	-	NA	-	NA	1+	NA	1+/1++
Esophagus								

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Degeneration/ Atrophy: epithelium	-	-	-	-	1+/1++/ 1+++	2+++	2++/2+++	1+/1+++/2++++
Tongue								
Degeneration/ Atrophy: epithelium	-	-	-	-	1+/1++	1+/1++	2+/3++	2++/1+++
Liver								
Cytoplasmic rarefaction	-	-	-	-	1++/1+++/ 1++++	-	1+/2++	1++/2+++
Single cell necrosis	-	-	-	-	-	1+	-	-
Centrilobular necrosis	-	-	-	-	-	-	1+	-
Hepatocellular vacuolation	-	-	-	-	-	1+	-	-
Colon								
Inflammation: chronic	-	-	-	-	1+	-	1+	-
Cecum								
Inflammation: chronic	1+	1+	-	-	1++	-	1+/1+++/ 1++	-
Heart								
Atrophy: fat	-	-	-	-	-	1++	-	1+
Adrenal								
Hyperplasia: cortical	1+	-	-	-	2+	1+	3+	1++
Dead/Unscheduled euthanasia								
Daily Dose (mg/kg/day)	0 (control)		3		10/6		30/12	
Number of Animals	M: 0	F: 0	M: 0	F: 0	M: 0	F: 2	M: 1	F: 2
Histopathology (n, severity of finding)								
Bone marrow								
Hypocellularity: hematopoietic	NA	NA	NA	NA	NA	1+/1++	1+++	1++++
Thymus								
Atrophy: lymphoid	NA	NA	NA	NA	NA	1++/1++++	1++++	1++
Lymph node: mesenteric								

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Atrophy: lymphoid	NA	NA	NA	NA	NA	2++	1+	1++/1+++
Lymph node: mandibular								
Atrophy: lymphoid	NA	NA	NA	NA	NA	1+	1++++	1+++
Spleen								
Atrophy: lymphoid	NA	NA	NA	NA	NA	2++	-	1++
Testis								
Depletion: germ cell	NA	NA	NA	NA	NA	NA	1+++++	NA
Epididymis								
Oligo/Aspermial	NA	NA	NA	NA	NA	NA	1+++++	NA
Uterus								
Atrophy	NA	NA	NA	NA	NA	1+++	NA	-
Ovary								
Atrophy	NA	NA	NA	NA	NA	1++	NA	-
Vagina								
Atrophy	NA	NA	NA	NA	NA	1++	NA	1+++
Esophagus								
Degeneration/ Atrophy: epithelium	NA	NA	NA	NA	NA	1+/1++	1+	1++
Tongue								
Degeneration/ Atrophy: epithelium	NA	NA	NA	NA	NA	-	1+	-
Liver								
Cytoplasmic rarefaction	NA	NA	NA	NA	NA	-	-	1++
Single cell necrosis	NA	NA	NA	NA	NA	1+	-	-
Hepatocellular vacuolation	NA	NA	NA	NA	NA	2+	-	-
Cecum								
Inflammation: chronic	NA	NA	NA	NA	NA	-	1+	-
Heart								
Atrophy: fat	NA	NA	NA	NA	NA	1++/1+++	1+++	1+/1+++
Adrenal								

Hyperplasia: cortical	NA	NA	NA	NA	NA	1+	-	2++
Recovery: All findings in this study recovered except for the following, which showed partial recovery: decreases in RBC at 30 mg/kg; decreases in RBC parameters, total protein, albumin and bone marrow hypocellularity in 1 female at 10/6 mg/kg/day.								

-: No toxicologically significant findings; +: Minimal; ++: Slight; +++: Moderate; ++++: Marked; +++++: Severe

The FDA's Assessment:

FDA generally agrees with the Applicant. See additional information below from the 13-week studies in rats and monkeys related to findings in the reproductive organs to assist with information presented under section 13.1 of the product label.

A 90 Day Oral Gavage Toxicity Study of AC220 (with a 30 Day Recovery) in the Albino Rat (#802411; GLP)

- Doses were 1 (Low dose, LD), 3 (mid dose, MD), and 10 mg/kg (high dose, HD).
- Adverse reproductive effects in females included ovarian cyst, abnormal vaginal epithelia and mucification. Those in males included small testis and epididymis, oligo/aspermia, and failure of sperm release. Findings were reversible.
- The findings in females started at the mid dose (AUC of 12,500 ng•h/mL) and the findings in males occurred at the high dose (10 mg/kg; AUC of 65,400 ng•h/mL).
- Based on the human AUC of quizartinib (10,200 ng•h/mL at the MRHD), the adverse reproductive effects in female rats occurred at an exposure comparable to human exposure. That in male rats occurred at ~6-fold the human exposure.

Parameters	Major findings; reproductive organs
Gross Pathology	HD (males) Epididymis: small (3/10) Testis: small (3/10), soft (1/10) HD (females) Ovary: cyst (1/10), dark foci (3/10)
Organ Weights	Absolute organ weight <u>HD</u> ↓ Testis (40%)

	↓Uterus (30%)
Histopathology	Peer review: yes • Epididymis: intratubular cellular debris in 2/10 HD males; oligo/aspermia in 2/3 HD males • Testis: seminiferous epithelium (minimal-severe) in 6/10 HD males; failure of sperm release (minimal-slight) in 6/10 HD males • Ovary: increased cysts in MD and HD females • Vagina: abnormal/increased epithelia; mucification of the mucosa (minimal-moderate): one each in LD and MD females and 6/10 HD females.

A 13 Week Oral Gavage Toxicity Study of AC220 in the Cynomolgus Monkey with a 4 Week Recovery Period (#803726; GLP)

- Doses were 3 (LD), 10/6 (MD), and 30/12 mg/kg (HD).
- Histopathology findings were seen in male (oligo/aspermia, germ cell depletion in testes) and female (uterine, ovarian, and vaginal atrophy) reproductive organs. Findings were reversible.
- Effects occurred starting at the MD in males (AUC of 4,060 ng•h/mL for quizartinib and on D91) and females (AUC of 2,440 ng•h/mL for quizartinib on D91).
- Based on the human AUC of quizartinib (10,200 ng•h/mL at the MRHD), adverse reproductive findings in animals occurred at 0.2 (females)- to 0.4 (males)- fold human exposures.

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Parameters	Major findings; reproductive organs						
Organ Weights	Reduced weight (% change compared to control) of reproductive organs at all dose levels. Findings resolved.						
</							

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Tissue/Finding	Sex	Male				Female			
		Dose (mg/kg/day)	0	3	10(6)	30(12)	0	3	10(6)
Testes	Number examined	4	4	4	6	—	—	—	—
	Depletion: germ cell					—	—	—	—
	Total Number affected	0	0	4	6	—	—	—	—
	Minimal	—	—	1	—	—	—	—	—
	Slight	—	—	3	1	—	—	—	—
	Moderate	—	—	—	4	—	—	—	—
Epididymis	Severe	—	—	—	1	—	—	—	—
	Number examined	4	4	4	6	—	—	—	—
	Oligo/Aspermia					—	—	—	—
	Total Number affected	0	0	0	6	—	—	—	—
Uterus	Marked	—	—	—	6	—	—	—	—
	Number examined	—	—	—	—	4	4	4	7
	Atrophy	—	—	—	—				
	Total Number affected	—	—	—	—	0	0	2	5
Ovary	Minimal	—	—	—	—	—	—	1	—
	Moderate	—	—	—	—	—	—	1	5
	Number examined	—	—	—	—	4	4	4	7
	Atrophy	—	—	—	—				
Vagina	Total Number affected	—	—	—	—	0	0	2	3
	Slight	—	—	—	—	—	—	2	3
	Number examined	—	—	—	—	4	4	4	7
	Atrophy								
	Total Number affected	—	—	—	—	0	0	2	3
	Minimal	—	—	—	—	—	—	1	1
	Slight	—	—	—	—	—	—	1	1
	Moderate	—	—	—	—	—	—	—	1

(Table excerpted from Applicant's submission)

Findings resolved

(Table excerpted from Applicant's submission)

Findings resolved

LD: low dose; MD: mid dose; HD: high dose.

5.5.2. Genetic Toxicology

The Applicant's Position:

Quizartinib demonstrated potential for mutagenicity in a bacterial reverse mutation assay (Ames test), but not in a mammalian cell mutation assay (mouse lymphoma thymidine kinase) or transgenic rodent gene mutation assay with Big Blue® rats. Quizartinib was negative in a chromosome aberration assay and in a single-dose rat bone marrow micronucleus assay although a rat micronucleus assay conducted in conjunction with the 28-day general toxicology study had an equivocal result.

Genotoxicity Assessments	
Report Title: AC010220 Bacterial Reverse Mutation Assay	
Study Number: 961163 (eCTD 4.2.3.3.1)	GLP Compliance: Yes
Key Study Findings: • Following exposure to quizartinib, increases in revertant colony counts with TA98 in the absence and presence of S9 mix, and TA100 in the presence of S9 mix. • Exposure to quizartinib in the presence of S9 mix caused partial absence of the background lawn of non-revertant bacteria indicating that quizartinib was toxic to the bacteria at high-dose concentrations.	
Test system: <i>S. typhimurium</i> (TA98, TA100, TA1535, TA1537) and <i>E. coli</i> (WP2uvrA)	
Test validity: Mean revertant colony counts for the vehicle controls were close to or within the laboratory historical control range. Positive controls induced increases in revertant colony counts.	
Report Title: AC010220 Mammalian Cell Mutation Assay	
Study Number: 962099 (eCTD 4.2.3.3.1)	GLP Compliance: Yes
Key Study Findings: • No substantial increases in mutant frequency were noted for quizartinib in the absence or presence of S9 mix at dose levels up to the limit of toxicity. • Quizartinib did not show any evidence of genotoxicity in this assay.	
Test system: Mouse lymphoma L5178Y TK ^{+/−} (clone 3.7.2) cells	
Test validity: Plating efficiencies for vehicle control cultures were within acceptable limits (65-120% for Day 2/viability). Positive controls caused increases in the small colony mutant frequency in each treatment regime.	

Genotoxicity Assessments	
Report Title: AC010220 Chromosome Aberration Assay	
Study Number: 961164 (eCTD 4.2.3.3.1)	GLP Compliance: Yes
Key Study Findings: • Cultures treated with quizartinib did not show any significant increases in the incidence of cells with aberrant metaphases at levels up to the limit of toxicity • A substantial reduction in the absolute number of analyzable metaphases was observed at the high dose for the 4-hour treatments.	
Test system: Human peripheral blood lymphocytes	
Test validity: Positive controls caused significant increases in the proportion of cells with chromosome damage.	
Report Title: AC010220 Bone Marrow Micronucleus Assay in Rats Following a Single Dose of Quizartinib	
Study Number: 961901 (eCTD 4.2.3.3.2)	GLP Compliance: Yes
Key Study Findings: • At quizartinib doses up to 100 mg/kg, no significant increases in the incidence of micronucleated immature erythrocytes were noted. • Quizartinib showed a marginal but statistically significant decrease in the proportion of immature erythrocytes at the 48-hour sampling time for animals in the highest dose group.	
Test system: Rat (Hsd:SD): (Males - 7 weeks; Females - 8 weeks); Single oral dose administration at 15, 50 and 100 mg/kg; positive control (cyclophosphamide) at 20 mg/kg; cells evaluated from bone marrow smears included micronucleated immature and mature erythrocytes, and proportion of immature erythrocytes in the total population (immature and mature erythrocytes).	
Test validity: Data for concurrent vehicle control were within ranges determined from laboratory historical data. Positive control induced clear, unequivocal increases in micronuclei.	
Report Title: AC010220: Micronucleus Test Component of the Rat 28-Day Oral Toxicity Study	
Study Number: 961165 (eCTD 4.2.3.3.2)	GLP Compliance: Yes

Genotoxicity Assessments	
Key Study Findings: At 15 mg/kg/day only, significant increases in the incidence of micronucleated immature erythrocytes were observed, although none of the individual values or group means for quizartinib fell outside the historical control range. As a result, it cannot be concluded whether the small apparent increase was treatment-related or due to variation between animals/groups. Therefore, the results of the study are considered equivocal.	
Test system: Rat (Crl:CD [SD]): (Males/Females; 9-10 weeks); oral daily dose administration at 5 and 15 mg/kg/day for 28 days; bone marrow samples were taken for bone marrow smears and 2000 immature erythrocytes per animal were examined for presence of micronuclei. The proportion of immature erythrocytes was also assessed for potential bone marrow toxicity. Positive control slides from 3 male and 3 female rats dosed orally with cyclophosphamide monohydrate at 20 mg/kg in a separate group were included.	
Test validity: Positive control slides showed significant increases in the incidence of micronucleated immature erythrocytes.	
Report Title: Transgenic Rat Gene Mutation Assay with Quizartinib	
Study Number: AF84WP.171.BTL (eCTD 4.2.3.3.2)	GLP Compliance: Yes
Key Study Findings: • All animals survived in the main study • Quizartinib did not cause elevated mutant frequencies at the <i>cH</i> gene in the liver, bone marrow or glandular stomach of treated animals and therefore was considered negative for induction of mutagenicity	
Test system: Rat (F344 homozygous Big Blue® transgenic): based on 7-day RF study in non-transgenic F344 rats at 15, 30 and 45 mg/kg/day which resulted in premature death at doses ≥30 mg/kg/day, 6 males/group (8-12 weeks) were administered quizartinib at 3.8, 7.5 and 15 mg/kg/day for 28 days daily dosing; positive control (N-ethyl-N-nitrosourea [ENU]) at 20 mg/kg/day was given for 6 non-consecutive days; bone marrow, liver and glandular stomach tissues were collected at necropsy and evaluated for mutation analysis via DNA isolation from the first 5 animals/group and analysis of <i>cH</i> mutants.	
Test validity: Vehicle control did not cause statistically elevated mutant frequency at the <i>cH</i> gene in the liver, bone marrow, or glandular stomach, and positive control induced a statistically significant increase in mutant frequency for all tissues tested.	

The FDA's Assessment:

The FDA agrees with the Applicant's conclusions on the genotoxicity assessment of quizartinib.

Quizartinib was positive in the Ames test and negative in both in vitro (mouse lymphoma thymidine kinase) and in vivo (transgenic rat model) mammalian cell mutation tests. FDA also agrees that quizartinib was not clastogenic and did not cause polyploidy in a chromosomal aberration assay (human peripheral blood lymphocytes). While quizartinib was negative in bone marrow micronucleus assays in a single dose study in rats, the in vivo micronucleus assay conducted in conjunction with the 28-day general toxicology study in rats was considered equivocal (positive results compared to concurrent control but within the historical control range).

5.5.3. Carcinogenicity

The Applicant's Position:

In accordance with International Conference on Harmonisation (ICH) S9, no studies have been conducted.

The FDA's Assessment:

FDA concurs with the Applicant's statement.

5.5.4. Reproductive and Developmental Toxicology

Embryo-fetal toxicity studies in rats showed no maternal toxicity and no evidence of quizartinib-related embryolethality up to 6 mg/kg/day. Fetotoxicity and teratogenicity were evident at 6 mg/kg/day, primarily by lower fetal weights, with effects on skeletal ossification, and fetal abnormalities (anasarca). The no observed adverse effect level (NOAEL) for embryo-fetal development was 2 mg/kg/day.

Report Title: An Oral Range-finding Teratology Study of AC220 in the Rat	
Study Number: 901971 (eCTD 4.2.3.5.2)	GLP Compliance: No
Key Drug-related Adverse Findings: Dams: • Treatment-related maternal toxicity included clinical signs (dehydration, skin pallor, thinness, swollen cranium, increased incidence of fur staining, and liquid vaginal discharge) at 20 mg/kg/day. One female at 10 mg/kg/day had brown liquid vaginal discharge and delivered dead fetal material on GD21. • Slightly lower body weight, body-weight gain and food consumption in dams at 10 mg/kg/day as well as reduced litter size and fetal body weights. • At 20 mg/kg/day embryo-fetal lethality as evidenced by total resorption noted in all animals and at 10 mg/kg/day in 1 of 5 animals. • At 10 mg/kg/day, a high number of late resorptions resulting in higher post-implantation loss occurred. Lower gravid uterus weight was observed due to smaller litters and lower fetal weights. Fetus: • At 10 mg/kg/day, lower fetal weight were noted. In all live litters from this group, fetuses had anasarca. Some showed generalized skin pallor an micrognathia. One live fetus had microcaudia.	
Methods	
Species/Strain: Rat/Crl:CD(SD)	Route of administration: oral at doses of 1, 3, 10 and 20 mg/kg/day
Number/Sex/Group: 5 females	Method of administration: gavage
Initial Age: Dams 11 weeks	Vehicle/Formulation: (b) (4) % HPβCD/Suspension

Report Title: An Oral Embryo-fetal Development Toxicity Study of AC220 in the Rat	
Study Number: 901985 (eCTD 4.2.3.5.2)	GLP Compliance: Yes
Key Drug-related Adverse Findings: - No treatment-related maternal toxicity was observed in dams. - The gravid uterus weights were slightly lower (-11% vs vehicle control) at 6 mg/kg/day and fetal weights were 12% to 13% less than controls at 6 mg/kg/day. - At 6 mg/kg/day, higher incidence of major malformations and minor external anomalies were noted. The most common abnormalities included anasarca, edema on the top of the hind paws and edema of the ventral cervical region. - Higher incidence of fetuses with incomplete ossification of the frontal bones and thoracic centrum variants were observed at 6 mg/kg/day.	
Methods	
Species/Strain: Rat/Crl:CD(SD)	Route of administration: oral at doses of 0.6, 2 and 6 mg/kg/day
Number/Sex/Group: 25 females Satellite Group: 3 females	Method of administration: gavage
Initial Age: Dams 10-11 weeks	Vehicle/Formulation: (b)(4)% HPβCD/Suspension

Toxicokinetics

Exposure to quizartinib and AC886 was increased with increasing dose increment. There was no notable accumulation of either analyte after 12 days of administration, apart from the slight increase in exposure at 6 mg/kg/day. C_{max} and AUC_{0-t} values of AC886 relative to quizartinib were 41% to 83% on GD 6 and 31% to 77% on GD 17 from 0.6 to 6 mg/kg/day.

Dose (mg/kg/day)	0.6	2	6
Number of Animals N	3	3	3
Toxicokinetics, Quizartinib			
C_{max} (ng/mL)			
GD 6	56.3	224	1160
GD 17	64.5	294	1770
T_{max} (h)			
GD 6	4	2	6
GD 17	4	2	6

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AUC_{0-t} (ng·h/mL)								
GD 6		726		3290		17,200		
GD 17		993		4390		28,000		
Toxicokinetics, AC886 (active metabolite)								
C_{max} (ng/mL)								
GD 6		43.9		172		478		
GD 17		49.5		202		551		
T_{max} (h)								
GD 6		2		4		6		
GD 17		6		4		6		
AUC_{0-t} (ng·h/mL)								
GD 6		601		2550		7160		
GD 17		741		2710		9070		
Reproductive and Developmental Toxicity – Margin of Exposure (MOE) Calculated to a 60 mg/day Quizartinib Dihydrochloride (53 mg freebase) Therapeutic Dose Base on Systemic Exposure (AUC ₀₋₂₄) observed in Study 2689-CL-2004								
	Species/Sex	Dose (mg/kg/day)	Quizartinib		AC886		Quizartinib + AC886	
			AUC ₀₋₂₄ (ng×hr/mL)	MOE ^b	AUC ₀₋₂₄ (ng×hr/mL)	MOE ^b	AUC ₀₋₂₄ (ng×hr/mL)	MOE ^b
Teratogenicity	Rat Female	2 ^a	4,390	0.53	2,710	0.64	7,100	0.50
		6	28,000	3.4	9,070	2.1	37,070	2.6

^a NOAEL

^b Based on Study 2689-CL-2004 AUC₀₋₂₄ of 8,276 ng×h/mL for quizartinib and 4,332 ng×h/mL for AC886 (see 2689-CL-2004 CSR appendix 16.1.13, eCTD 5.3.5.4).

The FDA's Assessment:

In general, the FDA concurs with the Applicant's description of the studies for the investigation of reproductive and developmental toxicology of quizartinib. The dose range-finding study (#901971) was not reviewed.

Study title/number: An Oral Embryo Fetal Developmental Toxicity Study of AC220 in the Rat (#901985; GLP-compliant)

Key Study Findings

- Quizartinib resulted in reduced fetal body weights and increased incidence of fetal abnormalities (anasarca and edema) at 6 mg/kg/day.
- There were no maternal toxicities at 6 mg/kg/day.
- The 6 mg/kg/day dose resulted in an exposure multiple of approximately 3.4-times the AUC at the MRHD.

Methods: Doses of 0.6, 2 and 6 mg/kg/day of quizartinib (as LD, MD and HD), given to SD rats by oral gavage. Pregnant rats received one daily dose on GD 6-17. Scheduled necropsy/cesarean section conducted on GD 21.

Observations and Results

Parameters	Major findings
Mortality (maternal)	All rats survived
Clinical Signs (maternal)	Not remarkable
Body Weights (maternal)	Group mean body weights were not remarkable. <u>Weight gains</u> HD: Significantly reduced mean body weight gain from GD 15-18 (↓17% of the control) and gravid uterine weight (↓19% of the control) due to reduced mean fetal weights. Reduction of periodic weight gains (↓11% of the control) occurred between GD 6-18 and GD 6-21; the changes were not statistically significant.
Food Consumption (g/animal/day; maternal)	HD: Statistically significant reduction between GD 15-18 (↓12% of the control)
Necropsy findings Cesarean Section Data	<u>Gravid uterus weight</u> HD: ↓11% of the control No other remarkable ovarian or uterine findings occurred in any dams.

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	Quizartinib did not affect the numbers of corpora lutea, implantation sites, live fetuses, dead fetuses or resorptions.																																								
Necropsy findings (fetal findings)	LD and MD: Not remarkable HD: Fetal weight ↓ 12-13% of the control. External, Visceral and Skeletal Findings at HD: Incidences that were statistically significantly increased from the control: <table> <tr> <th></th><th>Litters</th><th>Fetuses</th></tr> <tr> <td>External (examined)</td><td>25</td><td>331</td></tr> <tr> <td>Visceral (examined)</td><td>25</td><td>165</td></tr> <tr> <td>Skeletal (examined)</td><td>25</td><td>165</td></tr> <tr> <td>Major malformations (total findings)</td><td>11</td><td>58</td></tr> <tr> <td>External: anasarca (subcutaneous edema)</td><td>11 (44%)*</td><td>58 (18%)*</td></tr> <tr> <td>Minor external and visceral anomalies (total findings)</td><td>23</td><td>218</td></tr> <tr> <td>Thorax: edema (external)</td><td>9 (36%)</td><td>35 (11%)</td></tr> <tr> <td>Limb (hind paw): edema (external)</td><td>23 (92%)</td><td>217 (66%)</td></tr> <tr> <td>Minor skeletal anomalies (total)</td><td>17 (NS)</td><td>34</td></tr> <tr> <td>Frontal bone: incomplete ossification</td><td>7 (28%)</td><td>9 (5.5%)</td></tr> <tr> <td>Interparietal bone: incomplete ossification</td><td>6 (NS)</td><td>9 (5.5%)</td></tr> <tr> <td>Ossification center on 1st lumbar or 14th thoracic vertebrae</td><td>8 (NS)</td><td>9 (5.5%)</td></tr> </table> *Data in the parentheses: percentage of the total number of fetuses or litters. NS: not statistically significant Ossification delays at the HD were considered partly due to the smaller size of the fetuses in this group.			Litters	Fetuses	External (examined)	25	331	Visceral (examined)	25	165	Skeletal (examined)	25	165	Major malformations (total findings)	11	58	External: anasarca (subcutaneous edema)	11 (44%)*	58 (18%)*	Minor external and visceral anomalies (total findings)	23	218	Thorax: edema (external)	9 (36%)	35 (11%)	Limb (hind paw): edema (external)	23 (92%)	217 (66%)	Minor skeletal anomalies (total)	17 (NS)	34	Frontal bone: incomplete ossification	7 (28%)	9 (5.5%)	Interparietal bone: incomplete ossification	6 (NS)	9 (5.5%)	Ossification center on 1 st lumbar or 14 th thoracic vertebrae	8 (NS)	9 (5.5%)
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LD: low dose; MD: mid dose; HD: high dose

5.5.5. Other Toxicology Studies

The Applicant's Position:

Quizartinib was not considered to be a contact sensitizer and was not phototoxic. An impurities study to assess potential toxicity of five impurities of quizartinib showed no adverse effects in a 28-day rat study.

Antigenicity	
Report Title: A Sensitization Study of AC220 by Dermal Administration in Guinea Pigs-Modified Buehler Design	
Study Number: 20079155 (eCTD 4.2.3.7.1)	GLP Compliance: Yes
Key Study Findings: - No dermal reactions to 100% quizartinib in the test and challenge control animals occurred. Dermal scores were 0. - Following challenge with 2.5% w/v HCA, dermal scores of 1 or 2 were noted in 5/10 HCA test animals at the 24- and 48-hour scoring intervals. Dermal reactions in the remaining HCA test and HCA control animals were limited to scores of 0 or $\pm$. Group mean dermal scores were higher in the HCA test animals compared to the HCA challenge control animals. - Following challenge with 1.0% w/v HCA, dermal scores of 1 were noted in 2/10 HCA test animals at the 24- and 48-hour scoring intervals. Dermal reactions in the HCA challenge control animals were limited to scores of 0. Group mean dermal scores were higher in the HCA test animals compared to the HCA challenge control animals. - Based on these results, quizartinib is not considered to be a contact sensitizer in guinea pigs.	
Species/Strain: Hartley-derived albino guinea pig	Route of administration: dermal
Number/Sex/Group: 10	Method of administration: topical
Initial Age: 6-7 Weeks	Vehicle/Formulation: Suspension - Reverse Osmosis Deionized (RODI) water
Positive control: α -Hexylcinnamaldehyde	
Method: Guinea pigs were topically treated with 100% quizartinib, 0.3 g/site, once per week, for 3 consecutive weeks. Following a 2-week rest period, a challenge was performed; 20 test and 10 previously untreated (naïve) challenge control guinea pigs were topically treated with 100% quizartinib. Challenge responses in the test animals were compared with those of the challenge control animals. An α -Hexylcinnamaldehyde (HCA) positive control group consisting of 10 HCA test and 10 HCA control guinea pigs was included. The animals were treated as above with the HCA test animals receiving 5% w/v HCA in ethanol for induction and 2.5% and 1.0% w/v HCA in acetone for challenge.	

Impurity Qualification	
Report Title: A 28-day oral gavage toxicity Study of AC220 Impurities in Rats	
Study Number: 1258-023 (eCTD 4.2.3.7.6)	GLP Compliance: Yes
Key Study Findings: - Hematologic changes including reduced red cell parameters (RBC, hemoglobin and/or hematocrit) and reticulocytes, neutrophils and eosinophils were observed in all quizartinib-treatment groups, and correlated with decreased bone marrow cellularity. These changes were considered related to quizartinib and not the added impurities. - Hepatocellular effects including increased AST and ALT were noted at 5 mg/kg/day of quizartinib with (b) (4)% of impurities. These increases were likely related to the impurities as similar increases were not observed in animals receiving quizartinib alone; however, these effects were not considered adverse due to the small magnitude of change and lack of microscopic correlates. - Statistically significant organ weight changes of the testes, spleen, and thymus were observed in males and/or females. Although these changes were seen only in groups given quizartinib with impurities, they were not considered adverse due to the small magnitude of change and lack of microscopic correlates. - In summary, no adverse effects were noted for any parameter examined for quizartinib impurities concentrations of (b) (4)% or (b) (4)% after oral gavage administration for 28 days.	
Methods	
Species/Strain: Rat/Crl:CD(SD)	Route of administration: oral
Number/Sex/Group: 10	Method of administration: gavage
Initial Age: 6 Weeks	Vehicle/Formulation: (b) (4)% HPβCD/Suspension
Impurities included: (b) (4)	
Impurity levels: (b) (4) mg/kg/day, (b) (4) mg/kg/day representing (b) (4)% and (b) (4)% of 5 mg/kg/day quizartinib dose, respectively.	
Justification: In a 28-day rat toxicology study, quizartinib was administered at 5 and 15 mg/kg/day by oral gavage. The primary treatment-related findings included a dose-dependent decrease in RBC, hemoglobin, hematocrit, neutrophil, monocyte and eosinophil counts. Minimal bone marrow hypocellularity was observed at 5 mg/kg/day. Slight elevations in AST, ALT and ALP levels were noted only at 15 mg/kg/day. Thus, a level of 5 mg/kg/day represents a low dose where minimal drug-related changes were observed and measurable. The goal of this study was to evaluate the potential additional toxicity of two concentrations of impurities spiked into the parent compound quizartinib.	

Phototoxicity Assessment

Report Title: Neutral Red Uptake Phototoxicity Assay of AC220 in Balb/c 3T3 Mouse Fibroblasts	
Study Number: 20009465 (eCTD 4.2.3.7.7)	GLP Compliance: Yes
Key Study Findings: • Since quizartinib only showed cytotoxicity in the presence of UVA, the exact PIF could not be calculated (mean PIF >1.576) • Mean MPE was <0.15 • Results indicate no phototoxic potential of quizartinib based on ICH S10.	
Test system: BALB/3T3 mouse fibroblasts (clone A31)	
Method: Quizartinib dissolved in 1% DMSO/DPBS at concentrations up to 10.5 mg/L or the positive control article CPZ (range 0.1 to 120 mg/L) in mouse fibroblasts exposed to 5 J/cm ² of UVA and approximately 18 mJ/cm ² of UVB.	
Test validity: Cytotoxic and photocytotoxic responses of the positive control were as anticipated.	
Ocular Irritation Toxicity	
Report Title: An Acute Irritation Study of AC220 by Ocular Administration in Rabbits	
Study Number: 20079153 (eCTD 4.2.3.7.7)	GLP Compliance: Yes
Test system: Rabbit/NZW; 3 females administered a single ocular dose of 0.0354 g/eye with examination for irritation at 1, 24, 48, and 72 hours post administration	
Key Study Findings: • Exposure to quizartinib produced conjunctivitis in 3/3 test eyes at the 1-h scoring interval. Complete resolution of conjunctivitis occurred in 2/3 test eyes by the 48-h scoring interval and in the remaining test eye by the 72-h scoring interval. An additional ocular finding of quizartinib remaining in the eye was noted in all test animals. • Quizartinib is considered to be a mild irritant based on Kay and Calandra Evaluation Criteria • Classified as a nonirritant based on EEC Ocular Evaluation Criteria • Classified as equivocal based on FDA Evaluation Criteria due to a single animal with conjunctival redness of 2 at the 24- and 48-h scoring intervals	
Dermal Irritation Toxicity	
Report Title: An Acute Skin Irritation Study of AC220 by Dermal Administration in Rabbits	
Study Number: 20079156 (eCTD 4.2.3.7.7)	GLP Compliance: Yes

Test system: Rabbit/NZW; 3 males administered a single dermal dose of 0.57 g/site for 4 hours with examination at 1 hour after patch removal and 24, 14, 48, and 72 hours after patch application.

Key Study Findings:

- Quizartinib produced erythema at 3/3 test sites at the 1-h scoring interval. Dermal irritation resolved completely at 2/3 test sites by the 48-h scoring interval and at the remaining test site by the 72-h scoring interval.
- Quizartinib considered to be a slight skin irritant in rabbits according to the EPA-FIFRA Dermal Irritation Descriptive Classification Criteria.
- The calculated Primary Irritation Index for the test article was 0.83. According to the FDA Dermal Evaluation Criteria and the EEC Dermal Evaluation Criteria, quizartinib is considered to be a nonirritant.

The FDA's Assessment:

FDA agrees with the Applicant's conclusions on the impurity qualification study and the phototoxicity assessment. Ocular and dermal irritation/sensitization studies have not been reviewed.

The review of the juvenile animal study conducted in rats is included below.

Study title/study number: A 9-Week Oral Gavage Toxicity Study of Quizartinib with a 6-Week Recovery Period in Juvenile Rats/#AN16-C0010-P01)
(GLP compliant)

Key Study Findings

- Findings observed in juvenile rats were generally comparable to those in studies conducted in adult animals.
- High number of animals were euthanized early due to sequestration of bone marrow suppression.
- Other target organs of toxicity were the testis and epididymis.

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- No treatment-related changes were noted in growth and development, sexual maturation or in functional/behavioral evaluations.

GLP compliance: yes

<u>Methods:</u>	
Dose and frequency of dosing:	See table below for study design. 0, 0.3, 3, and 10 mg/kg (as control, LD, MD and HD) once daily for 9 weeks (from PND 10 to 70); 6-week recovery period (from PND 71 to PND 112 ± 1. Rats in Subsets 1-3 were treated via oral gavage once daily beginning on postnatal day (PND) 10 and continuing through PND 70 (or until the day prior to cohabitation for Subset 3). The recovery period was from PND 71 to PND112.
Route of administration:	Oral gavage (10 mL/kg)
Formulation/Vehicle:	(b) (4)
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	See table below for study design.
Age:	Female rats (F0 generation dams): 272-487 g; F1 generation pups: approximately 5 to 8 days of age (PND 5-8) at receipt; these F1 rats were weaned on PND 28.
Satellite groups/ unique design:	Toxicokinetics group (Subset 4). Reproductive group: Subset 3: one male rat and one female rat were pair housed (cohabitation). The day with confirmation of mating was designated as GD 1.
Deviation from study protocol affecting interpretation of results:	No

Table 7: Experimental Design- Juvenile Study in Rats

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Group No.	Test Material	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	No. of Juvenile Rats							
					Subset 1 ^a		Subset 2 ^b		Subset 3 ^c		Subset 4 ^d	
					M	F	M	F	M	F	M	F
1	Control Article	0	0	10	20	20	10	10	20	20	12	12
2	Quizartinib	0.3	0.03	10	20	20	10	10	20	20	48	48
3	Quizartinib	3	0.3	10	20	20	10	10	20	20	48	48
4	Quizartinib	10	1.0	10	20	20	10	10	20	20	48	48

M = Male; F = Female

^a Twenty (20) rats/sex/dose group were assigned to Subset 1 (main study).

^b Ten (10) rats/sex/dose group were assigned to Subset 2 (recovery study) and were given an approximately 6 week treatment-free period after the completion of dose administration.

^c Twenty (20) rats/sex/dose group were assigned to Subset 3 (reproductive study).

^d Rats assigned to TK collection.

Source: Text Table 1 in Applicant's Study report (Module 4.2.3.5.4)

Observation and Results: Changes from Control

F1 generation (Juvenile PND 10-PND 112): No drug-related or remarkable changes were noted in body weight, food consumption, ophthalmoscopy, motor activity, behavioral changes, sexual maturation, growth/bone evaluation, and preweaning developmental observation.

Findings in animals were consistent with the pharmacology of the drug or were previously noted in studies conducted in adult animals.

Parameters	Major findings
Mortality	Control: 1/62 LD: 2 (2/98 found dead) MD: 2 (2/98 found dead) The deaths in these 5 rats were not quizartinib-related, and most likely gavage errors and/or related to infections. HD: All animals euthanized earlier than the scheduled terminal sacrifice.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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	COD: The cause of death of HD animals may be attributable to effects secondary to bone marrow suppression (microscopically shown as marked to severe decreased cellularity) in these animals.
Clinical signs	HD: Dehydration, hunched posture, fecal changes, decreased motor activity, impaired (or lost) righting reflex, pale extremities, ataxia, cold to touch, abdominal distension, labored breathing, and staining/discharge.
Hematology	PND <36 HD: Severe marrow suppression with all three blood cell lineages affected, especially the white cells (severe decreases in neutrophil, lymphocyte, monocyte and eosinophil counts)
Immunophenotyping	MD (mainly on PND 71) ↓NK cells (CD3 ⁺ /CD161a ⁺) ↓B lymphocytes (CD3 ⁺ /CD45RA ⁺) ↓Total T lymphocytes (CD3 ⁺), helper T lymphocytes (CD3 ⁺ /CD4 ⁺) PND 113 ↓Helper T lymphocytes (CD3 ⁺ /CD4 ⁺), cytotoxic T lymphocytes (CD3 ⁺ /CD8a ⁺)
Bone Marrow Smear Evaluation	MD ↓M:E ratio: Minimal, in 4M and 1F, due to decreased erythroid line cells, occasionally accompanied by increased numbers of binucleated reticulocytes. The bone marrow smear findings plus the findings of decreased RBC, HGB, Hct and/or reticulocytes, and ↑MCV and MCH indicated quizartinib induced delayed maturation of erythroid cells. The effect was partially reversible.
Clinical Chemistry	Increased creatinine (males only) and BUN: of unknown toxicological significance (~20% of change). Creatinine levels remained slightly higher at the end of the recovery period.
Urinalysis	Not remarkable
Gross Pathology	MD • Testis

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	Small testis: 4/20 and 2/20: left and right Enlargement: 3/20 and 1/20 left and right • Epididymis: small (4/20 on both left and right sites) Small testis correlated microscopically with tubular degeneration/atrophy and enlargement correlated with tubular dilatation. Small epididymis correlated microscopically with reduced luminal sperm. Findings resolved.
Organ Weights	Reduced weight of testis, epididymis, seminal vesicles, thymus, spleen, and thyroid/parathyroid.
Histopathology	See tables below for pre-termed necropsy (HD) and termed necropsy (LD and MD, PND 71 and PND 113). Except for bone marrow hypocellularity, other findings were not observed in recovery animals.

LD: low dose; MD: mid dose; HD: high dose.

:- indicates reduction in parameters compared to control.

Table 8: Histopathological Findings Juvenile Rats – Main Study

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	Males			Females		
Group	1	2	3	1	2	3
Dose (mg/kg/day)	0	0.3	3	0	0.3	3
No. Animals Examined	19	20	20	20	20	19
Bone Marrow (No. Examined)	19	20	20	20	20	19
Decreased cellularity	(0) ^a	(0)	(10)	(0)	(0)	(5)
Minimal	0	0	8	0	0	5
Mild	0	0	2	0	0	0
Testis, Left (No. Examined)	19	20	20	—	—	—
Degeneration/atrophy, tubular	(0)	(0)	(8)	—	—	—
Minimal	0	0	2	—	—	—
Mild	0	0	1	—	—	—
Marked	0	0	4	—	—	—
Severe	0	0	1	—	—	—
Giant cells, multinucleated	(0)	(0)	(3)	—	—	—
Mild	0	0	3	—	—	—
Dilatation, tubular	(0)	(0)	(4)	—	—	—
Minimal	0	0	1	—	—	—
Mild	0	0	3	—	—	—
Testis, Right (No. Examined)	19	20	20	—	—	—
Degeneration/atrophy, tubular	(0)	(0)	(6)	—	—	—
Minimal	0	0	2	—	—	—
Moderate	0	0	1	—	—	—
Marked	0	0	2	—	—	—
Severe	0	0	1	—	—	—
Giant cells, multinucleated	(0)	(0)	(3)	—	—	—
Mild	0	0	3	—	—	—
Dilatation, tubular	(0)	(0)	(1)	—	—	—
Mild	0	0	1	—	—	—
Epididymis, Left (No. Examined)	19	20	20	—	—	—
Reduced sperm, luminal	(0)	(0)	(7)	—	—	—
Mild	0	0	4	—	—	—
Severe	0	0	3	—	—	—
Epididymis, Right (No. Examined)	19	20	20	—	—	—
Reduced sperm, luminal	(0)	(0)	(4)	—	—	—
Marked	0	0	1	—	—	—
Severe	0	0	3	—	—	—

^a Numbers in parentheses represent the number of animals with the finding.

Source: Text Table 46 in Applicant's Study report (Module 4.2.3.5.4)

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X	X	
Primary Reviewer Shwu-Luan Lee, PhD	Supervisor Brenda Gehrke, PhD	

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The proposed indication is for use of quizartinib (VANFLYTA®) 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.

The marketed formulation of quizartinib is as the salt in tablets; however, doses in the label are described as free base content. Quizartinib is available as 20 mg and 30 mg (salt form) tablets. In the assessment aid, doses are generally described as free base; however, there are instances where the applicant has described the dose in the salt form. **Table 9** provides the translation between the dose descriptions. Quizartinib dosing regimen is proposed as described in **Table 10**.

Table 9: Translation between free base and salt form of quizartinib

Free base content	Salt form
17.7 mg	20 mg
26.5 mg	30 mg
35.4 mg	40 mg
53 mg	60 mg

Table 10: Proposed dosing regimen for quizartinib

VANFLYTA (quizartinib) Initiation	Induction (up to 2 cycles) Starting on Day 8 (for 7 + 3 regimen)	Consolidation (up to 4 cycles) Starting on Day 6	Maintenance (up to 36 cycles) First Day of Maintenance Therapy
Dose (free base)	35.4 mg once daily	35.4 mg once daily	Administer 26.5 mg once daily Days 1 through 14 of the first cycle if QTcF is less than or equal to 450 ms.

VANFLYTA (quizartinib) Initiation	Induction (up to 2 cycles)	Consolidation (up to 4 cycles)	Maintenance (up to 36 cycles)
	Starting on Day 8 (for 7 + 3 regimen)	Starting on Day 6	First Day of Maintenance Therapy
			Increase the dose to 53 mg once daily on Day 15 of the first cycle if QTcF is less than or equal to 450 ms. Maintain the 26.5 mg once daily dose if QTcF greater than 500 ms was observed during induction or consolidation.
Duration (28-day cycles)	Two weeks in each cycle (Days 8 to 21)	Two weeks in each cycle (Days 6 to 19)	Once daily with no break between cycles for up to 36 cycles

The evidence of efficacy for the proposed indication comes from the pivotal study AC220-A-U302: A Phase 3, Randomized (1:1), Double-Blind, Placebo-Controlled Study: Quizartinib vs Placebo with Standard Chemotherapy in FLT3-ITD(+) ND AML (QuANTUM-First) demonstrating median (95% CI) OS was 31.9 (21.0, not estimable (NE)) months) in the quizartinib arm compared to 15.1 (13.2, 26.2) months in the standard chemotherapy arm.

In the safety cohort of 265 patients in the quizartinib arm, quizartinib at the proposed dosage resulted in a Grade ≥3 TEAE rate of 47.5%, and a serious TEAE rate of 54.0%. Dose reduction due to an AE occurred in 18.9% of patients. Dose interruption occurred in 34.0% of patients and dose discontinuation due to AE occurred in 20.4% of patients.

Quizartinib prolongs the QT interval in a concentration-related manner. In study AC220-A-U302, 34.3% of patients on the quizartinib arm had new occurrence of a QTcF >450 msec, compared to 17.9% in the placebo arm. In 7.5% of these patients, the QTcF >480 msec, and in 2.3% of patients it >500 msec. A >30 msec increase from baseline was observed in 55.1% of patients. The increase from baseline was >60 msec in 10.2% of patients.

The clinical pharmacology review focused on the evaluation of the proposed dosage, drug-drug interactions, QT interval prolongation, the impact of organ impairment, and the impact of FLT3-ITD VAF and *NPM1* mutation status. Population PK (PPK), exposure-response (E-R), and physiologically-based PK (PBPK) modeling analyses were also conducted and reviewed.

Recommendations

The Office of Clinical Pharmacology has reviewed the information and data contained in NDA 216993. This NDA is approvable from a Clinical Pharmacology perspective with the PMR discussed in Section 6.2.2.3 and included in Section 13.

Review Issue	Recommendations/Comments
Pivotal or supportive evidence of effectiveness	The evidence of efficacy for the proposed indication comes from the pivotal study AC220-A-U302: A Phase 3, Randomized (1:1), Double-Blind, Placebo-Controlled Study: Quizartinib vs Placebo with Standard Chemotherapy in FLT3-ITD(+) ND AML (QuANTUM-First) demonstrating median (95% CI) OS was 31.9 (21.0, not estimable (NE)) months) in the quizartinib arm compared to 15.1 (13.2, 26.2) months in the placebo arm.
General dosing instructions (free base)	Induction: (up to 2 cycles) Starting on Day 8 (for 7 + 3 regimen) 35.4 mg once daily from Day 8 to Day 21. Consolidation: (up to 4 cycles) Starting on Day 6, 35.4 mg once daily from Day 6 to Day 19. Maintenance: Starting dose: 26.5 mg once daily for two weeks if QTcF $\leq$450 ms, then increase the dose to 53 mg once daily if QTcF $\leq$450 ms.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The following dose modifications are recommended: Strong and moderate CYP3A4 inducers: Avoid coadministration with strong or moderate CYP3A4 inducers. Strong CYP3A4 inhibitors: Reduce the dose of VANFLYTA if coadministered with strong CYP3A4 inhibitors. QT/QTc prolonging drugs: Reduce the dose of VANFLYTA if increases in QT interval are detected. Monitor patients more frequently with ECG if coadministration of VANFLYTA with drugs known to prolong the QT interval is required. No clinically relevant differences in quizartinib or AC886 exposure were identified according to age, body weight, sex, race, weak or moderate CYP3A4 inhibitors, mild or moderate renal impairment, and mild or moderate hepatic impairment.

Review Issue	Recommendations/Comments
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to FDA's revisions.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Data are included in other sections of this document.

The Applicant's Position:

A comprehensive clinical pharmacology program characterizing the PK of quizartinib, intrinsic and extrinsic factors on quizartinib PK, drug-drug interactions (DDIs), and exposure-response (E-R) relationships was conducted in both AML subjects and healthy subjects and provides adequate understanding of quizartinib disposition and support for the intended dosing regimen of quizartinib for the indication of treatment of adult patients with newly diagnosed *FLT3*-ITD (+) AML.

The commercial tablet formulation of quizartinib provides adequate exposure levels for once daily (QD) dosing with linear PK over the intended doses. Food intake does not significantly impact the clinical PK, which is characterized by extensive metabolism and formation of the major circulating active metabolite AC886, formed via cytochrome P450 (CYP) 3A mediated oxidative metabolism. Population PK analysis showed that quizartinib PK varied during the different treatment phases in newly diagnosed AML subjects which was captured by including a phase effect on the relative bioavailability in the final model. The biological reasons for this are unknown. Quizartinib and AC886 are not inhibitors or inducers for CYP3A therefore autoinhibition or autoinduction is not anticipated.

Clinically relevant E-R relationships for efficacy and safety as well as the impact of intrinsic and extrinsic factors have been characterized. They indicate a need for cardiac monitoring based on a dose-dependent increase in QT intervals, the need to avoid coadministration of moderate or strong inducers of CYP3A, and requiring a dose reduction in the case of coadministration of strong CYP3A inhibitors. Quizartinib and AC886 are not anticipated to affect the PK of other drugs through CYP enzymes. Quizartinib is a weak inhibitor of intestinal P-gp and predicted to have no to weak effect on UGT1A1 substrates. Quizartinib and AC886 have minimal potential to affect other transporters at therapeutic concentrations. Mild and moderate renal or hepatic impairment have no clinically meaningful impact on the PK of quizartinib and AC886, except that no data is available for individuals with severe renal or hepatic impairment and use in these populations is not recommended. Therapeutic individualization is not indicated based on

age, sex, or race.

The dosing regimen used in Study AC220-A-U302 of subjects with newly diagnosed *FLT3*-ITD (+) AML is appropriate and adequately supported by the observed improvement in OS, the observed safety profile, and the data from a comprehensive clinical pharmacology program.

The FDA's Assessment:

FDA agrees with the Applicant's position that quizartinib (free base) showed linear PK in the dose range of 26.5 mg to 79.5 mg in healthy subjects and 17.7 mg to 53 mg in patients with AML. The highest dose proposed for use in patients with AML is 53 mg and falls within the linear range.

PPK analysis determined that the median quizartinib exposure (AUC_{ss} , $C_{max,ss}$, $C_{min,ss}$) was 71 to 73% higher in healthy subjects compared to subjects with AML following the same dosage.

In study AC220-A-U302, the PK of quizartinib in patients with newly diagnosed AML differed across the three treatment phases (induction, consolidation, and maintenance). Quizartinib clearance was slightly lower during consolidation treatment compared to induction treatment. Following the proposed dosage of 35.4 mg once daily (QD), median quizartinib steady state exposures (AUC_{ss} and $C_{max,ss}$) were 40% higher during consolidation compared to induction (AUC_{ss} = 4290 versus 3086 ng·hr/mL; $C_{max,ss}$ = 210 versus 151 ng/mL).

Quizartinib exposure during maintenance treatment is expected to be significantly higher than exposure during induction or consolidation treatment due to two factors: 1) proposed maintenance dosage of 53 mg QD which is higher than the 35.4 mg QD dosage for induction and consolidation, and 2) significantly lower quizartinib clearance during maintenance treatment compared to induction or consolidation treatment. Following the proposed dosage in study AC220-A-U302, quizartinib median steady state exposures (AUC_{ss} and $C_{max,ss}$) were 266% higher during maintenance treatment compared to induction treatment (AUC_{ss} = 11286 versus 3086 ng·hr/mL; $C_{max,ss}$ = 553 versus 151 ng/mL). This "phase effect" on quizartinib PK was not observed in other studies, which may be due to the design of other studies, use of quizartinib monotherapy versus combination therapy, differences in disease status over time and across studies, lower patient numbers, and limited PK samples. See Section 19.4.1.2 for additional details.

See Section 6.3.1 for FDA's assessment of general pharmacology and clinical PK.

See Section 6.2.2 for FDA's assessment of the proposed dosing regimen, E-R relationships of quizartinib, and therapeutic individualization.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

A 40-mg dose during the Induction and Consolidation Phases was selected based on the results of the Phase 1 Study 2689-CL-0005 (Altman, 2018) and Study AML18 (Burnett, 2013) in subjects with newly diagnosed AML in combination with standard chemotherapy. Both studies identified 40 mg QD for 14 days as a safe recommended dose with the potential for clinical efficacy when given in conjunction with standard chemotherapy. The 40 mg dose was further supported by data from an ex vivo plasma inhibitory activity (PIA) assay utilizing *FLT3*-ITD (+) cell lines with data from Study 2689-CL-2004 in R/R AML indicating that 30 mg is the minimum dose for complete and rapid inhibition of *FLT3* signaling in this assay. The potential impact of stromal signaling via *FLT* (the cognate *FLT3*-ligand) and resulting protection of leukemic blast cells from apoptosis (Sato, 2011; Yang, 2014) likely requires higher exposure levels, especially in the bone marrow compartment. Considering available safety data from Studies 2689-CL-0005, AML18, and AC220-007 (QuANTUM-R), the dosing regimen utilized in Study AC220-A-U302 thus represents an appropriate trade-off between safety and efficacy relevant considerations.

A 2-week escalating dose schedule was implemented as a risk minimization measure to monitor dose-dependent QT prolongation and was based on QT interval corrected with Fridericia's formula (QTcF) interval data from the Phase 2 Study 2689-CL-2004. The target dose of 60 mg QD was supported by Study 2689-CL-0011 of quizartinib monotherapy as maintenance in *FLT3*-ITD (+) AML, which showed that both 40 mg QD and 60 mg QD were well tolerated, with similar incidence of Grade 3/4 adverse events (AEs) and with rapid and durable inhibition of *FLT3* at the 60 mg QD dose in the PIA.

Safety and efficacy data from Study AC220-A-U302 demonstrate a significant survival benefit for the dosing regimen utilized with an adequate and manageable safety profile and a positive benefit-risk assessment when considering the overall poor outcomes in the intended patient population. A statistically significant effect of quizartinib exposure on OS was found in subjects with newly diagnosed AML, where higher exposure was associated with longer OS, supporting the overall clinical benefit of dose escalation to 60 mg. The estimated slope was relatively uncertain (relative standard error [RSE] 37%) and led to a modest E-R relationship. Quizartinib prolonged QTcF in a concentration-dependent manner. No E-R relationship was identified for the probability of the first occurrence of the investigated AEs; however, a quizartinib treatment effect was found for treatment-emergent AEs (TEAEs) leading to dose reduction/interruption, TEAEs leading to study drug discontinuation, events in the Torsade de Pointes (TdP)/QT prolongation standardized MedDRA query (SMQ), and myelosuppression.

The Applicant's Position:

Quizartinib should be administered in combination with standard chemotherapy at a dose of 40 mg QD for 2 weeks in each cycle of induction and consolidation, starting from Day 8 of induction or Day 6 of consolidation chemotherapy. During the Continuation Phase, quizartinib should be initiated at a starting dose of 30 mg (26.5 mg free base) QD and then increased after 2 weeks of treatment to the recommended dose of 60 mg (53 mg free base) QD if corrected QTcF was ≤ 450 ms. Treatment with quizartinib can be continued for up to 36 cycles (28-day cycles), as long as the patient derives clinical benefit.

The FDA's Assessment:

FDA agrees with the Applicant's proposed dosing regimen of 35.4 mg (free base) once daily for the induction and the consolidation phases. Of note, the 40 mg (salt form) once daily dose described in the Applicant's text above is equal to the 35.4 mg dose (free base).

FDA does not consider the Applicant's proposed dosing regimen for the maintenance phase to be sufficiently justified. See Section 6.2.2.3 for the PMR and Section 6.3.1 for FDA's assessment of the proposed dosing regimen for the continuation/maintenance phase. E-R analysis in patients who received at least one maintenance dose suggests that higher quizartinib exposure during maintenance does not result in improved survival. Given the quizartinib concentration-dependent QTcF prolongation and other safety events associated with quizartinib treatment, the proposed 53 mg once daily maintenance dose of quizartinib may expose patients to unnecessary toxicity without an improvement in survival compared to lower maintenance doses.

6.2.2.2. Therapeutic Individualization

Data:

Data are included in other sections of this document.

The Applicant's Position:

Clinically significant DDI were seen with strong CYP3A inhibitors and moderate CYP3A inducer efavirenz. Dose reduction is required in the case of strong CYP3A inhibitors, and moderate or strong inducers of CYP3A should be avoided. Quizartinib and AC886 have minimal or no potential for clinically relevant transporter-mediated DDI and minimal potential to impact the PK of other drugs given concomitantly. Additionally, quizartinib dose should be adjusted based on QTcF with electrocardiogram (ECG) monitoring.

Intrinsic factors including age, sex, and Black race, were identified in the population PK analysis as having statistically significant effects on the PK of quizartinib and AC886. However, these

effects were not considered clinically meaningful. Therefore, no dose adjustment is required in any of these subpopulations. Mild or moderate renal or hepatic impairment have no clinically meaningful impact on the PK of quizartinib or AC886, and dose adjustments are not warranted. Since there is no data on subjects with severe renal or hepatic impairment, the use of quizartinib in these populations is not recommended.

The FDA's Assessment:

FDA agrees with the Applicant's positions that dose reduction is required in the presence of strong CYP3A inhibitors and that concomitant use of strong or moderate CYP3A inducers should be avoided. See Section 6.3.2.4 for specific recommendations for dosage adjustment for concomitant use of strong CYP3A inhibitors.

FDA generally agrees that no dosage adjustments are necessary according to age, sex, body weight, race (in Black or African American, or, White or Asian) patients, mild or moderate hepatic impairment, mild or moderate renal impairment, or coadministration of weak or moderate CYP3A4 inhibitors.

FDA does not agree with the Applicant's proposed dose modification criteria in the continuation phase. The proposed product label currently reads:

(b) (4)

If a QTcF >500 ms is observed during induction or consolidation, the dose of quizartinib should not be escalated during the continuation phase.

FDA agrees with the Applicant's assessment of the impact of FLT3-ITD VAF and NPM1 mutations on OS and response rate. Baseline demographics and disease features including FLT3-ITD VAF and NPM1 mutation status are described in **Table 24**, while **Figure 3** shows the impact on overall survival (OS) (Section 8.1.2). The OS hazard ratios favoring quizartinib were observed in all VAF subgroups (highest in the subgroup with >50% VAF), consistent with the mechanism of action of quizartinib, and in the subgroup of patients with mutations in NPM1. This is consistent with the mechanism of action of quizartinib and with the published literature on the role of wildtype NPM1 as a negative prognostic factor. EFS and CR/CRc analyses conducted by the Applicant showed that results seen in the mutant NPM1 and wildtype NPM1 subgroups are consistent with the overall study population (**Table 48** and **Table 49**). The Applicant's exploratory subgroup analyses suggest a benefit on EFS and no suggestion of harm for other endpoints which, taken together with the high unmet medical need in NPM1 wildtype patients, supports approval in both subgroups. EFS hazard ratios of 0.760 in the wildtype NPM1

subgroup and 0.696 in the mutant NPM1 subgroup, suggest that there may be benefit of quizartinib treatment regardless of NPM1 status (Section 8.1.2).

6.2.2.3. Outstanding Issues

The Applicant's Position:

None.

The FDA's Assessment:

There is one outstanding question regarding whether the proposed dosing regimen for the maintenance phase is appropriate:

The randomized, controlled trial, QuANTUM-First, used planned maintenance dosage of 26.5 mg quizartinib once daily (QD) for two weeks followed by dose escalation to 53 mg QD if QTcF remained less than or equal to 450 ms. Maintenance treatment was to continue for up to 36 months. Subjects were randomized to quizartinib or placebo treatment before starting induction treatment but were not re-randomized prior to starting maintenance treatment. As a result, it is uncertain whether safety and efficacy outcomes, including overall survival, were impacted by maintenance quizartinib dose because the effect(s) of quizartinib dose and exposure during maintenance cannot be evaluated independently of the effects of quizartinib dose and exposure during induction and consolidation.

Additionally, the quizartinib dose and exposure during maintenance were directly impacted by QTcF interval due to the QTcF-dependent dose escalation. Factors associated with QTcF, including age and other patient and disease characteristics, may also confound the analysis of maintenance efficacy and safety according to quizartinib maintenance dose and exposure.

The E-R analyses did not identify any clear associations between OS or EFS and higher average quizartinib exposure from first maintenance dose up to time of event/censoring (see detailed analysis in Section 19.4.3.2). However, higher quizartinib exposure is associated with greater QTcF prolongation and may put patients at risk of a worse safety profile. The recommended 53 mg QD quizartinib maintenance dosage is expected to result in over 2-fold higher quizartinib exposure (AUC, C_{max} , C_{trough}) compared to the recommended 35.4 mg QD induction and consolidation dosage (see detailed analysis in Section 19.4.1.2). Therefore, the recommended quizartinib maintenance dosage may result in a worse safety profile without improvements to overall survival compared to lower maintenance dosages.

Based on the available information, the risk/benefit profile of the inclusion of quizartinib maintenance therapy, and the appropriate dose for maintenance therapy, are unclear. Additional information is necessary to determine a clinically beneficial maintenance dosage that

does not expose subjects to unnecessary toxicity or safety events and is tolerable. The additional data would address the known serious risks of QTcF interval prolongation, neutropenia, and other signals of serious risk related to the use of quizartinib in the maintenance setting.

FDA will issue the following PMR:

Conduct a randomized trial of quizartinib maintenance therapy that compares the recommended dosage of 53 mg daily to a lower dosage (e.g., 26.5 mg daily) to further characterize serious adverse reactions including but not limited to the rates of Grade ≥ 3 adverse reactions, Grade ≥ 3 neutropenia, QTcF interval prolongation, and dose reductions, interruptions, and discontinuations due to adverse reactions and provide an analysis of dose- and exposure-response relationships for safety. Incorporate systematically assessed patient-reported outcome assessments to further characterize safety and tolerability, including patient-reported symptoms, function, and overall side effect impact. Eligible patients will include newly-diagnosed, FLT3-ITD positive AML patients in complete remission following consolidation chemotherapy. The study should also provide an analysis of dose- and exposure-response relationships for efficacy, including overall survival and relapse-free survival.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Table 11 – Quizartinib Pharmacology and Pharmacokinetic Characteristics

	Quizartinib	AC886
Physicochemical Properties		
M _w [g/mol]	560.67	576.68
Aqueous solubility [mg/mL]	Water: 0.93 0.1 N HCl: 0.27 pH 2 to 3: $<6 \times 10^{-3}$ pH 4.5 to 8: $<4 \times 10^{-4}$	n.d.
Pharmacology		
Mechanism of Action	Selective ATP-competitive inhibitor of FLT3	
QT/QTc prolongation	Quizartinib prolongs QT intervals in a concentration-dependent manner. The most important mechanism of QT prolongation by quizartinib is through inhibition of slowly activating component of delayed rectifier potassium currents (I_{Ks} IC ₅₀ $<0.3 \mu\text{M}$ by quizartinib, $>2.9 \mu\text{M}$ by AC886). In Study AC220-A-U302, the	

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	Quizartinib	AC886
	median (90% CI) model-predicted changes from baseline of QTcF (ΔQTcF) at maximum plasma concentrations at steady state (Cmax,ss) during the Continuation Phase at 30 and 60 mg were 18.4 ms (16.3, 20.5) and 24.1 ms (21.4, 26.6), respectively.	
FLT3-ITD PD (PIA)	Rapid and near complete inhibition of FLT3 at 30 and 60 mg QD	
General Information		
Healthy volunteers vs subjects	Exposures of quizartinib plus AC886 were approximately 40% higher in healthy subjects versus R/R AML subjects. Additionally, quizartinib PK was time-varying in newly diagnosed AML subjects	
Steady-state Exposure ^b , Geometric mean (%CV ^c)		
C _{max} [ng/mL]	529 (60%)	262 (48%)
AUC _{0-24h} [ng·h/mL]	10200 (75%)	5790 (46%)
Accumulation Ratio ^d (AUC _{0-24h})	5.4 (4.4)	8.7 (6.8)
Minimally effective dose	Not determined	
Maximum Tolerated Dose	40 mg QD in addition to chemotherapy, 60 mg QD monotherapy	
Dose proportionality	Quizartinib showed linear pharmacokinetics in the dose range of 26.5 to 79.5 mg in healthy subjects and 17.1 to 53 mg in AML subjects.	
Variability	In newly diagnosed AML subjects, the inter-subject variabilities of quizartinib steady-state Cmax and AUCtau were 60%-71% and 75%-85%, respectively, and 48%-52% and 46%-51%, respectively, for AC886	
Absorption		
Absolute bioavailability	71%	n.d.
T _{max} median (minimum, maximum) [hours]	4 (2.0, 8.0)	5-6 (4.0, 120)
Effect of Food	Administration of quizartinib with a high fat, high calorie meal decreased quizartinib Cmax by 8% and increased AUCinf by 8%. The Tmax was delayed by 2 hours.	
Effect of ARA	Administration of quizartinib with lansoprazole decreased quizartinib Cmax by 14% and AUCinf by 5%.	
Distribution		
Geometric mean (%CV ^c) Vss [L]	275 (17%)	n.d.
Plasma protein binding ^e	≥99%	>99%
Blood to plasma ratio (minimum, maximum) ^e	0.79, 1.30	1.36, 3.19

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	Quizartinib	AC886
Elimination		
Geometric mean (%CV ^c) CL [L/h]	2.23 (29%)	n.d.
Effective t _{1/2} ^f Mean (SD) [hours]	81 (73)	136 (113)
Metabolism		
Metabolic Pathway ^e	Oxidation: CYP3A	Oxidation: formed and metabolized by CYP3A
Inhibitor/Inducer	Strong CYP3A inhibitor ketoconazole increased the Cmax of single-dose quizartinib by 17%, AUCinf by 94%, and the predicted steady-state quizartinib AUCtau and Cmax by 96% and 86%, respectively. Moderate CYP3A inducer efavirenz decreased quizartinib AUCinf and Cmax by 90% and 45%, respectively, and AC886 AUCinf and Cmax by 96% and 68%, respectively. In the PPK analysis, weak CYP3A inducers were not found to be a statistically significant covariate for quizartinib and AC886 PK parameters.	
Excretion		
Excretion Pathways	The principal route of excretion for total radioactivity from an oral dose was in the feces. The total radioactivity recovered in feces was 76.3% (4% unchanged quizartinib) and in urine was 1.64% through the 336-h collection period. The fecal total recovery up to 748 h was projected to be approximately 89%.	
Drug-drug Interactions		
	- Quizartinib and AC886 have minimal potential to affect the PK of other drugs through CYP enzyme pathways - Quizartinib is a weak P-gp inhibitor; quizartinib increased dabigatran AUC and Cmax by approximately 12% - Quizartinib and AC886 have minimal potential to affect other transporters at therapeutic concentrations - Quizartinib is predicted by a PBPK model to have minimal effect on UGT1A1 substrates - In vitro, quizartinib is a substrate for P-gp but not for BCRP, OATP1B1, OATP1B3, OCT1, OAT2, MATE1, or MRP2 - In vitro, AC886 is a substrate for BCRP but not for OATP1B1, OATP1B3, MATE1, or MRP2	

^a Measured for the dihydrochloride salt at 37°C

^b Predicted steady-state values for newly diagnosed AML subjects during continuation therapy on 60 mg quizartinib (53 mg free base)

^c Percent coefficient of variation

^d Mean (SD)

^e In vitro data

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^f In subjects with newly diagnosed AML

Sources: eCTD 3.2.S.1.2; eCTD 3.2.S.1.3; eCTD 4.2.1.3: 170506.EBH; eCTD 4.2.2.2: 2689-ME-0004; eCTD 4.2.2.3: AM16-H0064-R01; eCTD 4.2.2.4: PBC315-607; eCTD 4.2.2.6: NR0021, NR0033, NR0035, NR0036, NR0054, NR0060, AE-8377-G, GE-1693-G, GE-1771-G, GE-1758-G, OPT-2015-005, OPT-2015-039, TCRM-DMPK-2018-06, PBC315-333, XT133087; eCTD 5.3.1.1: AC220-A-U107, AC220-014, AC220-019; eCTD 5.3.3.1: AC220-006; eCTD 5.3.3.4: AC220-015, AC220-018, AC220-A-U104, AC220-PBPK002; eCTD 5.3.5.4: 2689-CL-2004; eCTD 5.3.3.5: AC220-PMx009

The Applicant's Position:

The pharmacology and PK of quizartinib and its active metabolite AC886 are well characterized.

The FDA's Assessment:

FDA generally agrees with the pharmacology and PK characteristics presented in **Table 11** with the exception of the dose proportionality range reported for patients with AML. Quizartinib exposure (AUC and C_{max}) increased proportionally in the dose range of 17.7 mg to 53 mg (free base) in patients with AML, and not 17.1 to 53 mg which is mistakenly reported in **Table 11**.

E-R analysis of QTcF prolongation indicated that higher quizartinib concentrations are associated with greater increases in QTcF interval. Clearance is expected to be lower during maintenance treatment compared to induction or consolidation, and maintenance quizartinib exposure is predicted to be higher than induction or consolidation quizartinib exposure following the proposed dosage. In a typical subject in Study AC220-A-U302, the median QTcF interval prolongation is expected to be +18.4 msec (90% CI 16.3 to 20.5 msec) at the maximum concentration at steady state ($C_{max,ss}$) following 26.5 mg QD during maintenance treatment and +24.1 msec (90% CI 21.4 to 26.6 msec) at $C_{max,ss}$ following 53 mg QD during maintenance treatment. See Section 19.4.3.4 for the detailed analysis of quizartinib concentration impact on QTcF prolongation.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. Ex vivo pharmacodynamic (PD) data (PIA) from Study 2689-CL-2004 show rapid and near complete inhibition at 30 mg QD and 60 mg QD, supporting that adequate target coverage can be expected under the proposed dosing regimen ([Nepomuceno, 2014](#)). Additionally, results from the E-R analysis for efficacy provide additional supporting information (see Sections 6.2.2.1 and 19.4.3.1).

The FDA's Assessment:

The primary evidence of effectiveness is the analysis of OS in Study AC220-A-U302 which is described in Section 8.1. Supportive evidence of effectiveness from the clinical pharmacology program is summarized below.

Using blood samples collected under protocol 2689-2004, an ex-vivo pharmacodynamic assay was conducted evaluating the inhibition of phosphorylation of FLT3 using plasma inhibitory assay (PIA) and STAT5. The assay was conducted on 47 samples collected day 8 and 15 samples collected day 15 of quizartinib treatment. Administration of either 26.5 or 53 mg/day quizartinib resulted in plasma levels that resulted in near complete FLT3-ITD inhibitory activity as measured by the PIA assay. Expansion of the assay to evaluate inhibition of FLT3-WT and KIT phosphorylation activity demonstrated reduced effects of quizartinib at both doses on these kinases compared to FLT3-ITD, with notably large reductions in KIT inhibitory activity.

The E-R analysis of efficacy supports the conclusion that quizartinib induction and consolidation is effective. After accounting for the impact of age on OS, the E-R analysis found that improved OS may be associated with either higher quizartinib exposure during induction treatment or treatment with quizartinib (versus placebo) (refer to Section 19.4.3.2 for detailed analysis).

The E-R analysis does not provide evidence of the effectiveness of quizartinib maintenance treatment. The maintenance E-R analysis identified that improved OS was associated with lower age and HSCT in subjects who received at least one dose of maintenance treatment. However, no significant associations were identified between OS and induction exposure, maintenance exposure, and/or treatment arm (i.e. quizartinib versus placebo). The E-R analyses are described in detail in Section 19.4.3.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes. Study AC220-A-U302 enrolled adult subjects from 18-75 years of age with *FLT3*-ITD (+) newly diagnosed AML and demonstrated a clinically meaningful improvement in survival in the overall population with a favorable benefit-risk assessment. Population PK analyses did not indicate body weight, age, sex, race, or other factors to result in clinically meaningful changes in exposure that would warrant dose adjustments. See also Section 6.3.2.3.

The FDA's Assessment:

The E-R analysis of efficacy supports the conclusion that the proposed 35.4 mg once daily dose

of quizartinib during induction and consolidation is acceptable from a clinical pharmacology perspective.

For maintenance treatment, the E-R analysis does not provide evidence that the proposed quizartinib maintenance dosage of 53 mg once daily is appropriate. The maintenance E-R analysis indicates that improved OS was associated with lower age and HSCT in subjects who received at least one dose of maintenance treatment. However, improved OS was not associated with induction exposure, maintenance exposure, or quizartinib treatment (versus placebo) in subjects who received at least one dose of maintenance treatment.

Safety analyses indicate that quizartinib is associated with safety events and that higher quizartinib concentrations are associated with greater QTcF prolongation. Therefore, E-R analyses suggests that the proposed maintenance dose of 53 mg once daily may expose patients to unnecessary toxicity without improving survival compared to lower maintenance doses. A PMR will address the need for additional data to determine an acceptable quizartinib maintenance dosage (refer to Section 6.2.2.3). The maintenance E-R analysis is described in detail in Section 19.4.3.2.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

No. Intrinsic factors, including age, sex, and race, may have an impact on quizartinib PK, but the changes seen in the population PK analysis are not clinically meaningful and do not warrant any dose adjustments. Mild or moderate renal or hepatic impairment have limited or no potential to impact the elimination of quizartinib or AC886, and dose adjustments are not warranted. Since there is no data on patients with severe renal or hepatic impairment, the use of quizartinib in these populations is not recommended.

The FDA's Assessment:

FDA agrees that no clinically meaningful differences in exposure are expected according to body weight, age, race (Black or African American, White, or Asian), mild or moderate hepatic impairment, and mild or moderate renal impairment. Of note, there was limited representation of racial subgroups other than White (65%), Asian (18%), or Black or African American (9%), and it is unknown if the PK of quizartinib or AC886 differs in other racial subgroups.

Body weight and race were associated with statistically significant impacts on quizartinib clearance. The median quizartinib AUC_{ss}, C_{max,ss}, and C_{min,ss} are 22 to 23% higher in a typical

patient weighing 65 kg compared to a typical patient weighing 85 kg, but this exposure difference is not expected to have a significant impact on clinical outcomes. The PPK model also predicted that Black and African American subjects would have 30 to 35% higher median AUC_{ss} and $C_{max,ss}$ compared to subjects of other races, but E-R analysis did not find any E-R safety associations where 30 to 35% higher exposure would result in higher rates of TEAEs. Therefore, Black and African American patients with previously untreated AML are not expected to have clinically significant differences in quizartinib exposure compared to patients of other races. See Section 19.4.1.2 for detailed analysis of covariate effects on exposure.

Renal Impairment: The results of the ADME study (AC220-006) showed that <2% of the total dose is excreted renally. Accordingly, renal impairment is expected to have a negligible impact on quizartinib elimination. This relationship between creatinine clearance and circulating drug concentrations was evaluated using population PK methods. Data from 932 subjects (273 healthy subjects and 659 acute myeloid leukemia (AML) patients) were included in the PPK model. Creatinine clearance (estimated by the Cockcroft-Gault equation) was assessed as a covariate in the PPK analysis on quizartinib and AC886 clearance. Creatinine clearance in subjects with mild and moderate renal impairment was not found to be a statistically significant covariate on quizartinib and AC886 clearance (PPK Report AC220-PMx009). There were insufficient data from subjects with severe renal impairment to draw meaningful conclusions regarding the impact of severe renal impairment on quizartinib clearance ($n = 4$ [0.4%]). Based on the PPK analyses, quizartinib dose adjustment is not required in patients with mild or moderate renal impairment. Data were insufficient to draw conclusions regarding the impact of severe renal impairment. Consequently, administration of quizartinib in subjects with severe renal impairment is not recommended.

Hepatic Impairment: There have been two studies evaluating the impact of hepatic impairment on quizartinib exposure.

Study AC220-016 was conducted in subjects with mild ($n=8$), moderate ($n=8$) hepatic impairment based on Child-Pugh classification, and healthy subjects ($n=14$) who received a single oral dose of 26.5 mg quizartinib. Noncompartmental analysis (NCA) of the PK data showed that mild hepatic impairment has no significant effect on quizartinib and AC886 exposures (**Table 12**). The effect of moderate hepatic impairment had no significant effect on quizartinib exposure, but resulted in a 35% decrease in AC886 exposure (**Table 12**).

Table 12: Study AC220-U016: PK Parameters in healthy subjects with normal or mild hepatic impairment based on Child Pugh Score following a single 30 mg dose of quizartinib

Exposure Parameters	Geometric Mean (%CV)		Geometric Mean Ratio (90% CI)
	Mild hepatic impairment (n=8)	Matched normal control (n=8)	
Quizartinib			

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AUC _{0-inf} (ng·hr/mL)	9462 (26)	7304 (54)	1.30 (0.81 – 2.06)
AUC _{0-504h} (ng·hr/mL)	7824 (47)	7088 (54)	1.10 (0.69 – 1.76)
C _{max} (ng/mL)	109 (31)	97.1 (37)	1.13 (0.83 – 1.52)
CL/F (L/hr)	2.8 (26)	3.63 (54)	n/a
t _{1/2} (hr)	115.5 (28)	85.8 (25)	n/a
AC886			
AUC _{0-inf} (ng·hr/mL)	3256 (21)	2716 (38)	1.20 (0.79 – 1.82)
AUC _{0-504h} (ng·hr/mL)	2721 (37)	2558 (41)	1.06 (0.71 – 1.60)
C _{max} (ng/mL)	23.7 (60)	19.7 (66)	1.20 (0.68 – 2.11)
t _{1/2} (hr)	108 (32)	114 (26)	n/a

AUC_{0-inf} = area under the plasma concentration–time curve up to infinity; AUC_{0-504h} = area under the plasma concentration–time curve up to 504 hours post-dose; CI = confidence interval; CL/F = apparent clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; n/a = not applicable; PK = pharmacokinetic; t_{1/2} = half-life.

Source: AC220-019 Final Study Report; Table 9.1, 9.2, 9.3, 9.4; Pages 55, 56, 58, 59

In cancer patients, hepatic function is routinely classified using the NCI-ODWG criteria. Evaluation of the liver scores in individual subjects showed that the ascites score was the main contributor to the classification of subjects into either the mild or moderate liver impairment categories for Child-Pugh. Based on the large difference in the number of subjects considered healthy subjects or impaired based on the liver classification system, and the high risk of QTcF prolongation, small changes in exposure may lead to potential risk of serious adverse events. As a result, data using the NCI-ODWG classification criteria were considered as they are more conservative.

The hepatic impairment subject population was re-evaluated using the NCI-ODWG criteria. This resulted in 7 additional subjects being considered to have normal liver function, 8 subjects meeting the criteria for mild hepatic impairment, and only a single subject meeting the criteria for moderate hepatic impairment. Repeating the analysis using the NCI-ODWG classification system showed that the effect of mild hepatic impairment has no clinically meaningful effect on quizartinib and AC886 exposure. In addition, a second study was conducted, enrolling subjects that met the NCI-ODWG criteria for moderate hepatic impairment.

Study AC220-A-U105 was conducted in subjects with moderate (n=6) and healthy subjects (n=6) based on NCI-ODWG criteria. The NCA showed that total quizartinib C_{max}, AUC_{last}, and AUC_{inf} were comparable for subjects with moderate hepatic impairment and control healthy subjects; geometric mean ratios were 95.1%, 109%, and 109%, respectively.

The unbound fraction (fu) of quizartinib at 4 hours post dose was lower in subjects with moderate hepatic impairment (mean of 0.00452, ranging from 0.00112 to 0.0108) compared with control subjects (mean of 0.00900, ranging from 0.00318 to 0.0180). The mean unbound C_{max} and AUC_{inf} of quizartinib were 55% and 49% lower, respectively, in subjects with

moderate hepatic impairment compared to control subjects.

These results should be interpreted cautiously as the mechanism for the decrease in free (unbound) drug in patients with moderate hepatic impairment is not well explained at this time. In AC220-A-U105, there were 17 PK samples per patient (~ 204 PK samples) available for use in the total drug AUC calculation. C_{max} and AUC for unbound drug were extrapolated from a single free drug determination per patient (~12 samples) using the 4 hour post dose PK sample. Quizartinib is over 99% protein bound, so the unbound fraction is quite small. Assay variability and the small sample size may have influenced this finding. **Table 13** summarizes quizartinib PK in AC220-A-U105.

Active metabolite (AC886) C_{max} and AUC_{inf} were 25% and 30% lower, respectively, in subjects with moderate hepatic impairment compared to control subjects. Mean $t_{1/2}$ was longer for subjects with moderate hepatic impairment (111.1 ± 48.7 hours) compared to control subjects (81.4 ± 20.7 hours).

Moderate hepatic impairment does not significantly impact quizartinib exposure. Dose adjustment for mild or moderate hepatic impairment is not required.

Table 13: Study AC220-U105: Statistical Comparison of Total Plasma Quizartinib Pharmacokinetic Parameters After Administration of 30 mg Quizartinib Tablet to Subjects with Normal Hepatic Function and Subjects with Moderate Hepatic Impairment

Pharmacokinetic Parameter	Geo LS Mean ^a (Moderate Hepatic Impairment)		Geo LS Mean ^a (Normal Hepatic Function)		Ratio (%) ^b (Moderate Hepatic Impairment/ Normal Hepatic Function)		
	n	Value	n	Value	Value	90% CI, Lower	90% CI, Upper
C_{max} (ng/mL)	6	84.9	6	89.2	95.1	77.1	117
AUC_{last} (ng·h/mL)	6	6970	6	6370	109	59.5	201
AUC_{inf} (ng·h/mL)	6	7250	6	6620	109	57.9	207

^a Geometric Mean = anti-ln LS means

^b Ratio (%) = Geometric Mean (Moderate Hepatic Impairment; Test)/Geometric Mean (Normal Hepatic Function; Reference)
ANOVA = analysis of variance; AUC_{inf} = area under the plasma concentration–time curve up to infinity; AUC_{last} = area under the plasma concentration–time curve up to the last quantifiable concentration post-dose; CI = confidence interval; C_{max} = maximum plasma concentration; ln = logarithm-transformed; LS = least square; n = number of observations used by mixed model.
Source: Final study report AC-220-U105, Table 14.4.9.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

Yes. Strong CYP3A inhibitors result in a clinically significant increase in exposure and warrant a

dose reduction to 50% of the regular dose when quizartinib is given concomitantly with strong CYP3A inhibitors. Moderate or strong inducers of CYP3A have the potential to impact the exposure to quizartinib and AC886 and should be avoided.

There were no clinically meaningful changes to quizartinib or AC886 plasma exposures when coadministered with food or gastric acid-reducing agents (ARAs). Quizartinib can be coadministered with gastric ARAs and without regard to food.

The FDA's Assessment:

Food Effect:

The impact of a high-fat (50%), high calorie (approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively, for a total of 1000 calories meal) on quizartinib and AC886 PK was evaluated in 63 healthy subjects administered a single oral 26.5 mg dose of quizartinib in Study AC220-019. No significant change in AUC or C_{max} was observed in the fed compared to the fasted subjects. Median T_{max} was 2 hours longer for quizartinib and 31 hours longer for AC886 when quizartinib was given with a high-fat meal compared to the fasted state (**Table 14**). These results support the labeling recommendation of administering quizartinib with or without food.

Table 14: PK Parameters of a single dose of quizartinib after a high-fat meal as compared with fasted state

Exposure Parameters	Geometric Mean (%CV)		Geometric Mean Ratio (90% CI)
	High-Fat Meal (n=29)	Fasted State (n=34)	
Quizartinib			
AUC _{0-inf} (ng·hr/mL)	9460 (43)	8730 (37)	1.08 (0.92 – 1.28)
AUC _{last} (ng·hr/mL)	8790 (40)	8340 (33)	1.05 (0.91 – 1.22)
C_{max} (ng/mL)	90.8 (22)	99.3 (26)	0.92 (0.82 – 1.02)
T_{max} (hr) ^a	6.0 (4- 12.0)	4.0 (2.0-8.0)	
AC886			
AUC _{0-inf} (ng·hr/mL)	2450 (44)	1970 (52)	1.24 (0.99 – 1.56)
AUC _{last} (ng·hr/mL)	1820 (75)	1750 (54)	1.04 (0.81 – 1.34)
C_{max} (ng/mL)	10.2 (88)	13.0 (61)	0.79 (0.59 – 1.04)
T_{max} (hr) ^a	36.0 (6-144)	5.0 (4-120)	n/a

^a T_{max} is reported as median (minimum, maximum)

AUC_{0-inf} = area under the plasma concentration–time curve up to infinity; AUC_{last} = area under the plasma concentration–time curve up to the last quantifiable concentration post-dose; CI = confidence interval; C_{max} = maximum plasma concentration; %CV = percent coefficient of variation; hr = hours; n/a = not applicable; T_{max} = time of maximum concentration.

Source: AC220-019 Final Study Report; Table 9.1, 9.2, 9.3, 9.4; Pages 55, 56, 58, 59

Effect of Strong and Moderate CYP3A4 inhibitors:

FDA generally agrees with the Applicant's position that dose reductions are warranted when quizartinib is given concomitantly with a strong CYP3A inhibitor. It is noted that during the first two weeks of maintenance a 33% (instead of 50%) dose reduction from 26.5 to 17.7 mg is recommended. The following dosage modifications are recommended:

- If the dose being administered is 35.4 mg, then the dose is reduced to 17.7 mg in the presence of a strong CYP3A inhibitor.
- If the dose being administered is 26.5 mg, then the dose is reduced to 17.7 mg in the presence of a strong CYP3A inhibitor.
- If the dose being administered is 53 mg, then the dose is reduced to 26.5 mg in the presence of a strong CYP3A inhibitor.

Based on results from Study AC220-015, no clinically significant differences in quizartinib exposure are expected with concomitant use of moderate CYP3A inhibitors.

In Study AC220-015, the effect of fluconazole, a moderate CYP3A inhibitor, or ketoconazole, a strong CYP3A inhibitor, on quizartinib and AC886 PK was evaluated using an open-label, randomized, placebo-controlled, parallel design study. Three groups of 31 healthy subjects each were evaluated for PK interactions:

Group 1	Ketoconazole 200 mg twice daily on Days 1 through 28	Quizartinib 26.5 mg single dose on Day 8
Group 2	Fluconazole 200 mg twice daily on Days 1 through 28	Quizartinib 26.5 mg single dose on Day 8
Group 3	Placebo twice daily on Days 1 through 28	Quizartinib 26.5 mg single dose on Day 8

Repeated coadministration of ketoconazole resulted in a 94% increase in quizartinib geometric mean $AUC_{0-\infty}$ and a 17% increase in quizartinib geometric mean C_{max} . Active metabolite AC886 geometric mean $AUC_{0-\infty}$ decreased by 15%, and its geometric mean C_{max} decreased by 60%. The time to reach maximal AC886 concentration was prolonged indicating that CYP3A4-mediated conversion of quizartinib to AC886 was inhibited. These changes are considered clinically relevant drug-drug interaction at steady-state for both exposure parameters.

Fluconazole coadministration had a lesser impact on quizartinib exposure. There was an 18% increase in quizartinib AUC_{0-504h} and an 11% increase in quizartinib C_{max} . The AC886 AUC_{0-504h} increased by 12% and AC886 C_{max} increased by 2%. The changes in exposure following fluconazole administration were not considered to be clinically significant.

Table 15 and **Table 16** summarize PK in Study AC220-015.

Table 15: PK Parameters of a single dose of 26.5 mg quizartinib with or without concomitant 200 mg ketoconazole BID or 200 mg fluconazole BID

Exposure Parameters	Geometric Mean (%CV)		
	200 mg ketoconazole BID + quizartinib	200 mg fluconazole BID + quizartinib	Quizartinib alone
Quizartinib			
AUC _{0-inf} (ng·hr/mL)	18706 (26)	11549 (34)	9626 (36)
AUC _{0-504h} (ng·hr/mL)	16979 (23)	10959 (32)	9249 (33)
C _{max} (ng/mL)	121 (23)	116 (26)	104 (23)
CL/F (L/hr)	1.42 (26)	2.29 (34)	2.75 (36)
t _{1/2} (hr)	149 (23)	112 (28)	102 (27)
AC886			
AUC _{0-inf} (ng·hr/mL)	2078 (26)	2798 (39)	2446 (60)
AUC _{0-504h} (ng·hr/mL)	1532 (24)	2419 (45)	2160 (61)
C _{max} (ng/mL)	5.27 (28)	13.4 (63)	13.1 (80)
t _{1/2} (hr)	227 (39)	148 (55)	116 (60)

AUC_{0-inf} = area under the plasma concentration–time curve up to infinity; AUC_{0-504h} = area under the plasma concentration–time curve up 504 hours post-dose; BID = twice daily; CI = confidence interval; CL/F = apparent clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; hr = hours; t_{1/2} = half-life.

Source: AC220-015 Final Study Report; Table 13, 15; Page 60, 63

Table 16: Fold change comparison of a single dose of 30 mg quizartinib with or without concomitant 200 mg ketoconazole BID or 200 mg fluconazole BID

Exposure Parameters	Geometric Mean Ratio (90% CI)	
	With 200 mg ketoconazole BID	With 200 mg fluconazole BID
Quizartinib		
AUC _{0-inf}	1.94 (1.69 – 2.23)	1.20 (1.04 – 1.37)
AUC _{0-504h}	1.84 (1.62 – 2.08)	1.18 (1.04 – 1.35)
C _{max}	1.17 (1.05 – 1.30)	1.11 (1.00 – 1.24)
AC886		
AUC _{0-inf}	0.85 (0.68 – 1.05)	1.14 (0.94 – 1.40)
AUC _{0-504h}	0.71 (0.58 – 0.86)	1.12 (0.92 – 1.36)
C _{max}	0.40 (0.31 – 0.51)	1.02 (0.80 – 1.31)

AUC_{0-inf} = area under the plasma concentration–time curve up to infinity; AUC_{0-504h} = area under the plasma concentration–time curve up 504 hours post-dose; BID = twice daily; CI = confidence interval; C_{max} = maximum plasma concentration.

Source: AC220-015 Final Study Report; Table 14, 16; Page 62, 65

Effect of Strong and Moderate CYP3A4 Inducers:

Study AC220-A-U106 determined that quizartinib AUC up to infinity (AUC_{0-inf}) decreased by 90% and C_{max} decreased by 45% following a single 53 mg dose of quizartinib with concomitant use of efavirenz (a moderate CYP3A inducer). The AUC_{0-inf} of AC886 decreased by 96% and the AC886 C_{max} decreased by 68%. The PPK data is inadequate to assess the impact of weak, moderate, or strong CYP3A inducer coadministration on quizartinib or AC886 PK. Due to the potential for decreased effectiveness with lower quizartinib exposure, FDA agrees with the Applicant's position to avoid concomitant use of strong or moderate CYP3A inducers.

Effect of Gastric Acid Reducing Agents:

Study AC220-018 evaluated the effect of a proton pump inhibitor (PPI), lansoprazole, 60 mg on days 1-5 on quizartinib and AC886 PK following a single oral dose of 26.5 mg quizartinib in 62 healthy subjects. Concomitant administration of lansoprazole had no meaningful effect on quizartinib AUC, C_{max} and T_{max} compared to quizartinib alone (**Table 17**). These results suggest that quizartinib can be taken concomitantly with PPIs without adjusting the quizartinib dose.

Table 17: PK Parameters of a single dose of quizartinib with concomitant lansoprazole as compared with fasted state

Exposure Parameters	Geometric Mean (%CV)		Geometric Mean Ratio (90% CI)
	Lansoprazole (PPI) + Quizartinib (n=32)	Quizartinib alone (n=30)	
Quizartinib			
AUC_{0-inf} (ng·hr/mL)	8260 (46)	8660 (37)	0.95 (0.80 – 1.13)
AUC_{last} (ng·hr/mL)	7830 (45)	8330 (35)	0.94 (0.90 – 1.11)
C_{max} (ng/mL)	93 (27)	105 (16)	0.86 (0.78 – 0.95)
AC886			
AUC_{0-inf} (ng·hr/mL)	2330 (55)	2850 (35)	0.82 (0.68 – 0.99)
AUC_{last} (ng·hr/mL)	2090 (63)	2780 (38)	0.75 (0.61 – 0.92)
C_{max} (ng/mL)	16.3 (92)	21.2 (67)	0.77 (0.57 – 1.04)

AUC_{0-inf} = area under the plasma concentration-versus-time curve up to infinity; AUC_{last} = area under the plasma concentration-versus-time curve up to the last quantifiable concentration post-dose; CI = confidence interval; C_{max} = maximum plasma concentration; %CV = percent coefficient of variation; n = number of subjects for whom the corresponding PK parameter was evaluated; PPI = proton pump inhibitor.

Source: AC220-018 Final Study Report; Table 9.1, 9.2, 9.3, 9.4; Page 56, 57, 59, 60

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Primary Reviewer

Team Leader

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{VANFLYTA; quizartinib}

Blaire Osborn, PhD

Ruby Leong, PharmD

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Table 18 – Listing of Clinical Studies Conducted by the Applicant Relevant to this Application

Study Identifier NCT No. Sponsor Status	Study Design	Study Population	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Subjects Enrolled	No. of Centers and Countries
Pivotal study to support efficacy and safety in newly diagnosed <i>FLT3</i>-ITD (+) AML							
AC220-A-U302 NCT 02668653 Sponsor: DSI completed^a	Randomized, double-blind, placebo- controlled	Subjects with newly diagnosed <i>FLT3</i> -ITD (+) AML	Combination therapy: Quizartinib + chemotherapy Induction Phase (up to 2 cycles): Ara-C for 7 days and anthracycline for 3 days, followed by quizartinib 40 mg/day or placebo for 14 days Consolidation Phase (3 options): • HDAC Days 1, 3, and 5 followed by quizartinib 40 mg/day or placebo for 14 days (4 cycles, if tolerated) • Allo-HSCT • HDAC Days 1, 3, and 5 followed by quizartinib 40 mg/day or placebo for 14 days (4 cycles, if tolerated) followed by allo-HSCT Continuation Phase: Quizartinib or placebo for 15 days of 30 mg/day then on Cycle 1, Day 16, 60 mg/day for up to 36 cycles (28 days/cycle)	Primary: OS Secondary: EFS, CR rate, rate of subjects achieving CR with <i>FLT3</i> -ITD MRD negativity, CRc rate, and rate of subjects achieving CRc with <i>FLT3</i> -ITD MRD negativity	Median duration of treatment exposure: Quizartinib 10.71 weeks Placebo 9.50 weeks	Planned: 536 Treated: Quizartinib: 265 Placebo: 268	193 centers across 26 countries

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Study Identifier NCT No. Sponsor Status	Study Design	Study Population	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Subjects Enrolled	No. of Centers and Countries
Supportive studies of efficacy and safety in combination with chemotherapy in newly diagnosed AML							
2689-CL-0005 NCT01390337 Sponsor: Ambit/DSI completed	Open-label, multiple-dose, dose-escalation study	Subjects with newly diagnosed <i>FLT3</i> -ITD (+) or <i>FLT3</i> -ITD (-) AML	Combination therapy: Quizartinib + daunorubicin+ cytarabine (Ara-C) Induction Phase (1 or 2 cycles): 60 mg/m² day daunorubicin IV on Days 1, 2, and 3 200 mg/m²/day Ara-C IV on Days 1 to 7 40 or 60 mg/day quizartinib on Days 4 to 10 or 4 to 17 Consolidation Phase (up to 3 cycles): 3000 mg/m² Ara-C IV every 12 hours two doses daily, on Days 1, 3, and 5, every 21 to 42 days 40 or 60 mg/day quizartinib on Days 4 to 10 or 4 to 17 every 21 to 42 days	Safety and tolerability, recommended Phase 2/3 dose of quizartinib in conjunction with chemotherapy	Overall 23.5 days	Planned: 6 to 52 Treated: 18	5 centers in the US
AC220-A-J102 NCT02834390 Sponsor: DSI completed	Multicenter, open-label	Subjects with newly diagnosed <i>FLT3</i> -ITD (+) or <i>FLT3</i> -ITD (-) AML	Combination therapy: Quizartinib+ chemotherapy Induction Phase (up to 2 cycles): Cytarabine for 7 days (Cycle 1) and 5 days (Cycle 2) and anthracycline for 3 days (Cycle 1) and 2 days (Cycle 2) followed by quizartinib 20 mg/day or 40 mg/day for 14 days Consolidation Phase (4 cycles, if tolerated): Cytarabine on Days 1, 3, and 5 followed by quizartinib 20 mg/day or 40 mg/day for 14 days	Safety and PK of quizartinib with standard induction and consolidation chemotherapy and determine the recommended dose for subsequent phases of development	NA	Planned: 6 to 18 (3 to 9 subjects at each level) Treated: 7	9 centers in Japan

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Study Identifier NCT No. Sponsor Status	Study Design	Study Population	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Subjects Enrolled	No. of Centers and Countries
Supportive studies of efficacy and safety of maintenance monotherapy after HSCT in AML							
2689-CL-0011 NCT01468467 Sponsor: Ambit/DSI completed	Open-label, multiple-dose, dose-escalation	Subjects with <i>FLT3</i> -ITD (+) or <i>FLT3</i> -ITD (-) AML	28-day cycles of quizartinib 40 or 60 mg/day, for up to 24 cycles	Safety and tolerability of quizartinib when given as maintenance therapy after allo-HSCT	Median duration of treatment exposure 574.0 days	Planned: up to 30 Treated: 13 ^b	5 centers in the US
Supportive studies of efficacy and safety in R/R AML							
AC220-007 (QuANTUM- R) NCT02039726 Sponsor: Ambit/DSI completed	Open-label, randomized (2:1), active- controlled (quizartinib versus salvage chemotherapy) study	Subjects with R/R <i>FLT3</i> -ITD (+) AML after induction chemotherapy or HSCT	28-day cycles of quizartinib: Starting dose of 30 mg/day, with dose escalation to 60 mg/day starting on Day 16 If on a strong CYP3A4 inhibitor: starting dose of 20 mg/day, with dose escalation to 30 mg/day starting on Day 16	Primary: OS Secondary: EFS	Median duration of treatment exposure: Quizartinib 97 days	Planned: 363 Treated: Quizartinib: 241 Chemotherapy: 94	94 centers across 19 countries
AC220-002 NCT00989261 Sponsor: Ambit/DSI completed	Open-label, multiple-dose study	Subjects with R/R <i>FLT3</i> -ITD (+) or <i>FLT3</i> - ITD (-) AML	Under Protocol Amendment 3 and earlier versions: 28-day cycles of quizartinib 200 mg/day (oral solution) As of Protocol Amendment 4: 28-day cycles of quizartinib 135 mg/day (males) or 90 mg/day (females) (oral solution)	CRc and CR rate	Median duration of treatment: 135 mg quizartinib QD 9.8 weeks; 90 mg quizartinib QD 10.4 weeks	Planned: 300 Treated: 333	102 centers across 9 countries
2689-CL-2004 NCT01565668 Sponsor: Ambit/ DSI completed	Open-label, randomized, multiple-dose study	Subjects with R/R <i>FLT3</i> -ITD (+) AML after 1 salvage regimen or	28-day cycles of 30 mg/day or 60 mg/day quizartinib (oral solution)	CRc rate and rate of Grade 2 or higher QTcF prolongation	Overall duration of treatment: 70 days	Planned: ~70 Treated: 74	50 centers across 4 countries

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Study Identifier NCT No. Sponsor Status	Study Design	Study Population	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Subjects Enrolled	No. of Centers and Countries
		HSCT					
CP0001 NCT00462761 Sponsor: Ambit/DSI completed	Open-label, multiple-dose, dose-escalation study	Subjects with R/R AML or previously untreated with ineligibility for induction chemotherapy	28-day cycles of quizartinib (oral solution) Intermittent dosing (including 14 days on and 14 days off): 12, 18, 27, 40, 60, 90, 135, 200, 300, or 450 mg/day Continuous dosing (28 days on): 200 mg/day or 300 mg/day	Safety, tolerability and PK of quizartinib	Intermittent dosing (median, days) 12 mg: 14.0 18 mg: 19.5 27 mg: 32.5 40 mg: 24.0 60 mg: 154.0 90 mg: 14.0 135 mg: 28.0 200 mg: 28.5 300 mg: 33.0 450 mg: 28.0 Continuous dosing (days) 200 mg: 30.0 300 mg: 29.5	Planned: 20 to 40 Treated: 76	6 centers across 2 countries
AC220-A-J101 NCT02675478 Sponsor: DSJ completed	Multicenter, open-label, dose-escalation and dose expansion study	Subjects with R/R <i>FLT3</i> -ITD (+) or <i>FLT3</i> - ITD (-) AML	28-day cycles of quizartinib: 20 mg/day (1 × 20 mg tablet PO daily) 30 mg/day (1 × 30 mg tablet PO daily) 60 mg/day (2 × 30 mg tablet PO daily)	Safety and PK	Median overall duration of treatment exposure 95.0 days	Planned: 15 to 21 Treated: 16	8 centers in Japan
AC220-A-J201 NCT02984995 Sponsor: DSJ completed	Multicenter, open-label, two- stage, single-arm study	Subjects with R/R <i>FLT3</i> -ITD (+) AML	28-day cycles of quizartinib Starting dose of 30 mg/day (1 × 30 mg tablet PO daily), with dose escalation to 60 mg/day (2 × 30 mg tablet PO daily) after Day 16	CRc rate	Median overall duration of treatment exposure 66.0 days	Planned: 25 to 41 Treated: 38	34 centers in Japan

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Study Identifier NCT No. Sponsor Status	Study Design	Study Population	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Subjects Enrolled	No. of Centers and Countries
Other studies pertinent of the NDA							
AC220-004 NCT01049893 Sponsor: Ambit/DSI completed	Phase 1, open-label, multiple-dose, dose-escalation study	Subjects with solid tumors	28-day cycle of quizartinib at 90 or 135 mg/day (oral solution) for MTD determination Continued treatment of expanded cohort for 28-day cycles at MTD	Safety and tolerability, PK, PD, and efficacy of quizartinib	Overall (days, minimum, maximum) (15, 56)	Planned: 6 to 45 Treated: 13	2 centers in the US
AC220-006 Sponsor: Ambit completed	Phase 1, open-label, single-dose study	Healthy male subjects	Single dose of quizartinib 60 mg containing approximately 100 µCi [¹⁴ C]-quizartinib (oral solution)	Absorption, metabolism, and excretion of quizartinib, exposure to and elimination of quizartinib metabolites, and safety and tolerability	NA, single dose	Planned: 6 Treated: 6	1 center in the US
AC220-008 Sponsor: Ambit completed	Phase 1, open-label, randomized, single-dose study	Healthy subjects	Single dose of quizartinib 20 mg (Part 1) or 60 mg (Part 2) (oral solution) In each part, subjects were randomly assigned to receive quizartinib with or without food.	Effect of food on PK of quizartinib and AC886, and safety and tolerability	NA, single dose	Planned: 56 Part 1: 8 Part 2: 48 Treated: 58	1 center in the US
AC220-012 Sponsor: Ambit completed	Phase 1, open-label, randomized, placebo-controlled, single-dose study	Healthy subjects	Single dose of quizartinib 60 mg (oral solution) Subjects were randomly assigned to receive quizartinib with placebo oral capsules PO (daily for 20 days), 400 mg ketoconazole (tablets PO daily for 20 days), or 600 mg rifampin (capsules PO daily for 16 days).	Effect of CYP3A inhibition by ketoconazole and CYP3A induction by rifampin on PK of quizartinib and AC886, and safety and tolerability	NA, single dose	Planned: 78 Treated: 77 (83 subjects enrolled, but 6 only received ketoconazole or rifampin and not quizartinib)	1 center in the US

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Study Identifier NCT No. Sponsor Status	Study Design	Study Population	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Subjects Enrolled	No. of Centers and Countries
AC220-014 Sponsor: Ambit completed	Phase 1, open-label, randomized, single-dose, parallel-group study	Healthy subjects	Single dose of quizartinib 60 mg (oral solution); 60 mg (tablets, 2 × 30 mg); 30 mg (tablet, 1 × 30 mg); or 90 mg (tablet, 3 × 30 mg)	Effect of formulation on PK, dose proportionality of PK after tablet administration, effect of food on PK after tablet administration (optional), and safety and tolerability	NA, single dose	Planned: up to 94 Treated: 80	1 center in the US
AC220-016 Sponsor: Ambit/DSI completed	Phase 1, open-label, single-dose, parallel-group study	Healthy subjects and subjects with hepatic impairment	30 mg	Effect of mild or moderate hepatic impairment (as defined by Child-Pugh criteria) on PK of quizartinib and AC886	NA, single dose	Planned: up to 32 Treated: 30	2 centers in the US
AC220-A-U105 NCT04473664 Sponsor: DSI completed	Phase 1, open-label, single-dose, parallel-group study	Subjects with normal hepatic function and subjects with moderate hepatic impairment (as defined by NCI-ODWG criteria)	30 mg	Effect of moderate hepatic impairment (as defined by NCI-ODWG criteria) on quizartinib PK	NA, single dose	Planned: up to 16 Treated: 12	3 centers in the US
AC220-015 Sponsor: Ambit/DSI completed	Phase 1, open-label, randomized, placebo-	Healthy subjects	30 mg	DDI: Effect of ketoconazole and fluconazole (strong CYP3A inhibitor)	NA, single dose	Planned: 102 Treated: 89	2 centers in the US

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Study Identifier NCT No. Sponsor Status	Study Design	Study Population	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Subjects Enrolled	No. of Centers and Countries
	controlled, single-dose study						
AC220-A-U106 NCT04459598 Sponsor: DSI completed	Phase 1, open-label, randomized, parallel-group, DDI study	Healthy subjects	60 mg	DDI: Effect of efavirenz (a moderate CYP3A inducer)	NA, single dose	Planned: up to 32 Treated: 31	1 center in the US
AC220-018 Sponsor: Ambit/DSI completed	Phase 1, open-label, single-dose, randomized, parallel-group study	Healthy subjects	30 mg	DDI: Effect of gastric pH modification by lansoprazole	NA, single dose	Planned: up to 64 Treated: 62 (63 subjects enrolled, but only 1 received lansoprazole and not quizartinib)	1 center in the US
AC220-019 Sponsor: Ambit/DSI completed	Phase 1, open-label, single-dose, randomized, parallel-group study	Healthy subjects	30 mg	Food effect study	NA, single dose	Planned: up to 64 Treated: 64	1 center in the US
AC220-A-U104 NCT04459585 Sponsor: DSI completed	Phase 1, open-label, 2-period (separated by ~96 hours), fixed-sequence DDI study	Healthy subjects	60 mg	Effect of quizartinib on the PK of a P-gp substrate dabigatran etexilate	NA, single dose	Planned: up to 20 Treated: 20	1 center in the US

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Study Identifier NCT No. Sponsor Status	Study Design	Study Population	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Subjects Enrolled	No. of Centers and Countries
AC220-A-U107 NCT04796831 Sponsor: DSI completed	Phase 1, open-label, non-randomized, single-dose study	Healthy subjects	60 mg and single, IV administration of 50 µg ¹⁴ C quizartinib solution for infusion	Absolute oral bioavailability of quizartinib	NA, single dose	Planned: up to 8 Treated: 8	1 center in the UK
AC220-A-U202 NCT03793478 Sponsor: DSI ongoing	Phase 1/2, open-label, multicenter, dose-escalation and dose-expansion study	Pediatric subjects (aged 1 month to <18 years and young adults aged up to 21 years) with R/R <i>FLT3</i> -ITD (+) AML	Combination therapy: Quizartinib + chemotherapy Re-induction (up to 2 cycles): FLA for 5 days, followed by quizartinib on Days 6 to 28 Optional consolidation (1 cycle; 3 options): • High intensity: Ara-C on Days 1 to 4+ Etoposide on Days 1 to 5 + quizartinib on Days 6-28 • Low intensity: Ara-C on Days 1 to 4 and 15 to 18 • Low intensity: quizartinib on Days 1 to 28 Allo-HSCT Continuation: Quizartinib QD for up to 12 cycles	Primary: CRc rate Secondary: CR and CRi rates, durations of CR/Cri/CRc, CR/CRi/CRc rates after completion of re-induction cycle 1, time to relapse, CIR, OS, ES, rate of HSCT	Up to 15 cycles/ 3 years of follow-up	Planned: Up to 65 (9 to 30 in dose escalation; 26 in dose expansion) Treated: 9 as of 08 Sep 2022	Planned at 40 sites in North America and Europe

^a Study AC220-A-U302 has participants remaining on study but since the primary analysis has occurred it is considered completed for regulatory purposes.

^b One subject enrolled in Study 2689-CL-0011 had previously received quizartinib in Study 2689-CL-0005. This subject was not counted twice in terms of number of subjects exposed to quizartinib.

Sources: respective CSRs in eCTD 5.3

The Applicant's Position:

As of 06 May 2022, the quizartinib clinical program consisted of 26 clinical studies conducted by the Applicant, including 13 studies in either newly diagnosed or R/R AML, 1 study in solid tumors, and 12 single-dose studies in healthy subjects and subjects with hepatic impairment. Of the 13 studies in subjects with AML, 10 completed studies are included in the evaluation of the safety and efficacy of quizartinib (3 in newly diagnosed AML, 1 in maintenance monotherapy after HSCT, and 6 in R/R AML). A pediatric study, AC220-A-U202, in R/R *FLT3*-ITD (+) AML (see Section 8.2.9) and a foreign study, AC220-A-A103, in Chinese subjects with newly diagnosed AML are ongoing studies and were excluded from the NDA. Additionally, Study DS3032-A-U105 was excluded as it was a combination study with milademetan and thus, was not using the target quizartinib treatment regimen.

The studies summarized in Table 18 provide the basis for the evaluation of clinical pharmacology, efficacy and safety of quizartinib in the indicated population with Study AC220-A-U302 providing the pivotal data supporting safety and efficacy of quizartinib in the proposed indication. Nine additional studies support the safety of quizartinib and are included in the All AML Pool and an additional 14 studies provide additional information pertinent to this application. The doses of quizartinib administered in these studies ranged from 12 mg to 450 mg QD, with treatment duration of up to 241 weeks.

The FDA's Assessment:

FDA agrees with the Applicant's description of their Clinical Studies Relevant to this Application.

The FDA review was based on data from NDA 216993, relevant published literature, and relevant information in the public domain.

Of note, Study AC220-A-U302 is the pivotal study that was the basis for establishing the safety and efficacy of quizartinib in newly diagnosed *FLT3*-ITD mutated patients. The Applicant submitted a complete dataset for this study, using a data cut date of August 13, 2021, at the time of the initial NDA submission (August 24, 2022). This data set will form the basis for this clinical review.

At the time of the NDA submission, the Applicant submitted complete datasets from 9 additional studies in patients with AML, 1 study in patients with solid tumors, and 12 completed studies in healthy volunteers (Table 18). The additional studies in patients with AML provide supporting evidence of efficacy, particularly Study AC220-007. Data from all of the additional studies were used to supplement the analysis of safety.

The Applicant submitted an updated data set for Study AC220-A-U302, using a data cut date of

04/12/2022, at the time of the 90-day safety update (SN0011; submitted to eCTD on 11/18/2022).

Summaries of data and statistical analyses by the reviewer were performed using JMP 16.0, R Statistical Software (version 3.6.3; R Core Team 2020), and SAS 9.4 (SAS Institute, Inc. Cary, NC). MedDRA Adverse Events Diagnostic Version 3.5 (MAED) (FDA, Silver Spring, MD) was used to look for safety signals.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The clinical development program of quizartinib in AML subjects consists of 13 clinical studies, 10 of which supported efficacy. Five Phase 1 studies and three Phase 2 studies examining the efficacy of quizartinib at different dose levels in subjects with *FLT3*-ITD (+) have been completed. Two large pivotal Phase 3 studies were conducted: Study AC220-007 in patients with R/R *FLT3*-ITD (+) AML and Study AC220-A-U302 in patients with newly diagnosed *FLT3*-ITD (+) AML.

The efficacy of quizartinib in the treatment of patients with newly diagnosed *FLT3*-ITD (+) AML is based on the data from a single pivotal Phase 3 study AC220-A-U302 (N = 539) in newly diagnosed AML subjects, with supplemental data from the three Phase 1 studies, 2689-CL-0005 (N = 18; newly diagnosed AML), AC220-A-J102 (N = 7; newly diagnosed AML), and 2689-CL-0011 (N = 13; post-HSCT AML), for the safety and preliminary efficacy of quizartinib in this indication.

In addition to the studies mentioned above, the results from Studies AC220-007, AC220-002, 2689-CL-2004, CP0001, AC220-A-J101, and AC220-A-J201 provide additional supporting data pertinent to the use of quizartinib in patients with AML and are described in the sections below.

8.1.1. Pivotal Study in Newly Diagnosed *FLT3*-ITD (+) AML - Study AC220-A-U302 (QuANTUM-First)

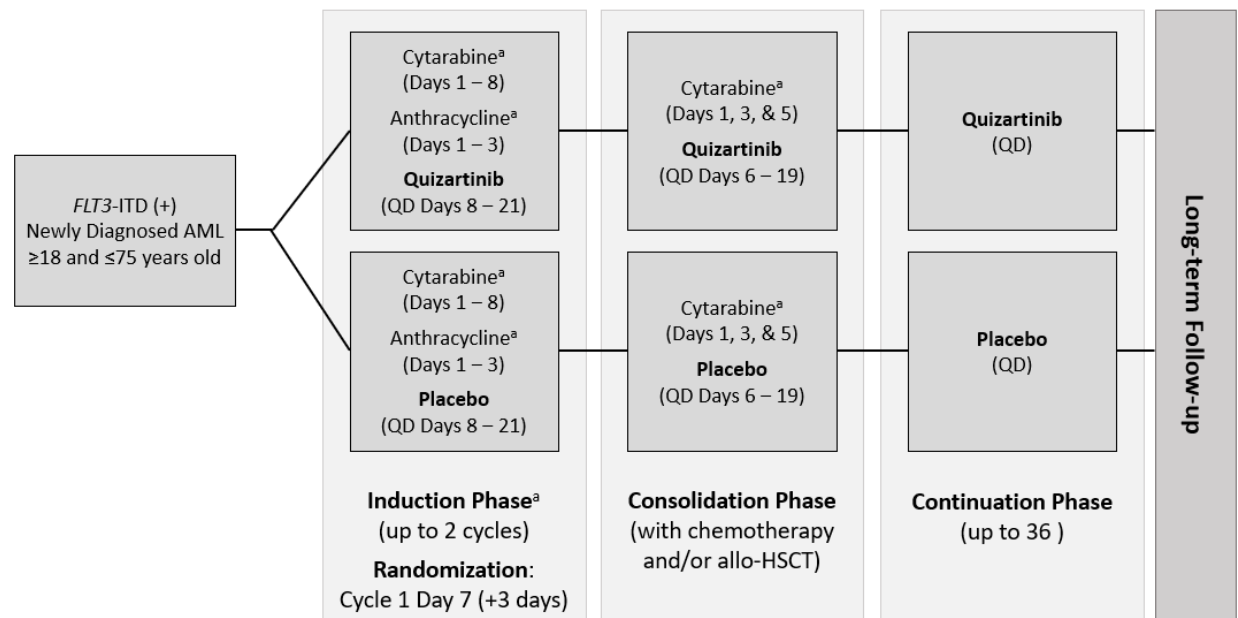
The primary evaluation of efficacy of quizartinib in the treatment of patients with newly diagnosed *FLT3*-ITD (+) AML is based on the data from the single pivotal Phase 3 study, AC220-A-U302 (N=539).

Trial Design

The Applicant's Description:

Study AC220-A-U302 was a Phase 3, randomized, double-blind, placebo-controlled, global study to compare the effect of quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles) on the primary endpoint of OS in subjects 18 to 75 years of age with newly diagnosed *FLT3*-ITD (+) AML. The study design from the Screening Visit through the Treatment Period is shown in Figure 1. The Long-term Follow-up Phase was to begin upon completion of 36 cycles of study drug (quizartinib/placebo) in the Continuation Phase or permanent discontinuation of study drug in any phase.

Figure 1 – Study Design Schematic (Screening to Treatment Period) for Study AC220-A-U302



^a During Induction Cycle 2 investigators may choose to administer the “7+3” chemotherapy regimen, or the “5+2” chemotherapy regimen, and quizartinib/placebo will therefore start on Day 8 or Day 6, respectively.

Following the disclosure within the RATIFY study of most relapses occurring within 24 months, the duration of the Continuation Phase was increased to 36 cycles. Patients were appropriately informed of available treatment options.

Trial Location: This study was conducted at 193 study sites across 26 countries in North America, Europe, and Asia/Other Regions.

Treatment assignment: 539 subjects were enrolled and randomized to one of the two treatment arms (quizartinib arm or placebo arm) in a 1:1 ratio through a stratified permuted block randomization procedure by an Interactive Voice/Web Response System (IXRS). Randomization was stratified by region (North America, Europe, Asia/Other Regions), age (<60 years old, ≥60 years old), and WBC count at the time of diagnosis of AML (<40×10⁹/L, ≥40×10⁹/L).

Blinding: This is a double-blind placebo-controlled study. Neither the subjects nor any of the investigators, Applicant, or contract research organizations (CROs) were aware of the quizartinib/placebo treatments received. During the course of the prior NDA review, 5 patients were unblinded at the request of the FDA, all of whom received quizartinib.

Study treatment: During the first induction cycle, patients received a standard 7+3 induction regimen with cytarabine 100 mg/m²/day (200 mg/m²/day allowed if institutional or local standard) by continuous intravenous (IV) infusion from Days 1 to 8 and anthracycline (daunorubicin 60 mg/m²/day or idarubicin 12 mg/m²/day) on Days 1, 2, and 3. Study drug (quizartinib 40 mg or placebo) was to be administered QD starting on Day 8 (at the end of the cytarabine infusion) for 14 consecutive days. Subjects could receive either a second cycle of identical induction chemotherapy or a five-day infusion of cytarabine and 2 daily doses of daunorubicin or idarubicin (5 + 2) according to institutional routine practice followed by 14 days of quizartinib 40 mg (or placebo) QD.

Patients achieving CR or CRi at the end of induction could proceed to consolidation, consisting of (1) treatment with HDAC (3.0 g/m² IV infusion every 12 hours on Days 1, 3, and 5, reduced to 1.5 g/m² for patients aged ≥60 years) followed by quizartinib (40 mg/day) or placebo for 14 days starting on Day 6 of each cycle (up to 4 cycles), or (2) allo-HSCT only (between the end of induction to within 3 months of starting continuation), or (3) treatment with HDAC followed by quizartinib (40 mg/day) or placebo followed by allo-HSCT.

Continuation monotherapy with quizartinib/placebo was to begin after induction and consolidation therapy upon blood count recovery. In the Continuation Phase, the dose of quizartinib/placebo started at 30 mg orally QD and increased to 60 mg/day on Cycle 1 Day 16 if the average QTcF of the triplicate ECG was ≤450 ms. Study drug continued for up to 36 cycles or until relapse, start of non-protocol-specified AML treatment, death, unacceptable toxicity, or study closure, whichever occurred first.

For subjects concomitantly receiving a strong CYP3A4 inhibitor, the dose of quizartinib was to be reduced from 40 to 20 mg QD during the Induction and Consolidation Phases and from 30 to 20 mg QD or from 60 to 30 mg QD during the Continuation Phase.

Duration of treatment: Total duration of treatment with study drug was up to 42 cycles (inclusive of the Induction, Consolidation, and Continuation Phases). All subjects who completed 36 cycles of quizartinib/placebo in the Continuation Phase or permanently discontinued study drug in any phase entered the Long-term Follow-up Phase.

Choice of the control arm: At the time of initiation of the global, multicenter study AC220-A-U302 (Sep 2016), chemotherapy with or without allo-HSCT was the standard for the treatment of AML. Hence, placebo along with standard combination chemotherapy was used as the comparator arm in the study.

In 2017, the multikinase Type I FLT3 inhibitor midostaurin was approved in the US for the treatment of newly diagnosed *FLT3*-TKD (+) or *FLT3*-ITD (+) AML based on the results of the RATIFY study ([Stone, 2017](#)). Approval status and accessibility varied globally following the US approval with limited availability of midostaurin in the European Union and Asia/Pacific regions, from which the majority of subjects were enrolled. At the time of this approval, screening/enrollment of Study AC220-A-U302 was well underway. As such, modifying the comparator from placebo to midostaurin in this global study would have significantly delayed critical results for an urgently needed treatment option for patients with newly diagnosed *FLT3*-ITD (+) AML. In this context, it is important to note that nonclinical and prior clinical data suggested that the second-generation, highly selective, Type II FLT3 inhibitor quizartinib may result in improved clinical activity for patients with newly diagnosed *FLT3*-ITD (+) AML ([Cortes, 2019](#); Aikawa, 2020) and Study AC220-A-U302 was conducted to clinically test this hypothesis in patients up to 75 years of age.

The Applicant consulted the scientific steering committee, medical experts in AML, and ethicists, who concluded that equipoise was maintained and the study should continue as a placebo-controlled study. The recommendation was based on the assessment that newly diagnosed *FLT3*-ITD (+) AML remains a poor prognostic and aggressive disease with a high unmet medical need, and that advancing a next-generation FLT3 inhibitor would provide patients the opportunity to gain access to additional treatment options. Given the poor prognosis of patients with *FLT3*-ITD (+) AML, the high risk of relapse in this population, and the limited global availability of midostaurin in key regions, no changes in the control arm of the Study AC220-A-U302 were implemented.

Dose modification/dose discontinuation: Guidelines for dose delay or dose modification and treatment discontinuation in response to specific AEs were specified in the study protocol. Study drug dose reduction or dose interruption were to be implemented for QTcF prolongation, other nonhematologic toxicities, myelosuppression, and concomitant administration of a strong CYP3A4 inhibitor. The minimum dose of study drug was not to be lower than 30 mg/day in any phase of the study in general and not lower than 20 mg/day for subjects receiving strong CYP3A4 inhibitors. If study drug was interrupted, missed doses were not to be made up.

Concomitant medications: Subjects were not allowed to receive concomitant chemotherapy, immunotherapy, radiotherapy, transplant, or any ancillary therapy for AML that was not specified in the protocol or that was considered to be investigational (ie, used for nonapproved indication[s] and in the context of a research investigation) while on study drug.

Medications associated with QT/QTc prolongation were prohibited. Exceptions were made for antibiotics, antivirals, and antifungals that were used as standard of care for the prevention or treatment of infections or if the investigator believed that beginning therapy with a potentially QTc-prolonging medication (such as antiemetic) was vital to an individual subject's care while on study. In that case, additional ECG monitoring was to be performed at the commencement

of such a medication or from when there was an increase in its dosage. Other drugs prohibited were strong or moderate CYP3A4 inducers.

Strong CYP3A4 inhibitors were to be avoided, if possible, but if necessary for subject care, strong CYP3A4 inhibitors were allowed with a corresponding dose reduction of study drug. There were no restrictions for moderate or weak CYP3A4 inhibitors.

Diagnostic Criteria: Subjects were enrolled based on *FLT3*-ITD (+) status as determined centrally using the (b) (4) *FLT3*-ITD clinical trial assay (CTA) for the determination of *FLT3*-ITD mutation status from bone marrow and/or blood samples. This CTA is a molecular assay that employs polymerase chain reaction (PCR) and capillary electrophoresis technology. The Applicant also collaborated with Invivoscribe Inc., to develop a PCR and capillary electrophoresis-based molecular assay for detecting *FLT3*-ITD mutations as an in vitro diagnostic assay for a companion diagnostic.

Inclusion/Exclusion criteria: The study enrolled subjects with newly diagnosed *FLT3*-ITD (+) AML.

Key inclusion criteria:

- Newly diagnosed, morphologically documented primary AML or AML secondary to myelodysplastic syndrome or a myeloproliferative neoplasm, based on the World Health Organization (WHO) 2008 classification (at screening)
- ≥ 18 years or the minimum legal adult age (whichever was greater) and ≤ 75 years (at screening) and receiving standard induction chemotherapy regimen as per protocol
- Presence of *FLT3*-ITD activating mutation in bone marrow ($\geq 3\%$ *FLT3*-ITD/total *FLT3*)
- Eastern Cooperative Oncology Group (ECOG) PS 0 to 2 (at the time the subject signed his/her first informed consent form)
- Adequate renal function (creatinine clearance > 50 mL/min), adequate hepatic function (total serum bilirubin $\leq 1.5 \times$ upper limit of normal [ULN]; serum alkaline phosphatase [ALP], aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\leq 2.5 \times$ ULN), and serum electrolytes within the institution's normal limits at the time of randomization (Day 7 of induction chemotherapy)

Key exclusion criteria:

- Diagnosis of acute promyelocytic leukemia (APL), French-American-British (FAB) classification M3 or WHO classification of APL with translocation, t(15;17)(q22;q12), or *BCR-ABL*-positive leukemia (ie, chronic myelogenous leukemia in blast crisis)
- Diagnosis of AML secondary to prior chemotherapy or radiotherapy for other neoplasms
- History of known central nervous system (CNS) leukemia, including cerebrospinal fluid positive for AML blasts; lumbar puncture was recommended for subjects with symptoms of CNS leukemia to rule out extramedullary CNS involvement
- QTcF > 450 ms or diagnosis of or suspicion of long QT syndrome (LQTS; including family history of LQTS); or uncontrolled or significant cardiovascular disease (eg, history of

congestive heart failure [CHF], uncontrolled hypertension, and history of clinically relevant ventricular arrhythmia)

Study assessments: During the Induction Phase, a bone marrow aspirate specimen and blood samples for hematology (complete blood count [CBC]) were collected on Day 21 (or up to Day 28) of Cycle 1 and Cycle 2. The investigator assessed the subject's response based on the local laboratory results using the modified International Working Group response criteria for AML (Cheson, 2003).

Starting on Day 21, blood samples for hematology (CBC) were also collected at least weekly to assess count recovery. If an accurate assessment of response could not be made based on the Day 21 bone marrow aspirate, then the bone marrow aspirate was to be repeated upon count recovery or Day 56 (± 3 days), whichever occurred first.

CR was defined as an absolute neutrophil count (ANC) of ≥ 1000 cells/mm³, a platelet count of $\geq 100,000$ cells/mm³, and bone marrow with $< 5\%$ blasts. CRi was defined as meeting all the criteria for CR with incomplete hematological recovery with residual neutropenia (ANC < 1000 cells/mm³) and/or platelet count $< 100,000$ cells/mm³. There should be no blasts with Auer rods or the presence of extramedullary disease (eg, CNS or soft tissue involvement).

During the Continuation Phase, a bone marrow aspirate specimen for relapse assessment and blood samples for hematology (CBC) were collected, and physical examination (including an evaluation for signs and symptoms of relapse) was performed at the visits specified in the study protocol. If relapse was suspected based on abnormal peripheral smears or development of cytopenias at any time during the Continuation Phase, a bone marrow aspirate specimen was to be collected for analysis of response/remission.

During the study treatment, subjects were monitored regularly in all phases for toxicities, including triplicate ECG for central reading, laboratory tests, electrolytes, and hematology monitoring. Dose modifications were required if the subject experienced QTcF prolongation based on study-supplied ECG machine read, other nonhematologic toxicities, or myelosuppression or had received concomitant strong CYP3A4 inhibitors during treatment.

The Long-term Follow-up Phase began upon completion of 36 cycles of study drug in the Continuation Phase or upon permanent discontinuation of study drug in any phase. During this phase, subjects were regularly assessed for relapse and survival status.

The FDA's Assessment:

FDA agrees with the Applicant's description of the trial design of the phase 3 Study AC220-A-U302. However, we note that there are typos in the study schema and text above describing the duration of continuous cytarabine infusion. The duration of continuous cytarabine was 7 days not 8 as noted in the text and in the study diagram above. Treatment with quizartinib or placebo would begin on day 8 after the completion of the cytarabine infusion.

FDA notes that the Applicant's definition of CR response is different from that specified in FDA's Guidance for Industry *Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment*, which specifies ANC > 1000 cells/mm³ and platelets > 100,000 cells/mm³ (as opposed to ≥ the respective cutoffs).

Study Endpoints

The Applicant's Description:

The primary endpoint for Study AC220-A-U302 was OS defined as the time from randomization until death from any cause. Subjects alive or lost to follow-up at the time of analysis were censored at the date when they were last known to be alive. OS is the most reliable cancer endpoint since it is precise and easy to measure, documented by the date of death, and bias is not a factor in endpoint measurement ([FDA, 2020](#)).

Secondary endpoints included EFS, CR rate, percentage of subjects achieving CR with *FLT3*-ITD MRD negativity, composite complete remission (CRc) rate, and rate of subjects achieving CRc with *FLT3*-ITD MRD negativity.

- EFS was defined as the time from randomization until the date of the earliest of any of the following: refractory disease or treatment failure as determined at the end of the Induction Phase (ITF), relapse, or death from any cause. In the clinical study protocol, ITF was defined as failure to achieve CR or CRi by the end of the Induction Phase. The assessment of response was allowed up to Day 56 from the start of the last cycle of induction. The Applicant incorporated the Agency's feedback to define ITF as failure to achieve CR within 42 days of the start of the last cycle of induction chemotherapy for the primary analysis of EFS and the original protocol definition of EFS was maintained as a sensitivity analysis.
- CR and CRc rates were the percentages of subjects achieving CR or CRc after induction, respectively.
- Percentages of subjects achieving CR with *FLT3*-ITD MRD negativity or CRc with *FLT3*-ITD MRD negativity following induction therapy. MRD is the presence of a small number of leukemic cells in the bone marrow or blood of subjects with AML below the level of detection using conventional morphologic assessment. The *FLT3*-ITD MRD assessment by next-generation sequencing was used to detect and quantify residual *FLT3*-ITD mutations present in a fraction of remaining leukemic cells in bone marrow or blood and assessments were made using a cutoff of 1×10^{-4} (1 in 10,000 cells).

Exploratory endpoints considered important to characterize overall efficacy were relapse-free survival (RFS), duration of CR, and cumulative incidence of relapse (CIR).

- RFS for subjects who achieved CR or CRi in the Induction Phase was defined as the time from randomization until documented relapse or death from any cause, whichever came first.
- Duration of CR was defined as the time from the first documented CR until the date of documented relapse or death from any cause, whichever came first.
- CIR (post hoc analysis) was defined as the cumulative incidence of relapse from randomization in all subjects who achieved a CR during the Induction Phase.

The FDA's Assessment:

FDA agrees with the Applicant's description of the study endpoints.

Statistical Analysis Plan (SAP) and Amendments

The Applicant's Description:

The primary analysis for OS was conducted after 287 OS events were observed with a minimum of 24 months of follow-up since the time of the last subject randomized. Sensitivity and supplementary analyses to examine the robustness of the OS results were conducted as appropriate. The comparison of the distribution of OS between treatments arms was made using a stratified log-rank test performed at a 2-sided $\alpha = 0.05$ level with the three stratification factors used for randomization. The median OS was calculated based on Kaplan-Meier estimates and the corresponding 95% confidence interval (CI) was calculated using the method provided by Brookmeyer and Crowley (Brookmeyer, 1982). The hazard ratio (HR) with 95% CI for treatment group was estimated using stratified Cox proportional hazards (PH) models, with the 3 stratification factors used for randomization per IXRS.

EFS was analyzed using the stratified log-rank test and stratified Cox PH model. Subjects who had no EFS events were censored at the last response assessment date. The primary analysis for EFS was based on the response assessment by Independent Review Committee (IRC) with ITF defined as not achieving response of CR, using a 42-day window from the start of the last cycle in induction for CR evaluation. The ITF definition in the original protocol considering CR and CRi by the end of induction (ie, within a 56-day window) was used in the sensitivity and supplementary analysis of EFS. Further details on these analyses are provided in the SAP.

Analysis sets: The Intent-to-treat (ITT) Analysis Set included all subjects who were randomized. The Safety Analysis Set included all subjects who received at least one dose of quizartinib/placebo.

Method for handling missing data: In general, missing or dropout data were not imputed for the purpose of data analysis, unless otherwise specified. In the case where AE and prior/concomitant medication start dates and/or stop dates were partial or missing, refer to Section 8.2.3 of the SAP for detailed imputation rules (Appendix 16.1.9). The censoring rules

for OS and EFS are detailed in the SAP.

Statistical methods for multiplicity: To control for the family-wise type I error rate for primary and secondary efficacy endpoints, a serial hierarchically ordered gatekeeping strategy was employed. The primary assessment of OS in the ITT Analysis Set was evaluated first, and if significant at a 2-sided alpha of 0.05, a statistical evaluation of EFS in the ITT Analysis Set was to be performed. After EFS evaluation, the order of other secondary endpoints to be tested was CR rate, rate of subjects achieving CR with *FLT3*-ITD MRD negativity, CRc rate, and rate of subjects achieving CRc with *FLT3*-ITD MRD negativity. Testing was to be stopped once one test in the sequence failed to be statistically significant. No interim analysis was planned or performed.

Planned subgroup analyses: Predefined subgroup analyses for OS based on demographics (age, sex, race, and geographical region) and baseline disease characteristics (baseline ECOG PS, WBC count at the time of diagnosis, choice of anthracycline used during the Induction Phase, AML cytogenetic risk score, *FLT3*-ITD VAF at randomization, and *NPM1* mutation status) were conducted.

The subgroup analyses of OS were conducted in a similar manner as the primary analyses of OS. However, the analyses were performed without stratification and no p-values were reported. Forest plots presenting the HRs and 2-sided 95% CIs by subgroup categories were provided on a single plot.

SAP amendments: There was one revision made to the initial SAP as summarized in Table 19. Version 2.0 incorporated cumulative changes made to the clinical study protocol up to and including version 7.0 (see Table 20) and was finalized before the database lock occurred.

Table 19 – SAP and Amendments

Version	Date	Key Revisions
1.0	01 Mar 2018	Initial version
2.0	11 Oct 2021	Update following Study Protocol version 7.0

The FDA's Assessment:

FDA agrees with the Applicant's description of the SAP. Note that EFS was the original primary endpoint for this trial, as discussed in the Protocol Amendments section below. The protocol was updated to utilize OS as an additional primary endpoint on 07 Apr 2020. The protocol was again updated on 28 Oct 2020 to make OS the sole primary endpoint. In addition, FDA conducted sensitivity analyses of OS by HSCT status and other subgroups in order to evaluate the effect of HSCT and/or other factors on OS. Please refer to Section 8.1.2 Study Results.

Protocol Amendments

The Applicant's Description:

The clinical Study Protocol AC220-A-U302 was revised 6 times over the course of study conduct as summarized in Table 20.

Table 20 – AC220-A-U302 Clinical Study Protocol and Amendments

Version	Date	Key Revisions
1.0	17 Dec 2015	Initial version
2.0	06 Apr 2017	Minor revision
3.0	20 Nov 2018	Extension of Continuation Phase from 12 to up to 36 cycles
4.0	26 Jun 2019	MRD test and definitions specified. Revision of risk mitigation measures to minimize cardiac toxicity: electrolyte monitoring and management of abnormalities, permanent discontinuation for recurrent QTcF >500 ms.
5.0	07 Apr 2020	Changed primary endpoint from EFS to two primary endpoints of EFS and OS. Analysis set to occur after 410 EFS events and 287 OS events for EFS and OS, respectively. Minimum follow-up for OS defined as 24 months.
6.0	28 Oct 2020	Changed primary endpoint to OS and moved EFS to secondary endpoints. Timing of primary analysis based on number of OS events and minimum follow-up of 24 months as previously defined. Hierarchical testing procedure including EFS was added to control FWER. Updated definition of EFS to be consistent with FDA AML Guidance issued Aug 2020.
7.0	26 May 2021	Changed statistical testing hierarchy and defined IRC assessment to be based on EFS definition consistent with FDA AML Guidance issued Aug 2020.

The FDA's Assessment:

We agree with the Applicant's description of protocol amendments.

8.1.2. Study Results – Study AC220-A-U302

Compliance with Good Clinical Practices

The Applicant's Position:

All studies were conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s). All studies were conducted in accordance with the Applicant's standard operating procedures, which comply with the principles of GCP. All studies were conducted with the approval of Ethics Committees

or Institutional Review Boards. Informed consent was obtained for all subjects. Where required, regulatory approval was obtained from the relevant health authority.

The FDA's Assessment:

We confirm the Applicant's position.

Financial Disclosure

Data:

Financial disclosure information was provided for clinical investigators involved in the covered clinical Study AC220-A-U302. The summary of financial disclosure information is provided in Appendix 19.2. There were 0 clinical investigators with disclosable financial interests.

The Applicant's Position:

No concerns were raised regarding the overall integrity of the study data.

The FDA's Assessment:

We confirm the Applicant's position.

Subject Disposition

Data:

Overall, 3468 subjects were screened for participation in the study, of whom 2929 subjects were screen failures. Of the screen failures, 2556 subjects were determined to be *FLT3*-ITD (–) per central testing, some of which did not satisfy other eligibility criteria, while 2358 (80.5%) were listed on the CRF as screen failures due to a negative results for *FLT3*-ITD status. In total, 539 subjects comprising the ITT Analysis Set were subsequently randomized into the study (268 subjects in quizartinib arm and 271 subjects in placebo arm). Six subjects (3 in each arm) did not receive any study treatment, hence, the safety population comprised of 533 subjects (265 subjects in quizartinib arm and 268 subjects in placebo arm), all of which entered the Induction Phase.

Table 21: Subject Disposition in Study AC220-A-U302

Evaluation	Quizartinib (N = 268) n (%)	Placebo (N = 271) n (%)	Total (N = 539) n (%)
Randomized	268 (100.0)	271 (100.0)	539 (100.0)
Randomized but not treated	3 (1.1)	3 (1.1)	6 (1.1)
Subject status ^a			

NDA Multi-disciplinary Review and Evaluation {NDA 216993}
{VANFLYTA; quizartinib}

Evaluation	Quizartinib (N = 268) n (%)	Placebo (N = 271) n (%)	Total (N = 539) n (%)
Entered Induction Phase	265 (100.0)	268 (100.0)	533 (100.0)
Received a second cycle of induction therapy	54 (20.4)	56 (20.9)	110 (20.6)
Discontinued study drug during Induction Phase	92 (34.7)	93 (34.7)	185 (34.7)
Entered Consolidation Phase	173 (65.3)	175 (65.3)	348 (65.3)
Study drug plus chemotherapy	75 (28.3)	86 (32.1)	161 (30.2)
HSCT only	6 (2.3)	6 (2.2)	12 (2.3)
Study drug plus chemotherapy followed by HSCT	92 (34.7)	83 (31.0)	175 (32.8)
Discontinued study drug during Consolidation Phase	57 (21.5)	83 (31.0)	140 (26.3)
Entered Continuation Phase	116 (43.8)	92 (34.3)	208 (39.0)
Completed Continuation Phase	21 (7.9)	23 (8.6)	44 (8.3)
Discontinued study drug during Continuation Phase	63 (23.8)	43 (16.0)	106 (19.9)
Ongoing in Continuation Phase	32 (12.1)	26 (9.7)	58 (10.9)
Entered Long-term Follow-up Phase	225 (84.9)	239 (89.2)	464 (87.1)
Discontinued from study drug during any phase, due to the following:	212 (80.0)	219 (81.7)	431 (80.9)
Refractory disease	41 (15.5)	70 (26.1)	111 (20.8)
Relapse	44 (16.6)	65 (24.3)	109 (20.5)
Adverse Event	58 (21.9)	23 (8.6)	81 (15.2)
Subject decision to stop study drug	25 (9.4)	23 (8.6)	48 (9.0)
Investigator decision	10 (3.8)	7 (2.6)	17 (3.2)
Other	16 (6.0)	11 (4.1)	27 (5.1)
Nonprotocol-specified AML therapy	12 (4.5)	6 (2.2)	18 (3.4)
Investigator decision	10 (3.8)	7 (2.6)	17 (3.2)
Failure to meet continuation criteria	5 (1.9)	12 (4.5)	17 (3.2)
Lost to follow-up	1 (0.4)	0	1 (0.2)

Evaluation	Quizartinib (N = 268) n (%)	Placebo (N = 271) n (%)	Total (N = 539) n (%)
Pregnancy	0	1 (0.4)	1 (0.2)
Death	0	1 (0.4)	1 (0.2)
Subjects having protocol-specified HSCT	102 (38.5)	91 (34.0)	193 (36.2)
Study status^b			
Ongoing with study drug	32 (11.9)	26 (9.6)	58 (10.8)
Alive, continuing in long-term follow-up	88 (32.8)	77 (28.4)	165 (30.6)
Discontinued from study	148 (55.2)	168 (62.0)	316 (58.6)
Death	133 (49.6)	158 (58.3)	291 (54.0)
Lost to follow-up	2 (0.7)	1 (0.4)	3 (0.6)
Withdrawal of consent	13 (4.9)	9 (3.3)	22 (4.1)

^a Percentages are based on the number of subjects in the Safety Analysis Set.

^b Percentages are based on the number of subjects in the ITT Analysis Set at the time of the data cutoff date.

Note: Percentages are based on the number of subjects randomized unless otherwise noted.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Table 14.1.1.1.1

The Applicant's Position:

Similar percentages of subjects in the quizartinib and placebo arm received 2 cycles of induction, discontinued study drug during Induction and Consolidation Phase. However, more subjects entered the Continuation Phase in the quizartinib arm compared to placebo. Also, similar percentages of subjects received protocol-specified HSCT.

While similar percentages of subjects discontinued study drug over all phases, there are notable differences in rates between the quizartinib and placebo arm due to refractory disease or relapse, with fewer such events on the quizartinib arm, while discontinuation of study drug due to AEs was more frequent in the quizartinib arm. Overall, there were a higher percentage of subjects alive and continuing in long-term follow-up and fewer study discontinuations, mainly due to fewer subjects dying, on the quizartinib arm compared to the placebo arm. These differences between arms are reflective of a treatment effect observed for quizartinib.

The FDA's Assessment:

FDA agrees with the Applicant's summary of subject disposition as of the data cutoff date of August 13, 2021. We note that the more patients discontinued study treatment due to AE on the quizartinib arm (21.6% quizartinib versus 8.6% placebo). However, discontinuation of study drug due to refractory disease or disease relapse was higher on the placebo arm (32% quizartinib versus 50% placebo). Since discontinuation of study drug due to disease

relapsed/refractory disease portends a poor outcome, it is not surprising that more quizartinib patients remained on study at the time of data lock (45% quizartinib versus 38% placebo) and that more patients had discontinued study due to death on the placebo arm (50% quizartinib versus 58% placebo). Lastly, consistent with remaining eligible for later stages of treatment, more quizartinib patients started the continuation phase than placebo treated patients (44% quizartinib versus 34% placebo).

Protocol Violations/Deviations

Data:

Table 22 – Major Protocol Deviations by Category (in ≥1% of Subjects in Either Treatment Arm) in Study AC220-A-U302 (ITT Analysis Set)

Category	Quizartinib (N = 268) n (%)	Placebo (N = 271) n (%)	Total (N = 539) n (%)
Subjects with any major deviation	141 (52.6)	136 (50.2)	277 (51.4)
Informed consent	17 (6.3)	11 (4.1)	28 (5.2)
Study-specific procedure(s) performed before informed consent obtained	4 (1.5)	2 (0.7)	6 (1.1)
Administered consent does not include updates or information required and approved by IRB/EC	7 (2.6)	7 (2.6)	14 (2.6)
Failure to obtain informed consent	3 (1.1)	2 (0.7)	5 (0.9)
Investigational product	47 (17.5)	36 (13.3)	83 (5.4)
IP (starting the incorrect dose as per protocol in any phase)	7 (2.6)	5 (1.8)	12 (2.2)
Coadministration of a strong CYP3A4 inhibitor and IP without IP dose reduction for >2 days	13 (4.9)	13 (4.8)	26 (4.8)
IP was not dose adjusted with QTcF prolongation per protocol	4 (1.5)	3 (1.1)	7 (1.3)
IP was not dose reduced per protocol requirements	5 (1.9)	4 (1.5)	9 (1.7)
IP was not dispensed or administered per protocol	9 (3.4)	7 (2.6)	16 (3.0)
Chemotherapy was not administered per protocol	9 (3.4)	7 (2.6)	16 (3.0)
Safety	35 (13.1)	41 (15.1)	76 (14.1)
SAE not reported within 24 hours	35 (13.1)	41 (15.1)	76 (14.1)

Category	Quizartinib (N = 268) n (%)	Placebo (N = 271) n (%)	Total (N = 539) n (%)
Study conduct/procedures	91 (34.0)	82 (30.3)	173 (32.1)
Subject did not meet inclusion criteria but was enrolled in the study	29 (10.8)	23 (8.5)	52 (9.6)
Subject met exclusion criteria and enrolled in the study	5 (1.9)	4 (1.5)	9 (1.7)
Subject did not achieve CR or CRi after the Induction Phase but entered the Consolidation Phase	5 (1.9)	4 (1.5)	9 (1.7)
(Continuation Phase) Subject failed to meet inclusion criteria but was enrolled in the Continuation Phase	4 (1.5)	2 (0.7)	6 (1.1)
Visits, assessments, or procedures not performed per protocol post-screening	12 (4.5)	6 (2.2)	18 (3.3)
Visits, assessments, or procedures not performed per protocol	61 (22.8)	52 (19.2)	113 (21.0)

Source: AC220-A-U302 CSR Table 7.11

The Applicant's Position:

Protocol deviations occurred at similar rates in both study arms and are not likely to affect the study results or the conclusions of the primary analysis.

The FDA's Assessment:

We agree with the Applicant's assessment. The rate of protocol violations was similar on both arms. Since the trial was randomized and double blinded and the rate of violations was similar on both arms, it is unlikely that protocol violations introduced bias into the study results. Therefore, all patients, including those with important protocol deviations, were included in our analysis of efficacy endpoints.

Table of Demographic Characteristics

Data:

Table 23 – Demographic and Baseline Characteristics in Study AC220-A-U302 (ITT Analysis Set)

Parameter	Quizartinib (N = 268)	Placebo (N = 271)	Total (N = 539)
Age (years)^a			
Mean (SD)	53.6 (13.07)	54.3 (12.81)	54.0 (12.93)

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Parameter	Quizartinib (N = 268)	Placebo (N = 271)	Total (N = 539)
Median (min, max)	56.0 (23, 75)	56.0 (20, 75)	56.0 (20, 75)
Age, n (%)			
<60 years	161 (60.1)	162 (59.8)	323 (59.9)
≥60, <65 years	37 (13.8)	44 (16.2)	81 (15.0)
≥65 years	70 (26.1)	65 (24.0)	135 (25.0)
Sex, n (%)			
Male	124 (46.3)	121 (44.6)	245 (45.5)
Female	144 (53.7)	150 (55.4)	294 (54.5)
Race, n (%)			
Asian	80 (29.9)	78 (28.8)	158 (29.3)
Black or African American	2 (0.7)	5 (1.8)	7 (1.3)
American Indian or Alaska Native	0	1 (0.4)	1 (0.2)
Native Hawaiian/Pacific Islander	0	0	0
White	159 (59.3)	163 (60.1)	322 (59.7)
Other	27 (10.1)	24 (8.9)	51 (9.5)
Ethnicity, n (%)			
Hispanic/Latino	7 (2.6)	15 (5.5)	22 (4.1)
Non-Hispanic/Non-Latino	236 (88.1)	234 (86.3)	470 (87.2)
Not reported	25 (9.3)	22 (8.1)	47 (8.7)
Region, n (%)			
North America	16 (6.0)	18 (6.6)	34 (6.3)
US	8 (3.0)	13 (4.8)	21 (3.9)
Canada	8 (3.0)	5 (1.8)	13 (2.4)
Europe	163 (60.8)	163 (60.1)	326 (60.5)
Asia/Other regions	89 (33.2)	90 (33.2)	179 (33.2)
ECOG PS, n (%)			
0	87 (32.5)	98 (36.2)	185 (34.3)
1	134 (50.0)	136 (50.2)	270 (50.1)
2	47 (17.5)	36 (13.3)	83 (15.4)
Missing	0	1 (0.4)	1 (0.2)

^a Age in years was calculated using the birth date and informed consent date.

Note: The baseline value is defined as the last non-missing value before initial administration of study drug.

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{VANFLYTA; quizartinib}

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Tables 14.1.2.1 and 14.1.1.1.3

The Applicant's Position:

Demographic and baseline characteristics for subjects in the ITT Analysis Set were consistent with a *FLT3*-ITD (+) newly diagnosed AML population. Subjects were evenly distributed among treatment arms by age, sex, race, and ECOG PS.

The FDA's Assessment:

FDA agrees with the Applicant's tabulations and assessment of demographic and baseline characteristics for the ITT population. It is notable that eligibility criteria for Study AC220-A-U302 included patients up to age 75. Consequently, 40% of the trial population was ≥60 years of age, with a full 25% ≥65 years old. This is an older trial population than was enrolled on the Ratify Study, which enrolled a younger population with an age cutoff of 60. Also of interest, due to the approval of midostaurin by FDA in April 2017, most patients for study AC220-A-U302 were enrolled from Europe and Asia in countries where midostaurin was not available at the time of patient enrollment.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 24 – AML History and Disease Characteristics in Study AC220-A-U302 (ITT Analysis Set)

Parameter	Quizartinib (N = 268)	Placebo (N = 271)	Total (N = 539)
Time from diagnosis to randomization (weeks)^a			
Mean (SD)	1.98 (0.790)	1.96 (0.926)	1.97 (0.860)
Median (min, max)	1.86 (0.9, 5.3)	1.71 (1.0, 9.1)	1.71 (0.9, 9.1)
Antecedent hematological disorder, n (%)			
Yes	25 (9.3)	16 (5.9)	41 (7.6)
No	243 (90.7)	255 (94.1)	498 (92.4)
WHO classification^b, n (%)			
AML with recurrent genetic abnormalities occurring in ≥2% of subjects			
AML with t(8;21)(q22;q22); RUNX1-RUNX1T1	8 (3.0)	9 (3.3)	17 (3.2)

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Parameter	Quizartinib (N = 268)	Placebo (N = 271)	Total (N = 539)
AML with mutated <i>NPM1</i> ^c	142 (53.0)	140 (51.7)	282 (52.3)
AML with mutated <i>CEBPA</i> ^{c, d}	61 (22.8)	65 (24.0)	126 (23.4)
AML with myelodysplasia-related changes	23 (8.6)	16 (5.9)	39 (7.2)
AML not otherwise categorized occurring in ≥2% of subjects			
AML minimally differentiated	24 (9.0)	23 (8.5)	47 (8.7)
AML without maturation	47 (17.5)	41 (15.1)	88 (16.3)
AML with maturation	37 (13.8)	48 (17.7)	85 (15.8)
Acute myelomonocytic leukemia	40 (14.9)	59 (21.8)	99 (18.4)
Acute monoblastic/monocytic leukemia	38 (14.2)	31 (11.4)	69 (12.8)
Myeloid Sarcoma	0	1 (0.4)	1 (0.2)
Risk status with specific cytogenetic patterns^e, n (%)			
Favorable	14 (5.2)	19 (7.0)	33 (6.1)
Intermediate	197 (73.5)	193 (71.2)	390 (72.4)
Unfavorable	19 (7.1)	27 (10.0)	46 (8.5)
Unknown or missing	38 (14.2)	32 (11.8)	70 (13.0)
<i>FLT3</i>-ITD (+) by central testing, n (%)	267 (99.6)	271 (100)	538 (99.8%)
<i>FLT3</i>-ITD VAF by central laboratory testing^f (<i>FLT3</i>-ITD/total <i>FLT3</i>), n (%)			
≥3 to ≤25%	94 (35.1)	98 (36.2)	192 (35.6)
>25 to ≤50%	143 (53.4)	138 (50.9)	281 (52.1)
>50%	30 (11.2)	35 (12.9)	65 (12.1)
>25%	173 (64.6)	173 (63.8)	346 (64.2)
Unknown	1 (0.4)	0	1 (0.2)
WBC count at diagnosis of AML, n (%)			
<40 × 10 ⁹ /L	135 (50.4)	137 (50.6)	272 (50.5)
≥40 × 10 ⁹ /L	133 (49.6)	134 (49.4)	267 (49.5)

^a Duration of disease is defined as (randomization date minus disease diagnosis date + 1)/7.

^b Some subjects were reported in more than one category.

^c *NPM1* and *CEBPA* data are based on the (b) (4) central data.

^d *CEBPA* mutation assessment as determined by all mutations present.

^e Favorable: inv(16), t(16;16), t(8;21), t(15;17); Intermediate: normal, +8, +6, -y; Unfavorable: del5q, -5, del7q, -7, complex (Grimwade, 2001)

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^f *FLT3*-ITD VAF refers to *FLT3*-ITD/Total *FLT3*.

^g The represented *FLT3*-ITD VAF ranges convert to *FLT3*-ITD AR (*FLT3*-ITD/WT *FLT3*) ranges of ≥ 0.03 to ≤ 0.33 , >0.33 to ≤ 1 , >1 , and >0.33 , respectively.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Table 14.1.3.1.1

The Applicant's Position:

Relevant baseline characteristics, including AML history and relevant genetic, morphologic, and cytogenetic characteristics were well balanced between arms. The study population had predominantly high-risk features based on cytogenetic risk factors as well as tumor burden, both of which are associated with a worse prognosis. The most frequent FAB type was acute myelomonocytic leukemia, and the majority of subjects in both the quizartinib and placebo arms had an intermediate or unfavorable risk status according to cytogenetic patterns.

The FDA's Assessment:

We agree with the Applicant's assessment of the ITT population. The baseline demographics were similar between treatment arms in terms of disease characteristics including cytogenetic risk group, *FLT3*-ITD VAF level, and presenting WBC count. FDA has confirmed the tabulations.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

The median relative dose intensity (ie, the percentage of intended dose administered) was 100% (range: 20%, 207%) in the quizartinib arm and 100% (range: 40%, 200%) in the placebo arm.

All subjects were administered concomitant medications during the study and the use of concomitant medications was generally comparable between subjects in the quizartinib arm and the placebo arm. Major protocol deviations due to the use of prohibited medications were reported in none of the subjects in the quizartinib arm and in 1 (0.4%) subject in the placebo arm.

No rescue medication was used in Study AC220-A-U302.

The Applicant's Position:

Treatment compliance was high and comparable between the quizartinib arm and placebo arm, indicating that quizartinib treatment had comparable tolerability to placebo and concomitant medication use was balanced between the treatment arms.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Table 25 presents the drug exposures by treatment phases. It shows that a second course of induction was administered to 20% (109/539) of the patients, 65% (348/539) initiated at least one cycle of consolidation, and 39%

(208/539) initiated maintenance. Among the patients who entered maintenance, 64% (134/208) completed at least 12 cycles, 36% (75/208) completed at least 24 cycles and 16% (34/208) completed all 36 planned cycles of maintenance.

Table 25: Numbers of Treatment Cycles by Treatment Phase, Safety Data Set (N = 539)

Treatment Cycles	Treatment Phase		
	Induction (N = 533) [‡]	Consolidation (N = 335) [*]	Continuation (N = 208) [‡]
1	424 (79%)	123 (37%)	--
2	109 (20%)	94 (28%)	--
3	--	71 (21%)	--
4	--	47 (14%)	--
< 12	--	--	74 (36%)
≥ 12	--	--	134 (64%)
≥ 24	--	--	75 (36%)
= 36	--	--	34 (16%)

[‡]533 out of 539 subjects finished at least 1 cycle of induction treatment.
^{*}348 out of 539 subjects were initiated consolidation treatment, among whom 335 finished at least 1 cycle of consolidation treatment.
[‡]208 out of 539 subjects had at least 1 cycle of continuation treatment, among whom 134 (64%) had at least 12 cycles of continuation treatment

Source: FDA analysis

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 26 – Primary Analysis of Overall Survival in Study AC220-A-U302 (ITT Analysis Set)

Statistics	Quizartinib (N = 268)	Placebo (N = 271)	Analysis (Quizartinib vs. Placebo)
Subjects (%) with events (deaths)	133 (49.6)	158 (58.3)	—
Subjects (%) without events (censored)	135 (50.4)	113 (41.7)	—
Alive at the time of data cutoff date	120 (44.8)	103 (38.0)	—
Withdrawal of consent	13 (4.9)	9 (3.3)	—
Lost to follow-up	2 (0.7)	1 (0.4)	—

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Statistics	Quizartinib (N = 268)	Placebo (N = 271)	Analysis (Quizartinib vs. Placebo)
Stratified log-rank test^a			
p-value (2-sided)	—	—	0.0324
Stratified Cox regression analysis^a			
Hazard Ratio (relative to placebo)	—	—	0.776
95% CI	—	—	(0.615, 0.979)
Median OS (months)^b	31.9	15.1	—
95% CI	(21.0, NE)	(13.2, 26.2)	—
OS rate (%) (95% CI)^c at:			
6 months	82.3 (77.1, 86.4)	79.1 (73.7, 83.5)	—
12 months	67.4 (61.3, 72.7)	57.7 (51.6, 63.4)	—
24 months	54.7 (48.4, 60.5)	44.7 (38.7, 50.6)	—
36 months	49.9 (43.7, 55.9)	41.1 (35.0, 47.0)	—
48 months	48.4 (41.9, 54.5)	37.0 (29.8, 44.2)	—

^a Stratification factors include region (North America, Europe, Asia/Other regions), age (<60, ≥60 years old), and WBC count at the time of diagnosis of AML (<40 × 10⁹/L, ≥40 × 10⁹/L).

^b Median OS is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method.

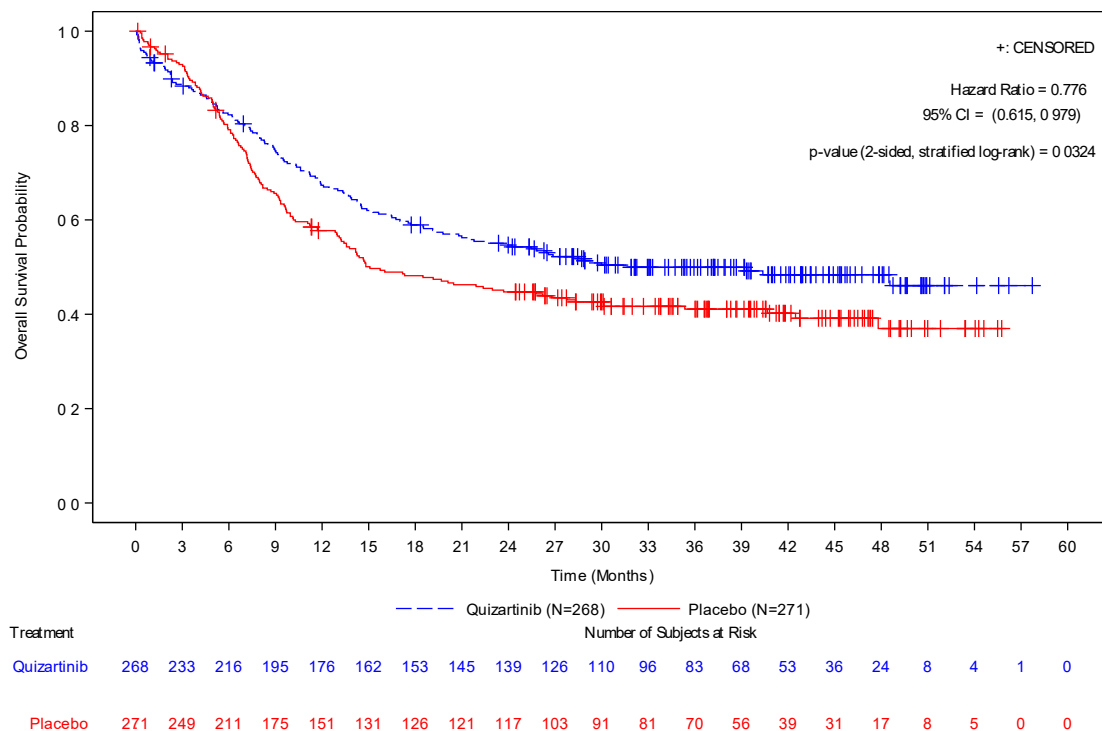
^c Estimated using the Kaplan-Meier method.

Note: Denominator for percentages is the number of subjects in the ITT Analysis Set.

OS is defined as the time from the date of randomization to the date of death from any cause.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Table 14.2.1

Figure 2 – Kaplan-Meier Plot of Overall Survival in Study AC220-A-U302 (ITT Analysis Set)



Note: Statistical model for HR and p-value: stratified Cox PH model and stratified log-rank test.
Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Figure 14.2.1

Table 27 – Overall Survival Using Sensitivity and Supplementary Analyses in Study AC220-A-U302 (ITT Analysis Set)

OS Analysis	Median OS ^a (95% CI for Median)		HR Relative to Placebo (95% CI)	Nominal p-value (2-sided)
	Quizartinib	Placebo		
Unstratified	31.9 (21.0, NE)	15.1 (13.2, 26.2)	0.774 (0.614, 0.975) ^b	0.0290 ^b
Censored at start of HSCT conditioning regimen	20.8 (14.3, 28.9)	12.9 (9.2, 14.7)	0.752 (0.562, 1.008) ^c	0.0550 ^c

^a Median OS is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method.

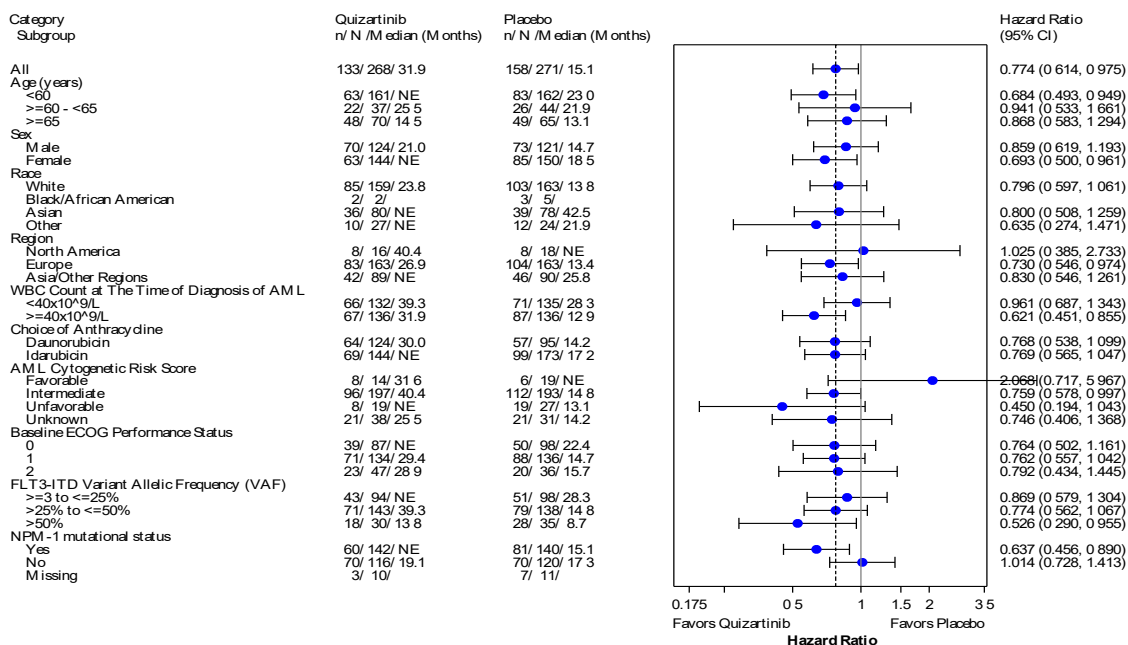
^b Log-rank test and Cox PH model were not adjusted for stratification factors.

^c Stratification factors include: region (North America, Europe, Asia/Other regions), age (<60, ≥60 years), and WBC count at the time of diagnosis of AML (<40 × 10⁹/L, ≥40 × 10⁹/L).

Note: OS is defined as the time from the date of randomization to the date of death from any cause.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Table 14.2.1.2

Figure 3 – Forest Plot of Overall Survival in Study AC220-A-U302 (ITT Analysis Set)



Notes: HR was obtained from unstratified Cox PH model. The dotted line indicates the HR for the overall OS analysis. Median, median OS from Kaplan-Meier analysis.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Figure 14.2.1.3

The Applicant's Position:

Study AC220-A-U302 demonstrated a statistically significant and clinically meaningful improvement in OS for quizartinib in combination with chemotherapy then as continuation therapy compared with chemotherapy and placebo followed by placebo as continuation therapy in a population of subjects with newly diagnosed *FLT3*-ITD (+) AML. While Study AC220-A-U302 was not powered to evaluate differences between the prespecified subgroups, the improvement in OS was observed across most of these subgroups in favor of quizartinib.

The improvement in OS is of particular relevance because Study AC220-A-U302 was conducted in a population of subjects with predominantly high-risk features based on cytogenetic risk factors as well as tumor burden, both of which are associated with a worse prognosis and shorter median OS (Levis, 2004) and for whom new and effective therapies represent a particularly high unmet need. The study included younger (≤ 60 years) and older (> 60 years; upper limit was 75 years) subjects notably those who are eligible for intensive therapy, for whom current treatment options remain unsatisfactory.

The FDA's Assessment:

FDA conducted independent analyses on the primary endpoint OS and found the primary analysis results were consistent with those reported by the Applicant (Table 26 and Figure 2). However, due to plateauing of the survival curves just above and below the median, the median estimates may exaggerate the survival benefit. Furthermore, there was a detrimental effect of OS in the first few months. During Induction, there was a higher number of deaths due to adverse events for quizartinib versus placebo (7.2% vs. 4.5%). The data cut-off was performed when all patients had either discontinued or had at least 24 months of follow-up. Median follow-up time was 39.2 months in both arms. Most of the censoring occurred after 24 months post-randomization.

FDA sensitivity analyses of OS are presented in **Table 28**, including unstratified analysis, stratification factors per eCRF (rather than randomization system as in primary analysis), Per Protocol Set, and censoring OS at the start of conditioning for HSCT. The results of FDA sensitivity analyses of OS from the unstratified analysis and the censoring OS at the start of conditioning for HSCT were comparable to that reported by the Applicant (Table 27). These sensitivity analyses are supportive of the primary analysis result.

Table 28: Sensitivity analyses of OS in QuANTUM-First (ITT Analysis Set)

	Number of death (%)		Median OS in months		HR (95% CI)	Two-sided p-value
	Quizartinib N = 268	Placebo N = 271	Quizartinib N = 268	Placebo N = 271		
Primary analysis					0.78 (0.62, 0.98)	0.0324
Unstratified analysis	133 (50)	158 (58)	31.9	15.1	0.77 (0.61, 0.97)	0.0289
Stratified per eCRF					0.77 (0.61, 0.97)	0.0265
Per protocol Set	130 (49)	155 (57)	39.3	15.1	0.76 (0.60, 0.97)	0.0243
Censoring OS at start of conditioning for HSCT	85 (32)	110 (41)	20.8	12.9	0.75 (0.56, 1.00)	0.0555

Source: FDA analysis

Subgroup analyses were conducted to understand if any patient subgroup was driving the early detriment in mortality. Appendix 19.5.1 presents subgroup results for OS by 3 months, 6 months, or any time. While there is some heterogeneity amongst the subgroups in terms of treatment effect, no single subgroup appears to be driving the early detriment in OS.

Review of the subgroup analysis presented in the Figure 3 Forest Plot above resulted in additional questions about the nature of quizartinib's effect. The following clinical comments are exploratory hypotheses motivated by these results.

Clinical reviewer comments: In terms of age, we see that while all age groups appeared to benefit from quizartinib treatment, the youngest age group appeared to derive the greatest benefit. It is notable that this age group, patients <60, is analogous to the patient population

enrolled on the midostaurin pivotal study. However, it is important to remember that age is an independent risk factor for survival in AML, which was again demonstrated with median survival for patients ≥ 65 on both arms being inferior to the younger patients.

Another two subgroups that are interesting to consider were based on presenting WBC count and FLT3-ITD VAF level. Again, while the point estimate for all level of these subgroups showed benefit with quizartinib treatment, patients presenting with WBC $\geq 40 \times 10^9/L$ or higher FLT3-ITD VAF level appeared to show greater benefit from quizartinib treatment. This might not be surprising since active FLT3-ITD is thought to drive a particularly proliferative form of AML. Therefore, the higher presenting WBC could indicate greater reliance on the oncogenic signaling from the mutant FLT3-ITD and greater sensitivity to loss of that signal. Along the same line, a higher presenting FLT3-ITD VAF would also argue for greater reliance on FLT3 signaling in the AML clones existing at presentation and sensitivity to loss of that signaling.

Results of the NPM1 subgroup are interesting. NPM1 mutations frequently cooccur with FLT3-ITD mutations and was thought to improve the risk category of the FLT3-ITD AML, at least for FLT3-ITD that has a low VAF. The results above suggest that quizartinib benefits patients that have both FLT3-ITD and NPM1 mutant AML while being neutral for those with FLT3-ITD and WT NPM1. It is not clear why this might be the case. Two things to point out are that the most recent ELN AML guidelines now consider FLT3-ITD with either NPM1 Wt or NPM1 mutant to be intermediate risk disease (Döhner, 2022). The second is that on the control arm, patients with NPM1 mutant disease had a lower median OS than patient with NPM1 Wt disease. Therefore, the result observed on Study AC220-A-U302 regarding NPM1 status likely reflects a combination of 1) recent recognition that in the presence of any level of FLT3-ITD, NPM1 status no longer predicts significant prognostic difference and 2) the relative underperformance of NPM1 mutant/overperformance of NPM1 Wt patients on the placebo arm of the trial. Lastly, it is difficult to make firm conclusions based on this post-hoc subgroup analysis. As noted in Section 6.2.2.2, the results for EFS in the NPM1 Wt subgroup were supportive of positive benefit of quizartinib (HR 0.760).

The last group that suggested a surprising result was response by cytogenetic risk group. While intermediate, unfavorable, and even unknown cytogenetic risk groups appeared to benefit from quizartinib treatment, patients with favorable risk disease appeared to benefit on the placebo arm. Patients in this risk group have either t(15;17), t(8;21), inv(16), or t(16;16). Since patients with t(15;17) were excluded from Study AC220-A-U302, patients in this group were represented by t(8;21), inv(16), or t(16;16) also known as core binding factor AML. This group is considered favorable risk due to its sensitivity to standard treatment and overall better prognosis than other forms of AML. It is unclear why patients that have these cytogenetic rearrangements and FLT3-ITD would benefit more from chemotherapy with placebo than from chemotherapy with

quizartinib. Given the small number of events, this result might be driven by a few chance events and not generalizable to a larger population of such patients.

In addition, FDA conducted the analyses of continuation (i.e., maintenance) treatment effect. Of the 539 randomized patients, 208 patients entered the Continuation Phase (116 [44%] in the quizartinib arm and 92 [34%] in the placebo arm). We define patients who entered the Continuation Phase as the Continuation Analysis Set. In the Continuation Analysis Set, 66/116 (57%) on the quizartinib arm and 49/92 (53%) patients on the placebo arm were treated for >12 cycles of continuation, and 18/116 (16%) and 16/92 (17%) patients, respectively, completed the planned 36 cycles of continuation therapy.

CDTL Comments: Of note, the 208/539 (39%) randomized patients who entered the continuation/maintenance phase on QuANTUM-First was greater than the number who entered maintenance on the RATIFY trial of midostaurin (29%).

As shown in **Table 29**, patients on the quizartinib arm who entered the Continuation Phase were numerically younger and more likely to have WBC $\geq 40 \times 10^9/L$ at baseline.

Table 29: Demographics and disease characteristics at baseline (Continuation Analysis Set)

		Quizartinib N = 116	Placebo N = 92
Age (year)	Median (range)	53 (23, 73)	56 (20, 74)
	≥ 60	39 (34)	42 (46)
Gender	Male	53 (46)	38 (41)
Race	White	69 (59)	54 (59)
	Asian	38 (33)	26 (28)
	Black/Other/unknown	9 (8)	12 (13)
ECOG PS	0	42 (36)	35 (38)
	1	57 (49)	50 (54)
	2	17 (15)	7 (8)
WBC at diagnosis	$\geq 40 \times 10^9/L$	60 (52)	37 (40)
FLT3 ITD Category at Baseline	≥ 3 to $\leq 25\%$	44 (38)	42 (46)
	$> 25\%$ to $\leq 50\%$	59 (51)	42 (46)
	$> 50\%$	12 (10)	8 (9)
Cytogenetic risk	Favorable	5 (4)	10 (11)
	Intermediate	84 (72)	60 (65)
	Poor	8 (7)	9 (10)
	Missing	19 (16)	13 (14)
Mutated NPM1	Yes	69 (59)	60 (65)

Source: FDA analysis

Time to initiation of continuation therapy was longer on the quizartinib arm than the control arm. For patients who received continuation therapy, median time from randomization to initiation of continuation therapy was 7.3 months (range: 2.7, 13.6) on the quizartinib arm and 6.5 months (range: 3.7, 16.7) on the control arm.

As shown in **Table 30**, more quizartinib patients (94/116 [81%]) entering the continuation phase achieved CR by the end of Induction than placebo patients (72/92 [78%]). Furthermore, more patients in the quizartinib arm (70 [60%]) started continuation following HSCT (with or without consolidation chemotherapy) than the placebo arm (49 [53%]).

Table 30: Status at the initiation of the Continuation Phase (Continuation Analysis Set)

	Quizartinib N = 116	Placebo N = 92
Response at the end of the Induction Phase, n (%)		
CR	94 (81)	72 (78)
CRi	20 (17)	15 (16)
No CR or CRi	1 (0.1)	2 (2)
Missing or unknown	1 (0.1)	3 (3)
Continuation therapy was started after n (%)		
Consolidation chemotherapy	46 (40)	43 (47)
HSCT	4 (3)	3 (3)
Both consolidation chemotherapy and HSCT	66 (57)	46 (50)
Time to Continuation Phase (months)		
Mean (SD)	7.2 (2.1)	6.9 (2.2)
Median (min, max)	7.3 (2.7, 13.6)	6.4 (3.7, 16.7)

Source: FDA analysis

Below Sections A and B summarized the results of the FDA analyses of the continuation therapy.

Section A: Unadjusted and adjusted analyses of efficacy in the continuation phase

Unadjusted Analyses

This section presents crude analyses of efficacy in the continuation phase. These analyses condition on subgroups based on post-randomization events such as entering continuation and receiving HSCT. For simplicity, outcomes are defined from randomization. In general, such

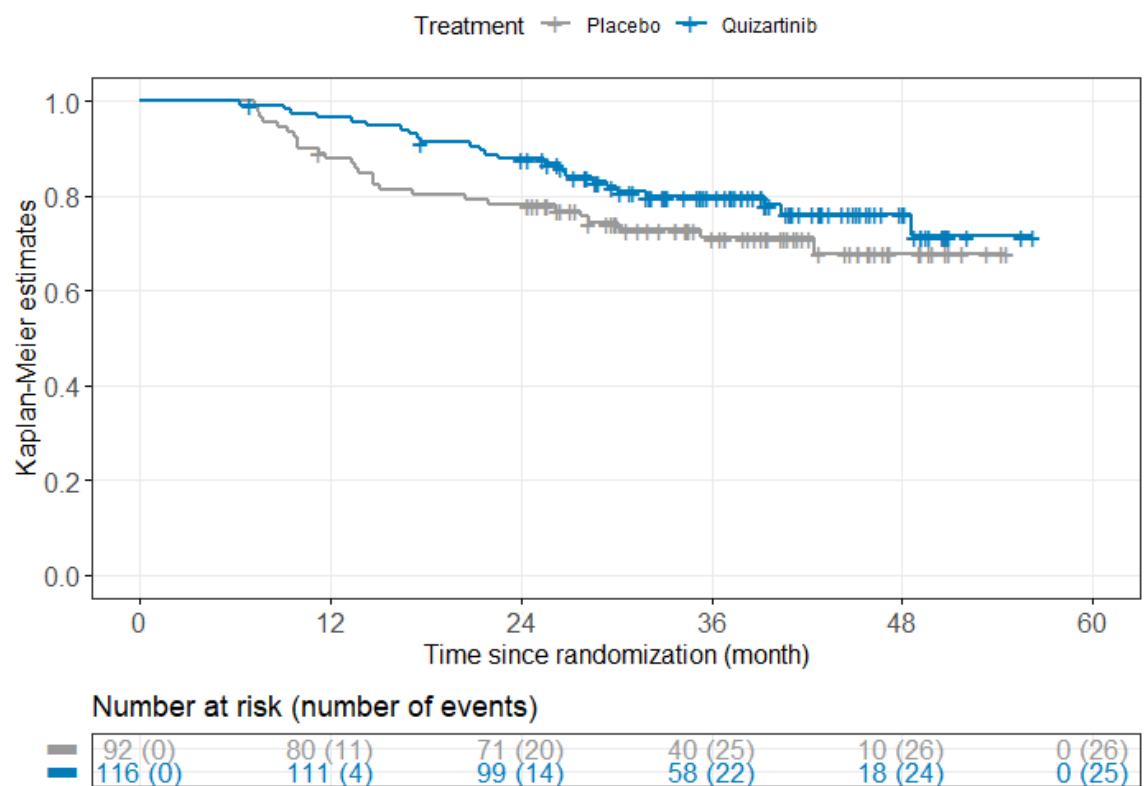
analyses are biased, since randomization is broken, and baseline covariates are no longer guaranteed to be balanced. Furthermore, such analyses do not account for differences in time from randomization to continuation or HSCT. Despite potential biases, these analyses are presented to provide a simple overview of efficacy for such subgroups and to provide context for subsequent analyses. Section B below presents analyses which adjust for covariate imbalance and differences in time to continuation or HSCT.

Figure 4 and **Figure 5** present Kaplan-Meier curves of OS and RFS in the 208 patients from the Continuation Analysis Set. As of the data cutoff date (13 August 2021), a total of 51 patients died (25 and 26 in the quizartinib and placebo arm, respectively); median OS was not reached for either arm, and HR = 0.68 (95% CI: 0.4; 1.18) from unstratified Cox model in favor of quizartinib (see Figure 4). The treatment effect appears to plateau around 12 months after randomization.

Similar results are observed in the RFS analysis among 166 patients from the Continuation Analysis Set who achieved CR at the end of Induction. 22 (23%) patients relapsed out of 94 quizartinib patients and 8 (9%) died; 24 (33%) patients relapsed out of 72 placebo patients and 5 (7%) died. Median RFS was only reached in the quizartinib arm at 48.6 months but not reached in the placebo arm, with a HR = 0.74 (95% CI: 0.44; 1.23) from unstratified Cox model in favor of quizartinib. The treatment effect appears to plateau around 12 months after randomization (Figure 5), similar to OS.

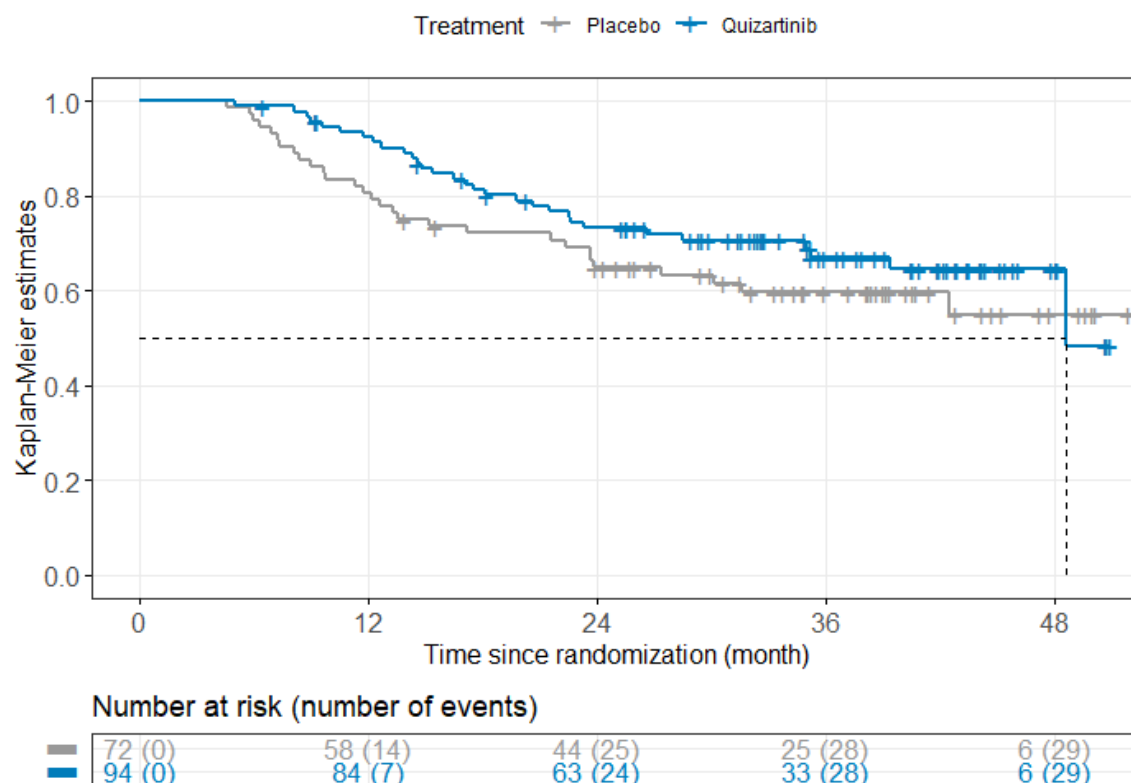
Figure 4: Kaplan-Meier plot of OS (Continuation Analysis Set)

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Source: FDA analysis

Figure 5: Kaplan-Meier plot of RFS (Continuation Analysis Set who achieved CR at the end of the Induction Phase)



Source: FDA analysis

Subgroup analyses of OS by HSCT status were examined. OS results for Continuation, broken down by HSCT status prior to continuation, are shown in Figure 6 and Table 31.

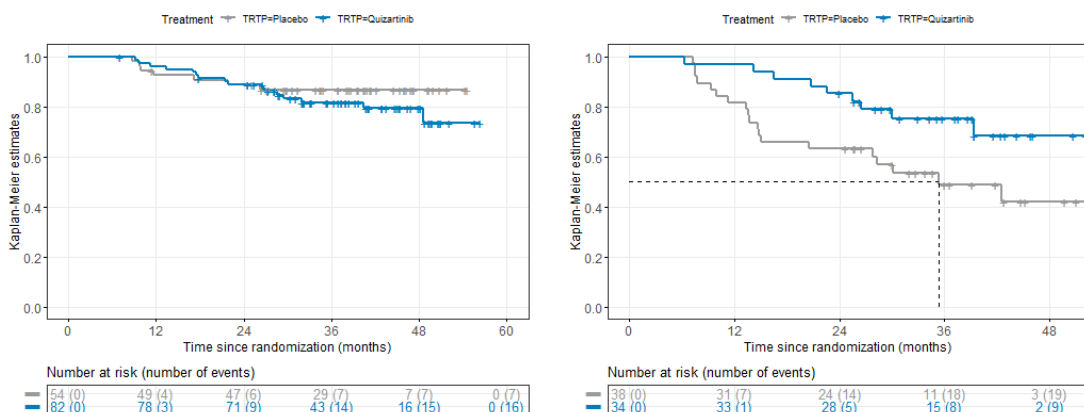
Figure 6 and Table 31 show a different effect on OS in patients who received HSCT (OS HR 1.46 [95%CI 0.60, 3.54]) compared to those who did not receive HSCT (OS HR 0.43 [95%CI 0.19, 0.94]). These results suggest that quizartinib may not be beneficial for patients after HSCT.

Figure 6: Kaplan-Meier plot of OS by HSCT status (Continuation Analysis Set)

With HSCT, entered Continuation

Without HSCT, entered Continuation

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Source: FDA analysis

Table 31: Crude subgroup analysis of OS by HSCT (Continuation Analysis Set)

	With HSCT prior to Continuation		Without HSCT prior to Continuation	
	Quizartinib N = 82	Placebo N = 54	Quizartinib N = 34	Placebo N = 38
Subjects with events, n (%)	16 (20)	7 (13)	9 (26)	19 (50)
Subjects without events, n (%)	66 (80)	47 (87)	25 (73)	19 (50)
Alive at data cutoff	64 (78)	46 (85)	22 (65)	18 (47)
Lost to follow-up	0	0	2 (6)	0
Withdrawal of consent	2 (2)	1 (2)	1 (3)	1 (3)
Median (95% CI), months*	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	35.4 (20.5, NE)
HR (95% CI)**	1.46 (0.60, 3.54)		0.43 (0.19, 0.94)	

*: NE = not estimable.

**: HR = hazard ratio, estimated from unstratified Cox model.

Source: FDA analysis

Additional analyses considering only “protocol-specified HSCT,” using different index dates (i.e., time of entering continuation, time of HSCT) showed similar results to those presented above. Table 32 presents numbers of patients having HSCT prior to continuation by protocol specified HSCT status and treatment.

Table 32: Numbers of HSCT prior to Continuation by Protocol Specified HSCT Status and Treatment

With HSCT prior to Continuation	Quizartinib N = 82	Placebo N = 54	Total N = 136
Protocol Specified	70	49	119

Non-Protocol Specified	12	5	17

Source: FDA analysis

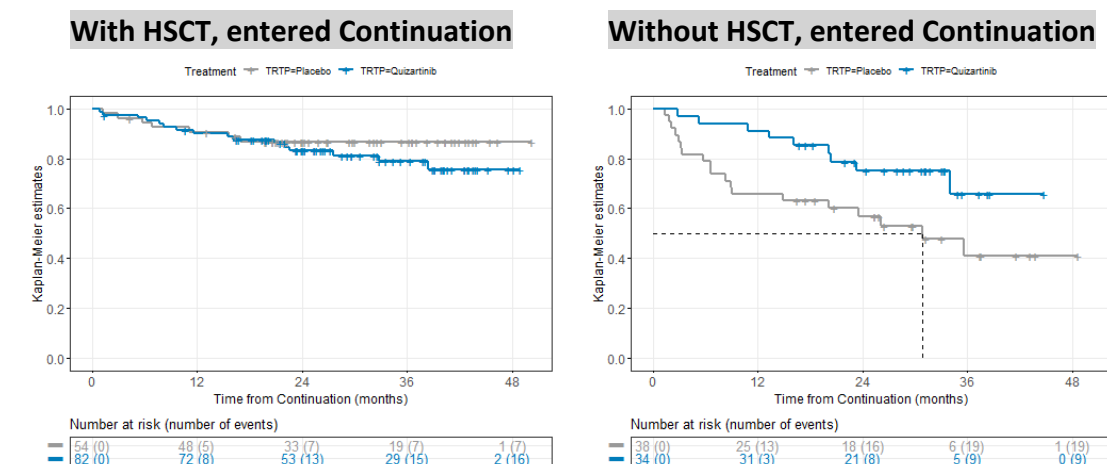
In summary, in the exploratory subgroup analysis of the 89/208 (43%) of patients who received maintenance therapy with VANFLYTA or placebo following consolidation chemotherapy without HSCT, the OS HR was 0.40 (95% CI: 0.19, 0.84). Of 119/208 (57%) of patients who received maintenance therapy with VANFLYTA or placebo following HSCT, the OS (from randomization) HR was 1.62 (95% CI: 0.62, 4.22).

Adjusted Analyses

FDA conducted adjusted analyses to potentially account for variability in the timing of post-randomization events by setting the landmark time to the time of HSCT or the time of continuation therapy. For patients who entered continuation, the hazard ratio for OS (from start of continuation) was 0.69 (95% CI: 0.4, 1.20). This is similar to the hazard ratio obtained for OS defined from time of randomization.

Figure 7 presents a comparison of patients who entered continuation by HSCT status (with vs. without) from the start of continuation therapy. Figure 7 suggests that the survival benefit was mainly observed in patients who entered the continuation phase without HSCT.

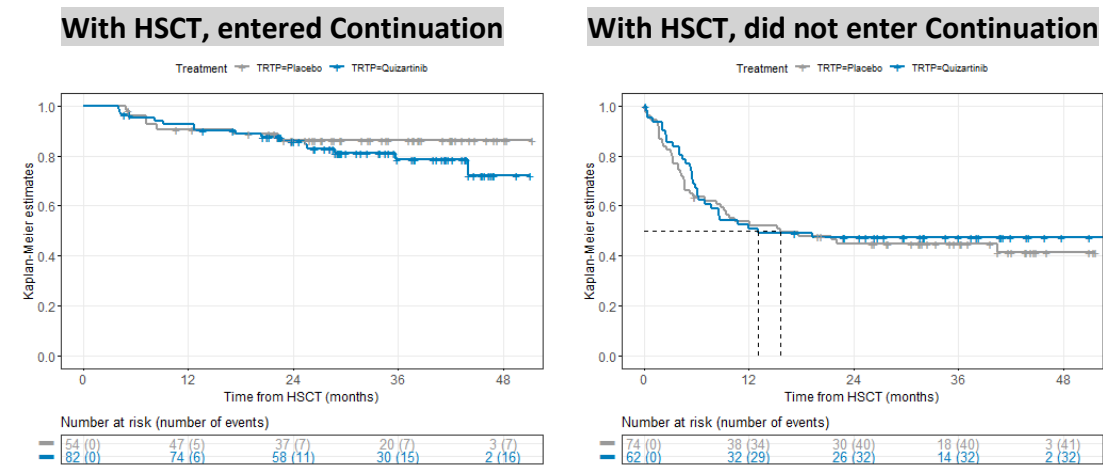
Figure 7: Kaplan-Meier plot of OS from Continuation by HSCT status (Continuation Analysis Set)



Source: FDA analysis

Figure 8 presents a comparison of patients who received HSCT (i.e., HSCT Analysis Set) by continuation status (entered vs. did not enter) from the date of HSCT. Figure 8 suggests no survival benefit from continuation quizartinib treatment in patients who underwent HSCT.

Figure 8: Kaplan-Meier plot of OS from HSCT by Continuation status (HSCT Analysis Set)



Source: FDA analysis

Additional adjusted analyses are described in Section 19.5.2. These include the Applicant’s analyses (propensity score adjustment) as well as additional FDA analyses (landmark analyses and time-varying Cox model analyses).

Section B: Impact of quizartinib on MRD status in the continuation phase

FDA sought to determine whether there was evidence of increased activity for quizartinib in the setting of MRD positivity prior to continuation. The protocol specified that MRD was to be captured at the following times: Screening; End of Induction; Consolidation Last Cycle; Post-HSCT; Continuation Cycle 1, Day 1; Continuation Cycle 4, Day 1; and End of Treatment (i.e., completion of 36 cycles of continuation or permanent discontinuation).

Out of 368 CR + CRi responders, 321, 239 and 162 had at least one MRD assessment in Induction, Consolidation, and Continuation, respectively. Out of 208 patients who entered Continuation, 137 patients (74/116 [64%] quizartinib and 63/92 [69%] placebo) had MRD data available at the initiation of this phase of treatment.

Based on the MRD cutoff of 0.01%, 13 patients (7 and 6 in the quizartinib and placebo arms, respectively) were MRD positive and 124 patients (67 and 57 in the quizartinib and placebo arms, respectively) were MRD negative at the initiation of Continuation. We define patients in

the Continuation Analysis Set who were MRD positive (or negative) *at the initiation of Continuation* as the MRD+ (or MRD-) Continuation Analysis Set.

Given the small and post-hoc nature of the MRD+ Continuation Analysis Set, statistical inference has limited value. Descriptive analyses are presented in Table 33, where the conversion rate from MRD+ to MRD- during the Continuation Phase is summarized.

Table 33: Conversion from MRD positive to MRD negative during the Continuation Phase (MRD+ Continuation Analysis Set; Cutoff 0.01%)

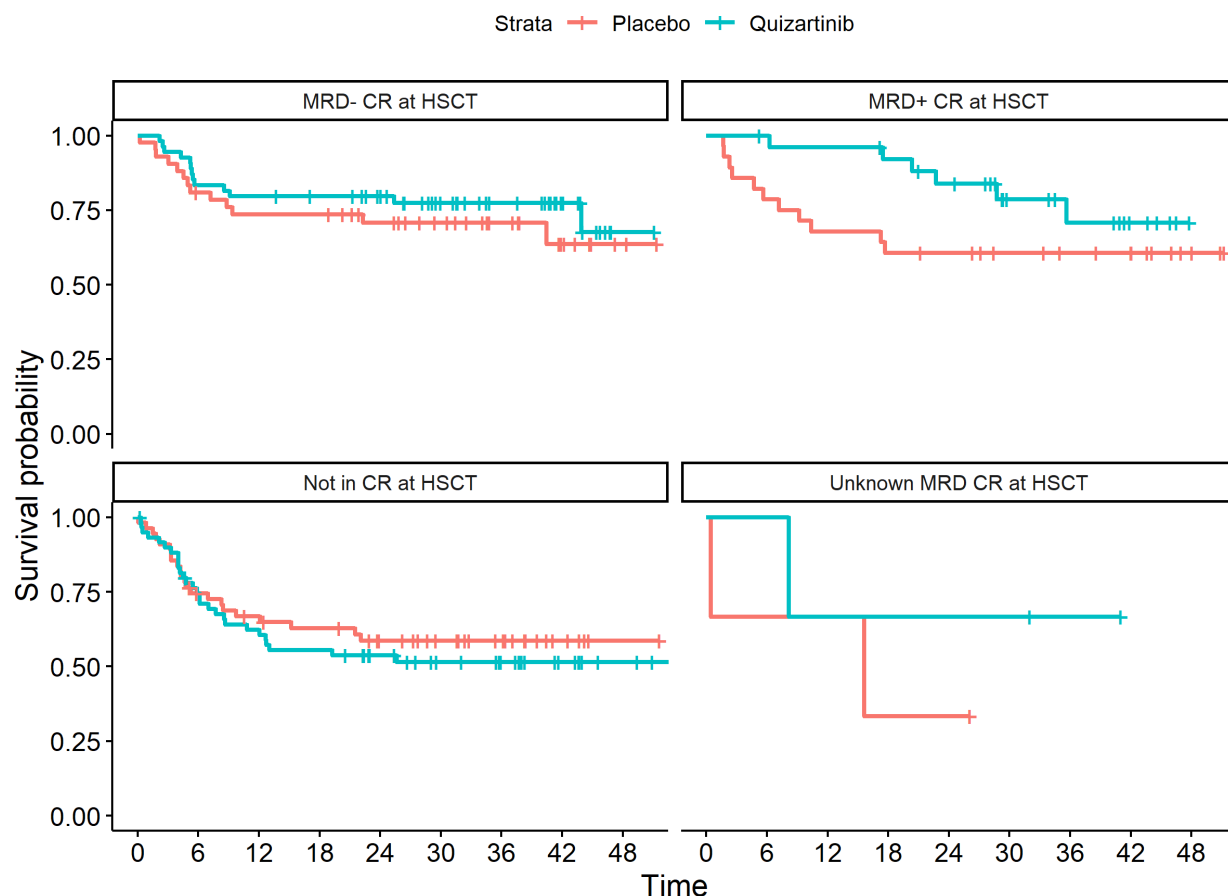
	Quizartinib N = 7	Placebo N = 6
Patients who converted to MRD- during Continuation, n	2	1
Patients with HSCT prior to Continuation, n	3	3
Patients who converted to MRD-, n	1	1
Patients without HSCT prior to Continuation, n	4	3
Patients who converted to MRD-, n	1	0

Source: Applicant's information response dated 9 January 2023

Among 124 patients in the MRD- Continuation Analysis Set, 70 (56%) and 54 (44%) started continuation with and without HSCT respectively. The OS analyses in this subgroup are generally similar to those in Continuation Analysis Set (see Appendix 19.5.3). Therefore, the findings by HSCT status do not appear to vary by MRD status.

The ASH presentation by MJ Levis *et al* [Blood 140, no. Supplement 1 (2022): 546-548] suggested that the effect of quizartinib may vary for patients who receive HSCT depending on MRD status *prior to* HSCT. The analyses presented are of OS from time of HSCT by MRD status (MRD+ vs. MRD-). The Kaplan-Meier curves are reproduced below in Figure 9, with the addition of the categories of "Not in CR at HSCT" and "Unknown CR MRD at HSCT".

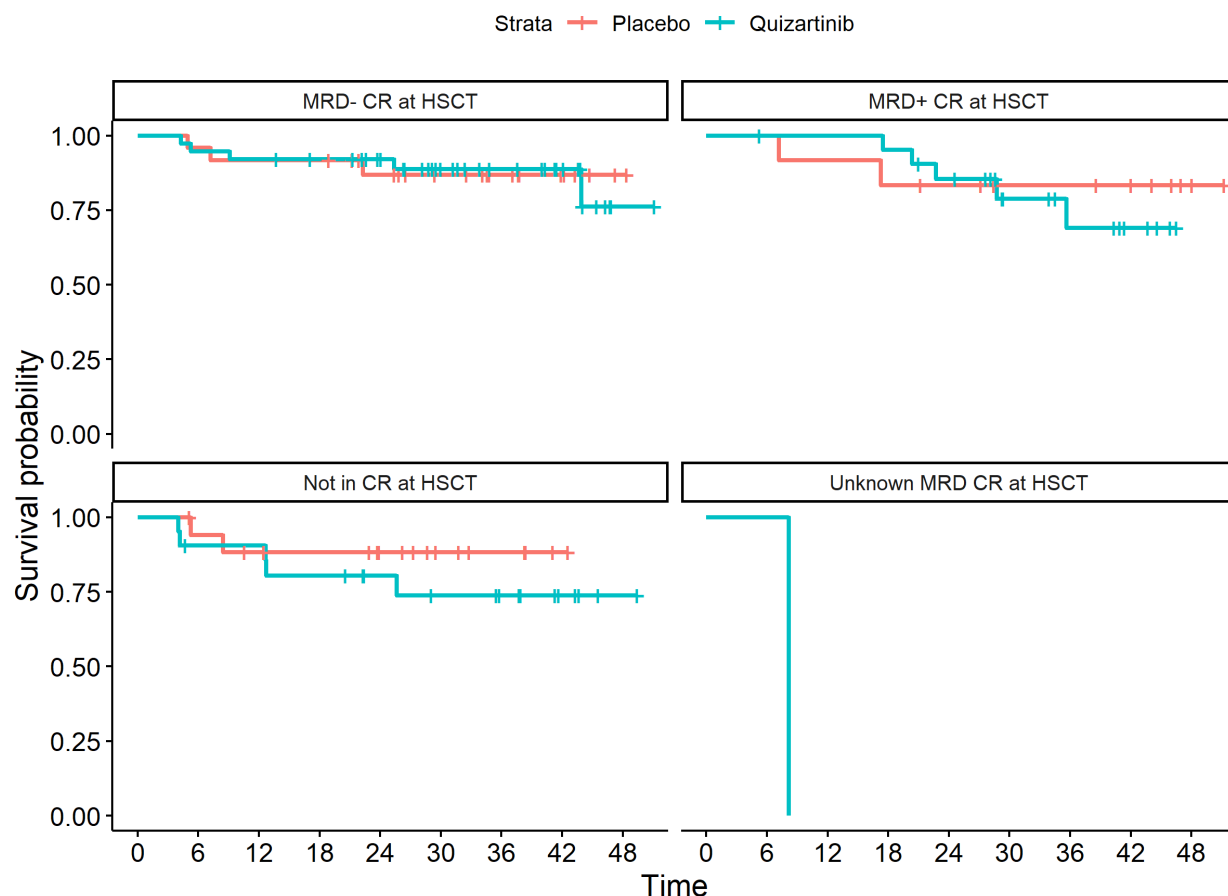
Figure 9: OS by Treatment, MRD Status (+, -, Not in CR, and Unknown MRD CR) for All HSCT Receivers, Reproduced Analysis of Levis *et al* 2022



Source: FDA analysis

Note that these analyses include all patients who received HSCT, *regardless of whether they continued to maintenance therapy*. Figure 10 displays the same subsets for all patients who also received maintenance, with OS as measured from the time of maintenance initiation.

Figure 10: OS by Treatment, MRD Status (+, -, Not in CR, and Unknown MRD CR) for HSCT Receivers Who Received Maintenance Therapy



Source: FDA analysis

Reviewer's Comment: There is no discernible difference in the treatment effect across the various subgroups in Figure 9 and Figure 10. While Figure 9 suggests a possible difference in the treatment effect of quizartinib on OS for patients who receive HSCT by MRD status, this is not clearly reflected in the subset of patients that received maintenance therapy. The small sample size and post-hoc selection of such subgroups makes inference challenging. However, to the extent that MRD status might be useful in identifying which patients might benefit from maintenance quizartinib therapy, the available data are insufficient to make any such recommendation. As noted below, the MRD data are further limited by the fact that a sizeable percentage of the MRD data was either missing or >90 days prior to HSCT.

FDA evaluated overall survival results based on MRD status prior to HSCT for patients who received maintenance (i.e., continuation) therapy. In this analysis, an MRD cutoff of 0.01% is utilized. Table 34 presents the MRD status for such patients. For these analyses, FDA considered patients with missing MRD status to be "unknown"; Levis 2022 considers such patients to be MRD+. Other minor differences between the MRD definitions are noted in Table 34. Of note, the

most recent MRD assessment was >90 days prior to HSCT for 10 patients in the placebo arm and 17 patients in the quizartinib arm.

Table 34: MRD Status Prior to HSCT for Patients who Received Maintenance Therapy

	Quizartinib (n=82)	Placebo (n=54)
MRD prior to HSCT (latest assessment)		
MRD+	21 (26)	19 (35)
MRD-	49 (60)	33 (61)
Missing	12 (15)	2 (4)
MRD prior to HSCT (latest assessment within 90 days)		
MRD+	11 (13)	16 (30)
MRD-	42 (51)	26 (48)
Missing	29 (35)	12 (22)
MRD prior to HSCT (Levis 2022)		
MRD+ ¹	33 (40) ²	20 (37) ³
MRD-	48 (59)	34 (63)
Missing	1 (1)	0 (0)
Time from latest MRD assessment to HSCT		
Median days (range)	53 (9, 230)	50 (9, 291)

¹Patients with missing MRD status were considered to be MRD+ in this analysis.

²One patient randomized to the quizartinib arm received two transplants and was MRD- prior to the first HSCT and MRD+ prior to the second HSCT.

³One patient randomized to the placebo arm received two transplants and was MRD+ prior to the first HSCT and MRD- prior to the second HSCT.

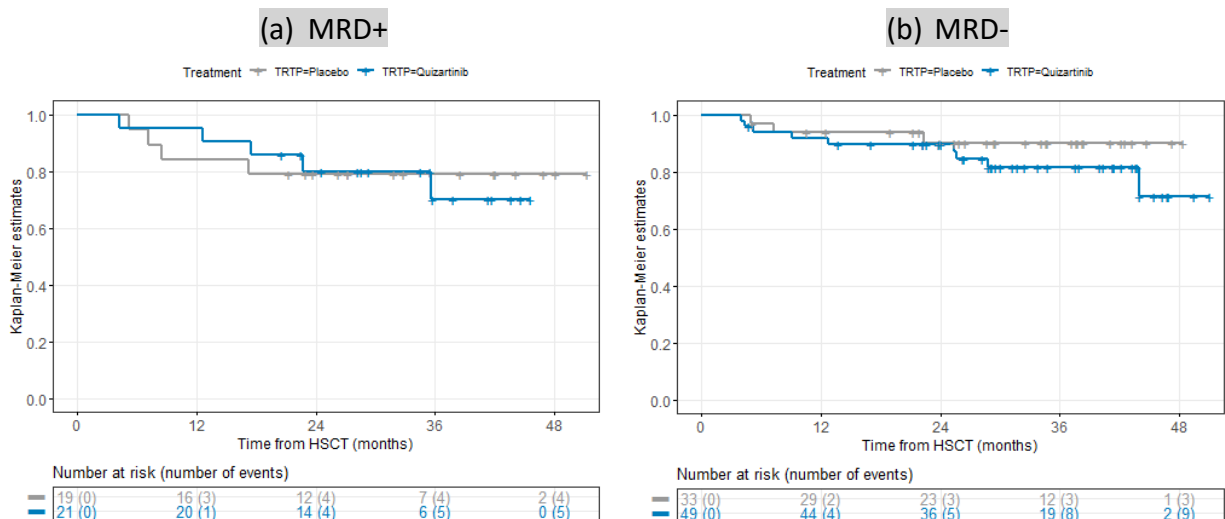
Source: FDA analysis

Figure 11 presents OS Kaplan-Meier curves by the most recent MRD status prior to HSCT for patients who received maintenance therapy; estimates of the corresponding hazard ratios are presented in Table 35. Figure 12 and Table 36 present these results with the restriction that MRD must have been assessed within 90 days prior to HSCT. In both figures, OS is defined as time from HSCT to death.

This exploratory subgroup analysis does not reveal any discernable trend regarding the role of MRD status in patients who receive both HSCT and maintenance therapy, however, we reiterate that the interpretation should be taken with caution because of the small sample size and post-hoc selection of such subgroups.

Figure 11: OS by treatment, MRD status prior to HSCT (most recent MRD assessment)

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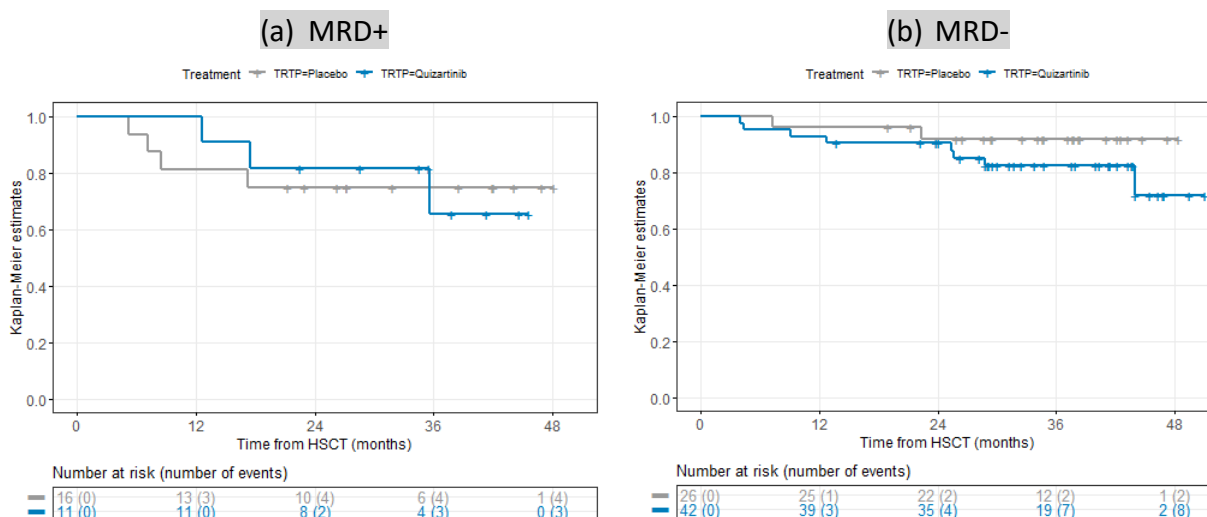
Source: FDA analysis

Table 35: Estimated Treatment Effect of Quizartinib vs. Placebo for Patients who Receive HSCT and Maintenance by MRD Subgroup (Most Recent MRD Assessment prior to HSCT)

MRD status	#events/N	HR (95% CI)
(a) MRD+	9/40	1.09 (0.29, 4.05)
(b) MRD-	12/82	1.92 (0.52, 7.11)

Source: FDA analysis

Figure 12: OS by treatment, MRD status prior to HSCT (most recent MRD assessment within 90 days)



Source: FDA analysis

Table 36: Estimated Treatment Effect of Quizartinib vs. Placebo for Patients who Receive HSCT and Maintenance by MRD Subgroup (Most Recent MRD Assessment within 90 Days prior to HSCT)

MRD status	#events/N	HR (95% CI)
(a) MRD+	7/27	1.04 (0.21, 4.29)
(b) MRD-	10/68	2.44 (0.52, 11.53)

Source: FDA analysis

Data Quality and Integrity

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets; these were sufficiently complete to allow for a thorough review of efficacy. Furthermore, no data integrity concerns were reported following completion of site inspections by the Applicant.

The FDA's Assessment:

We agree with the data quality and integrity assessment.

Efficacy Results – Secondary and other relevant endpoints

Data:

The same analysis methods and testing used for the primary EFS analysis were applied to the sensitivity and supplementary analyses; nominal p-values are presented. Both EFS sensitivity analyses in Table 37 are based on CR or CRc evaluation at the end of the Induction Phase (using the per-protocol 56-day window from the start of the last cycle of induction chemotherapy).

Table 37 – Event-free Survival Primary and Sensitivity/Supplemental Analyses in Study AC220-A-U302 – IRC Assessment (ITT Analysis Set)

EFS Analysis	Median EFS ^a (95% CI) (Months)		HR ^b Relative to Placebo (95% CI)	2-sided p-value ^b
	Quizartinib (N = 268)	Placebo (N = 271)		
Primary analysis ITF definition: Not achieving CR by Day 42 from the start of the last induction cycle	0.03 (0.03, 0.95)	0.71 (0.03, 3.42)	0.916 (0.754, 1.114)	0.2371
Sensitivity/supplemental analysis ITF definition: Not achieving CR by the end of the Induction Phase (with up to a 56-day window from the start of the last induction cycle)	5.0 (1.8, 9.0)	3.4 (1.7, 5.5)	0.818 (0.669, 0.999)	0.0323 ^c
Sensitivity analysis ITF definition: Not achieving CRc (CR or CRi) by the end of the Induction Phase (with up to a 56-day window from start of last induction cycle [original protocol definition] ^d)	11.9 (8.1, 16.5)	5.7 (4.0, 6.9)	0.729 (0.592, 0.897)	0.0031 ^c

^a Median EFS is from a Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method.

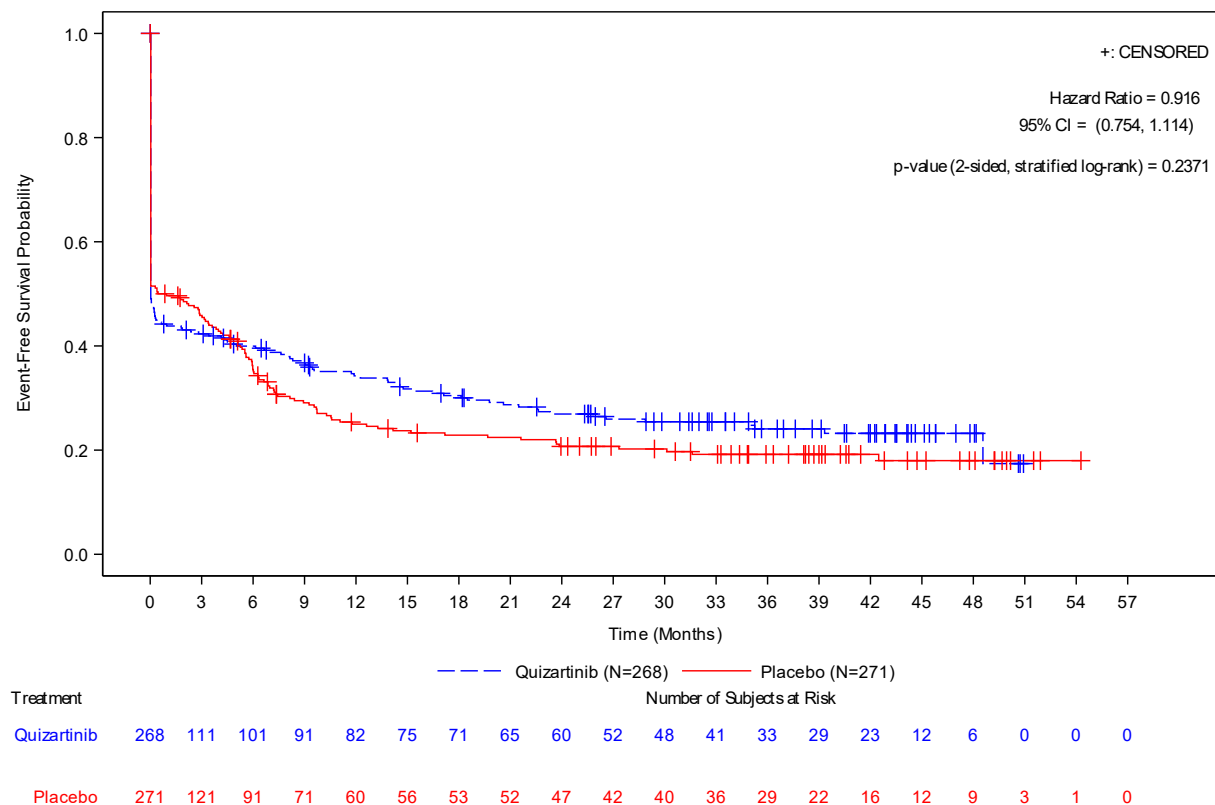
^b Stratification factors include region (North America, Europe, Asia/other regions), age (<60, ≥60 years old), and WBC count at the time of diagnosis of AML (<40 × 10⁹/L, ≥40 × 10⁹/L)

^c Nominal p-value.

^d In the study protocol, a BM assessment was to be done between Day 21 and Day 28 of the induction cycle. In case BM assessment was too early to provide an accurate assessment of response due to delayed count recovery, the BM assessment was to be repeated upon recovery or Day 56, in order to obtain a reliable assessment of response at the end of induction.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Tables 14.2.2 and 14.2.2.3

Figure 13 – Kaplan-Meier Plot of Event-free Survival – Induction Treatment Failure, Defined as Not Achieving Complete Remission by Day 42 From the Start of the Last Induction Cycle – IRC Assessment (ITT Analysis Set)



Notes: Statistical model for HR and p-value: Stratified Cox PH and stratified log-rank test.
Source: AC220-A-U302 CSR Figure 14.2.2

Table 38 – Event-free Survival and Reasons for Censoring – Induction Treatment Failure, Defined as Not Achieving Complete Remission by Day 42 From the Start of the Last Induction Cycle – IRC Assessment (ITT Analysis Set)

Statistics	Quizartinib (N = 268)	Placebo (N = 271)
ITF, defined as not achieving CR by Day 42 from the start of the last induction cycle (primary analysis)		
Subjects (%) with events	198 (73.9)	213 (78.6)
Refractory disease	136 (50.7)	131 (48.3)
Relapse	30 (11.2)	53 (19.6)

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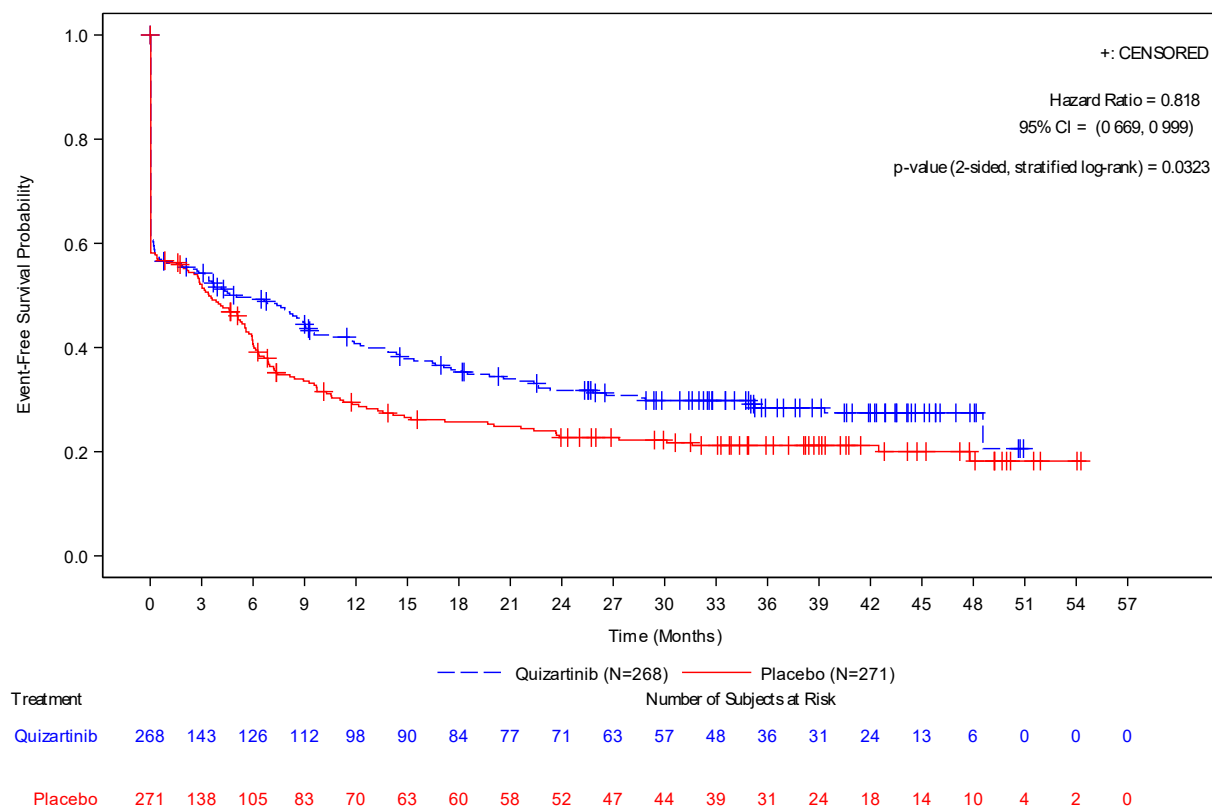
Statistics	Quizartinib (N = 268)	Placebo (N = 271)
Death	32 (11.9)	29 (10.7)
Subjects (%) without events (censored)	70 (26.1)	58 (21.4)
No postbaseline response assessment, no death date	1 (0.4)	1 (0.4)
Had CR, no relapse, no death date	69 (25.7)	57 (21.0)

Notes: The denominator for percentages is the number of subjects in the ITT Analysis Set.

EFS was defined as the time from the date of randomization to the date of refractory disease, relapse, or death from any cause, whichever occurred first. The primary analysis for EFS was based on the response assessment by IRC with response of CR only, using a 42-day window from the start of the last cycle in induction for CR evaluation as defined in the AML guidance (FDA, 2020).

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Table 14.2.2

Figure 14 – Kaplan-Meier Plot of Event-free Survival – Sensitivity/Supplemental Analysis – Induction Treatment Failure, Defined as Not Achieving Complete Remission by the End of the Induction Phase – IRC Assessment (ITT Analysis Set)



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Note: Up to a 56-day window from the start of the last induction cycle. Statistical model for HR and nominal p-value: Stratified Cox PH model and stratified log-rank test.
Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Figure 14.2.2.3

Table 39 – Event-free Survival and Reasons for Censoring – Sensitivity/Supplemental Analysis – Induction Treatment Failure, Defined as Not Achieving Complete Remission by the End of the Induction Phase – IRC Assessment (ITT Analysis Set)

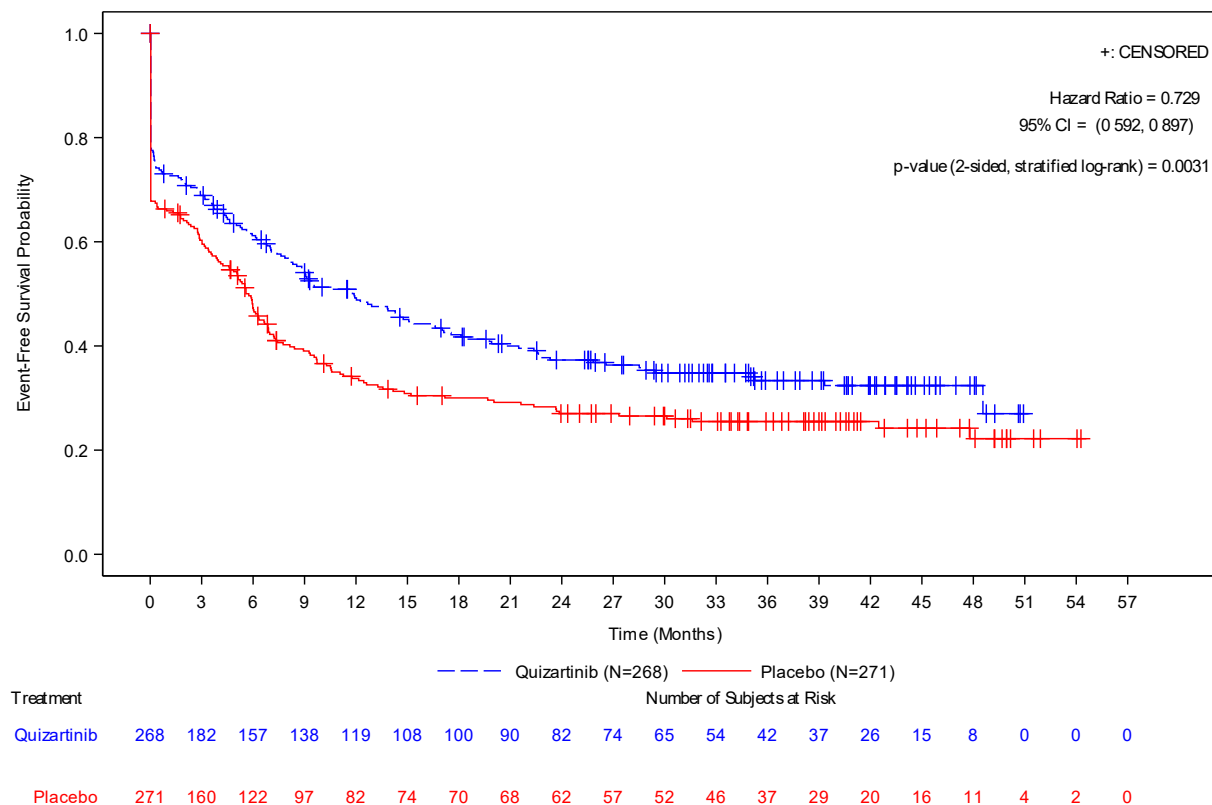
Statistics	Quizartinib (N = 268)	Placebo (N = 271)
ITF, defined as not achieving CR by the end of the Induction Phase (sensitivity analysis)		
Subjects (%) with events	185 (69.0)	208 (76.8)
Refractory disease	103 (38.4)	113 (41.7)
Relapse	44 (16.4)	63 (23.2)
Death	38 (14.2)	32 (11.8)
Subjects (%) without events (censored)	83 (31.0)	63 (23.2)
No postbaseline response assessment, no death date	1 (0.4)	1 (0.4)
Had CR, no relapse, no death date	82 (30.6)	62 (22.9)

Notes: The denominator for percentages is the number of subjects in the ITT Analysis Set.

EFS was defined as the time from the date of randomization to the date of refractory disease, relapse, or death from any cause, whichever occurred first, up to a 56-day window from the start of the last induction cycle.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Table 14.2.2.3

Figure 15 – Kaplan-Meier Plot of Event-free Survival – Sensitivity/Supplemental Analysis – Induction Treatment Failure, Defined as Not Achieving Composite Complete Remission by the End of the Induction Phase – IRC Assessment (ITT Analysis Set)



Note: Up to a 56-day window from the start of the last induction cycle. Statistical model for HR and nominal p-value: Stratified Cox PH model and stratified log-rank test.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Figure 14.2.2.3

Table 40 – Event-free Survival and Reasons for Censoring – Sensitivity/Supplemental Analysis – Induction Treatment Failure, Defined as Not Achieving Composite Complete Remission by the End of the Induction Phase – IRC Assessment (ITT Analysis Set)

Statistics	Quizartinib (N = 268)	Placebo (N = 271)
ITF, defined as not achieving CRc by the end of the Induction Phase (sensitivity analysis)		
Subjects (%) with events	170 (63.4)	196 (72.3)
Refractory disease	58 (21.6)	87 (32.1)
Relapse	61 (22.8)	75 (27.7)
Death	51 (19.0)	34 (12.5)

Statistics	Quizartinib (N = 268)	Placebo (N = 271)
Subjects (%) without events (censored)	98 (36.6)	75 (27.7)
No postbaseline response assessment, no death date	1 (0.4)	1 (0.4)
Had CR, no relapse, no death date	97 (36.2)	74 (27.3)

Notes: The denominator for percentages is the number of subjects in the ITT Analysis Set.

EFS was defined as the time from the date of randomization to the date of refractory disease, relapse, or death from any cause, whichever occurred first, up to a 56-day window from the start of the last induction cycle.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Table 14.2.2.3

Table 41 – Analysis of Response in Study AC220-A-U302 – IRC Assessment (ITT Analysis Set)

Statistics	Quizartinib (N = 268)	Placebo (N = 271)
CR rate; n (%) [95% CI^a]	147 (54.9) [48.7, 60.9]	150 (55.4) [49.2, 61.4]
Duration of CR (months); median [95% CI^b]	38.6 [21.9; NE]	12.4 [8.8; 22.7]
CRc rate; n (%) [95% CI^a]	192 (71.6) [65.8, 77.0]	176 (64.9) [58.9, 70.6]
Duration of CRc (months); median [95% CI^b]	27.2 [17.7; NE]	12.4 [8.7; 22.7]
CRi Rate^c; n (%) [95% CI^a]	45 (16.8) [12.5, 21.8]	26 (9.6) [6.4, 13.7]
Duration of CRi^c (months); median [95% CI^b]	11.5 [5.9, 21.8]	8.7 [4.5, NE]
Rate of CR with <i>FLT3</i>-ITD MRD negativity; n (%) [95% CI^a]		
Cutoff: 1×10^{-4} ^d	54 (20.1) [15.5, 25.5]	51 (18.8) [14.3, 24.0]
Not detectable (0) ^e	29 (10.8) [7.4, 15.2]	19 (7.0) [4.3, 10.7]
Rate of CRc with <i>FLT3</i>-ITD MRD negativity; n (%) [95% CI^a]		
Cutoff: 1×10^{-4} ^d	66 (24.6) [19.6, 30.2]	58 (21.4) [16.7, 26.8]
Not detectable (0) ^e	37 (13.8) [9.9, 18.5]	20 (7.4) [4.6, 11.2]

Statistics	Quizartinib (N = 268)	Placebo (N = 271)
Rate of CRi with <i>FLT3</i>-ITD MRD negativity; n (%) [95% CI ^a]		
Cutoff: 1×10^{-4} ^d	12 (4.5) [2.3, 7.7]	7 (2.6) [1.0, 5.2]
Not detectable (0) ^e	8 (3.0) [1.3, 5.8]	1 (0.4) [0.0, 2.0]

^a Based on the Clopper-Pearson method.

^b The median is from a Kaplan-Meier analysis. The CI for the median was computed using the Brookmeyer-Crowley method.

^c CRi was not specified as a secondary endpoint but is included for completeness.

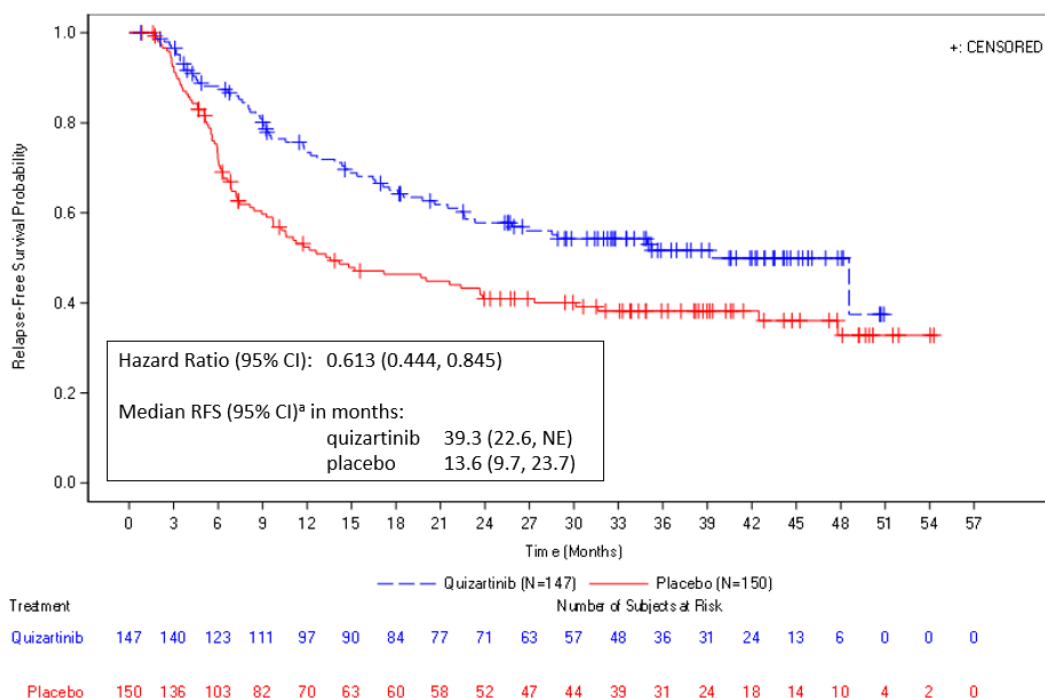
^d MRD negativity based on assessments to detect the fraction of *FLT3*-ITD leukemic cells present in bone marrow or blood by the end of induction on all clones and cutoff of 0.0001 (1 in 10,000 cells).

^e MRD negativity based on assessments by the end of induction on all clones and a cutoff of 0 (detectable/not detectable)

Notes: Based on assessments by the end of induction. The denominator for percentages is the number of subjects in the ITT Analysis Set.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Tables 14.2.3, 14.2.5, 14.2.5.1, and 14.2.5.2 and AC220-A-U302 CSR Supplemental Table 14.2.3.7

Figure 16 – Kaplan-Meier Plot of Relapse-free Survival for Subjects Achieving Complete Remission in Induction – IRC Assessment (ITT Analysis Set)



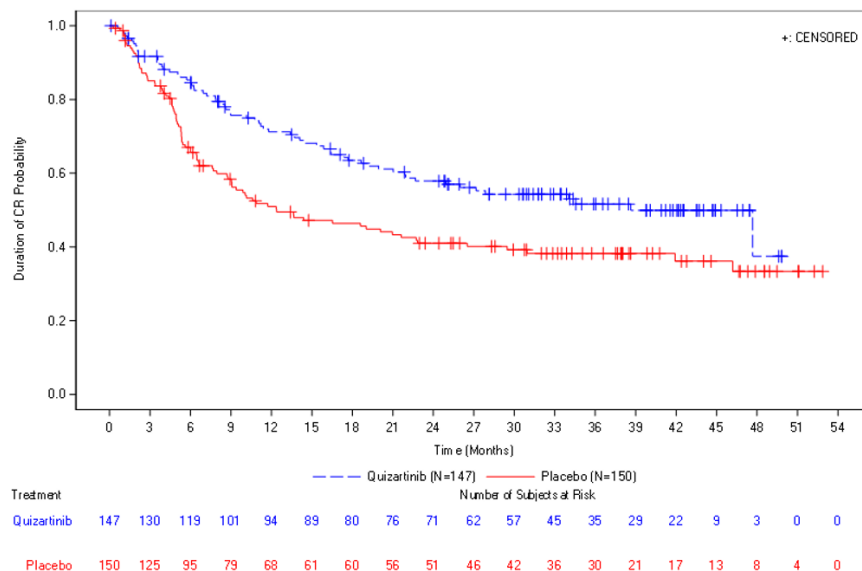
NDA Multi-disciplinary Review and Evaluation {NDA 216993} {VANFLYTA; quizartinib}

^a The median RFS is from a Kaplan-Meier analysis. The CI for the median was computed using the Brookmeyer-Crowley method.

Note: Subjects without a documented CR are excluded from the analysis.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Table 14.2.4.1 and Figure 14.2.3.2

Figure 17 – Kaplan-Meier Plot of Duration of Complete Remission – IRC Assessment (ITT Analysis Set)



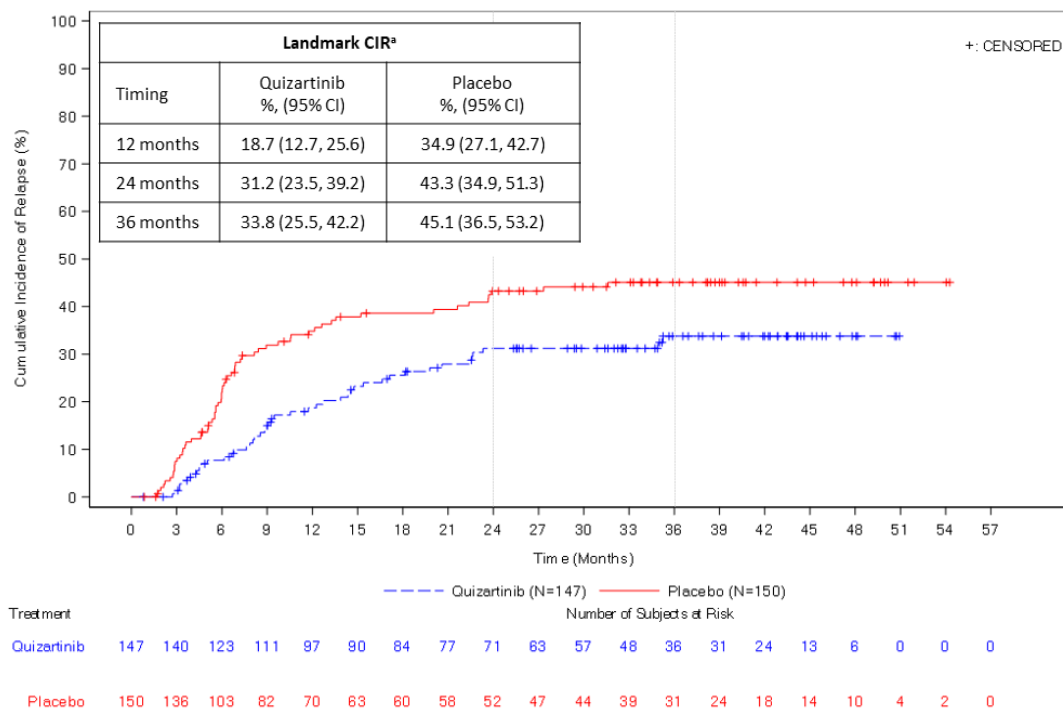
Note: Subjects without a documented response of CR are excluded from the analysis. Duration of CR is the time from the first documented CR until the date of documented relapse or death from any cause, whichever comes first. The median duration of CR is from a Kaplan-Meier analysis. The CI for the median was computed using the Brookmeyer-Crowley method.

Subjects without a documented response of CR were excluded from the analysis.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Figure 14.2.4

A post hoc analysis was performed to analyze the CIR from randomization in all subjects who achieved a CR in the Induction Phase, treating death prior to relapse as a competing risk. Rates of CIR were estimated using a nonparametric method and were summarized descriptively at the following timepoints: 12, 24 and 36 months (Figure 18).

Figure 18 – Post Hoc Analysis of the Cumulative Incidence of Relapse for Subjects Who Achieved Complete Remission in the Induction Phase – IRC Assessment (ITT Analysis Set)



^a CIR is the cumulative incidence of relapse from randomization in all subjects who achieved a CR during the Induction Phase. Estimated using the cumulative incidence function.

Data cutoff date: 13 Aug 2021. Source: AC220-A-U302 CSR Figure 14.2.2.5 and Table 14.2.2.5

The Applicant's Position:

The primary analysis for the secondary endpoint of EFS was based on a definition of ITF as not achieving a CR within 42 days from the start of the last induction cycle per the FDA AML Guidance (FDA, 2020) and was not statistically significant. Because the primary analysis of EFS was not statistically significant, formal hierarchical testing was not continued and results of other secondary efficacy endpoints are presented descriptively. Of note, in the original protocol, EFS was based on ITF defined as a failure to achieve a CR or a CRi at the end of the Induction Phase, using a window of up to 56 days from the start of the last induction cycle. At the time of the update to the EFS definition, all subjects randomized in the study, including those who were ongoing, had completed the Induction Phase.

A prespecified sensitivity analysis for EFS was performed using a definition of ITF as failure to achieve CR by the end of induction (ie, within the protocol-specified 56 day window). This analysis provides additional supportive evidence for the efficacy of quizartinib (see Table 37).

Numerically higher CRc rates were evident in the quizartinib arm compared with the placebo arm and were primarily driven by higher rates of CRi in the quizartinib arm than in the placebo arm. Similar rates of CRc with *FLT3*-ITD MRD negativity at the end of induction were observed between the treatment arms at a 1×10^{-4} cutoff. However, when MRD was assessed as detectable versus not detectable (at a cutoff of 0), differences between quizartinib and placebo were observed, suggesting the use of quizartinib in combination with chemotherapy leads to deeper responses (Table 41).

While the rates of CR and CR with *FLT3*-ITD MRD negativity at the end of induction were similar between treatment arms (see Table 41), both the median duration of CR and the median RFS were substantially longer in subjects who did achieve a CR during induction on the quizartinib arm when compared to the placebo arm, with a difference of 26.2 months and 25.7 months, respectively. In a post hoc analysis, the CIR in subjects achieving a CR in the Induction Phase also shows a higher percentage of subjects in the placebo arm experiencing relapse at 24 months and 36 months. Taken together, these data indicate that quizartinib delays relapse in subjects who achieve a CR during the Induction Phase, which further supports the clinical benefit of quizartinib in the claimed indication.

The FDA's Assessment:

FDA analyses for EFS, the key secondary endpoint:

The primary analysis results of EFS are presented in Table 42 and Figure 19: Kaplan-Meier plot of EFS on QuANTUM-First (ITT Analysis Set). Most EFS events are treatment failure, defined as failure to achieve CR within 42 days of start of the last cycle of induction. There is a numerically higher treatment failure rate in the quizartinib arm (51%) than the placebo arm (48%), causing a bigger drop of the Kaplan-Meier curve in the quizartinib arm at Day 1, and therefore, a crossing hazards pattern due to higher relapse rate in the placebo arm after Day 1. The estimated HR is 0.92 (95% CI: 0.75, 1.11) in favor of quizartinib but the corresponding two-sided p value of 0.2371 does not cross the efficacy boundary of 0.05, which is consistent with that reported by the Applicant (Table 37).

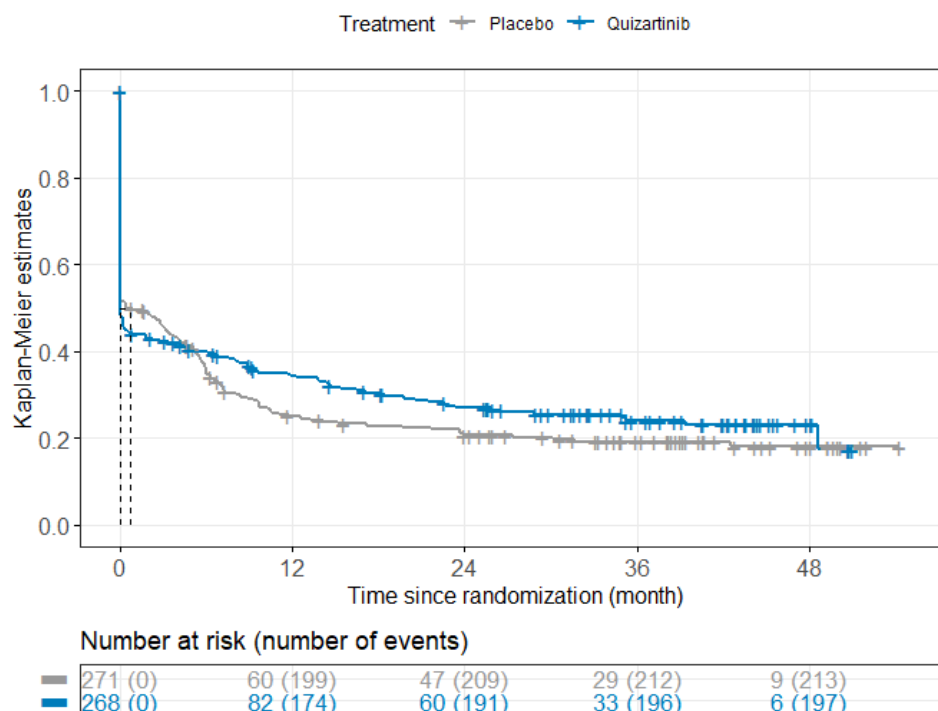
Table 42: Primary analysis of EFS (ITT Analysis Set)

	Quizartinib N = 268	Placebo N = 271
No. events (%)	198 (74)	213 (79)
Treatment failure	136 (51)	131 (48)
Relapse	30 (11)	53 (20)
Death	32 (12)	29 (11)
No. censoring (%)	70 (26)	58 (20)
Median, month (95% CI)	0.03 (0.03, 1.8)	0.7 (0.03, 3.6)
HR (95% CI)	0.92 (0.75, 1.11)*	
Two-sided p-value	0.2371*	

*: HR = hazard ratio. HR and p-value are based on Cox model and log-rank test stratified by age, region and WBC at AML diagnosis.

Source: FDA analysis

Figure 19: Kaplan-Meier plot of EFS on QuANTUM-First (ITT Analysis Set)



Source: FDA analysis

FDA conducted sensitivity analyses of EFS as well. Below Table 43 shows the results of the EFS sensitivity analyses, including Sensitivity analysis 1 where the 42-day window for achievement of CR is removed and Sensitivity analysis 2 where treatment failure is defined as failure to achieve CR or CRi by the end of induction without a 42-day window. In Sensitivity analysis 2, HR estimations are lower because of greater treatment failure rate in the placebo versus quizartinib arm. The corresponding Kaplan-Meier curves (not shown but similar to Figure 14 and Figure 15) do not feature the same crossing pattern as in the primary analysis (Figure 19).

The differences in EFS analyses are driven by longer times to response observed in the quizartinib arm. The median time to CR was 28 days (range: 15, 105) and 23 days (range: 14, 91) in the quizartinib and placebo arm, respectively. Among CRc responders, the median time to CRc was 26 days (range: 12, 105) and 22 days (range: 14, 91), respectively.

Table 43: Sensitivity analysis of EFS (ITT Analysis Set)

	No. treatment failure (%)		HR (95% CI)	Two-sided p-value
	Quizartinib N = 268	Placebo N = 271		
Primary analysis	136 (51)	131 (48)	0.92 (0.75, 1.1)	0.2371
Sensitivity analysis 1 (no ITF window)	103 (38)	113 (42)	0.82 (0.67, 1)	0.0323
Sensitivity analysis 2 (no ITF window, ITF=CR+CRi)	58 (22)	87 (32)	0.73 (0.59, 0.9)	0.0031

Source: FDA analysis

FDA analyses for the other secondary endpoints:

As the EFS analysis result was not significant, other secondary endpoints were not formally tested and results are considered descriptive only. Table 44 shows that rates of CR, CR with FLT3-ITD MRD negativity, and CRc with FLT3-ITD MRD negativity at the end of induction were similar between treatment arms. The CRi rate was numerically higher for quizartinib compared to placebo.

Table 44: Analysis of other secondary endpoints (ITT Analysis Set)

n (%)	Quizartinib N = 268	Placebo N = 271
CRc (CR + CRi)	192 (72)	176 (65)
CR	147 (55)	150 (55)
CRi	45 (17)	26 (10)
CRc with FLT3-ITD MRD negativity	66 (25)	58 (21)
CR with FLT3-ITD MRD negativity	54 (20)	51 (19)

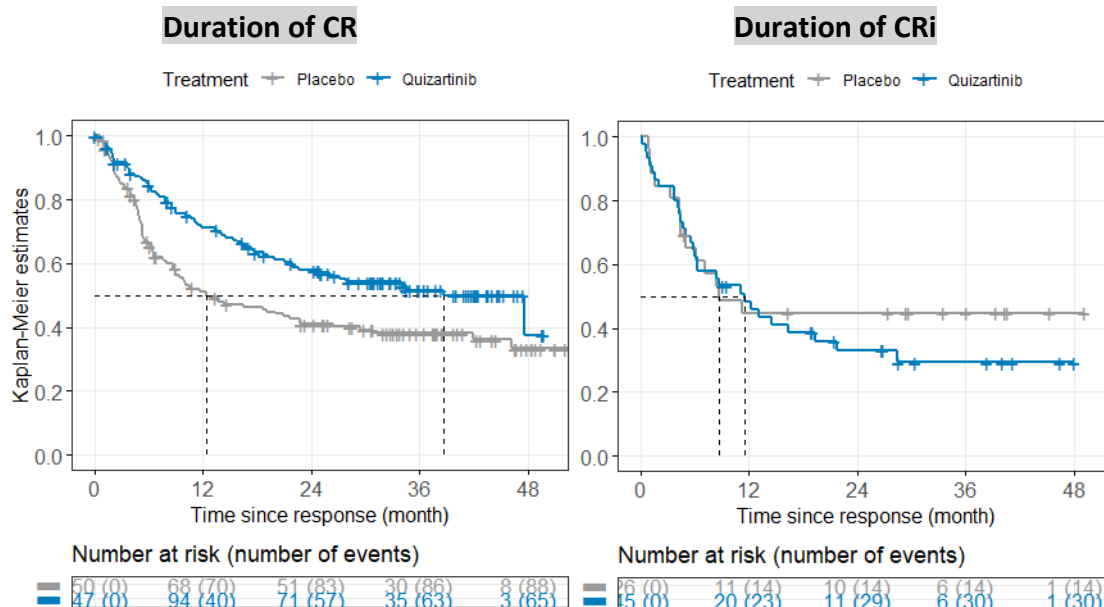
Source: FDA analysis

The clinical adjudication of CR responses agreed with the Applicant's assessment of this endpoint on both arms of Study AC220-A-U302.

Figure 20 shows the Kaplan-Meier plots of duration of response (both CR and CRi). Duration of CR was defined as the time from the first documented CR until the date of documented relapse or death from any cause, whichever came first. Median duration of CR was 38.6 versus 12.4 months in the quizartinib versus placebo arms, respectively; durability of CRi was similar between two arms. Note that these analyses are based on non-randomized subgroups defined by a post-randomization event (CR or CRi). In general, such analyses are biased, since

randomization is broken, and baseline covariates are no longer guaranteed to be balanced. Therefore, results from the analyses should be interpreted with caution.

Figure 20: Kaplan-Meier plot of duration of response (ITT Analysis Set who achieved CR or CRi at the end of induction)



Source: FDA analysis

Dose/Dose Response

Data:

The data leading to establishing the dose and dose regimen used in Study AC220-A-U302 are summarized in Section 6.2.2.

The Applicant's Position:

As with other receptor tyrosine kinase inhibitors, maintaining adequate target coverage is important in achieving clinical efficacy. The dosing regimen was established by considering available clinical efficacy and safety data from prior clinical studies, including ex vivo PD data. The efficacy, safety, and tolerability data from Study AC220-A-U302 confirm that the dosing regimen utilized represents an appropriate balance between safety and efficacy considerations.

The FDA's Assessment:

See FDA's assessment in Section 6.2.2 above.

Durability of Response

Data:

See under the Section Efficacy Results.

The Applicant's Position:

As discussed under the Section Efficacy Results – Secondary and other relevant endpoints, in subjects achieving a CR in the Induction Phase, the response is maintained for a substantially longer duration compared to placebo as measured by the median duration of CR. The Kaplan-Meier plot of the duration of CR shows sustained separation of the curves for up to 3 years and no notable differences in the demographics and baseline disease characteristics of the responders were observed between the 2 treatment arms.

The FDA's Assessment:

See FDA's Assessment under the section "Efficacy Results – Secondary and other relevant endpoints" above.

Persistence of Effect

Data:

Overall, more subjects in the quizartinib arm than the placebo arm entered the Continuation Phase (Table 21: Subject Disposition in Study AC220-A-U302) and approximately 30% of subjects in the quizartinib arm were treated for more than 1 year (Table 70). Addition of quizartinib to standard chemotherapy resulted in a 16.8-month prolongation of median OS and the survival benefit was maintained over time as demonstrated by higher OS rates for quizartinib compared to placebo at 12, 24, 36, and 48 months (Table 26). Additionally, there was sustained separation in RFS curves (see Figure 16). The duration of CR was approximately 3 times longer in subjects treated with quizartinib compared to placebo with sustained separation of the CR curves out to 3 years (see Figure 17), and lower CIR rates were seen in subjects who achieved CR treated with quizartinib compared with those in the placebo arm (see Figure 18).

The Applicant's Position:

Quizartinib in combination with standard chemotherapy delays relapse and thereby results in improved OS.

The FDA's Assessment:

FDA was able to obtain similar results for the endpoints OS, DOR, and RFS to that presented above under Data section provided by the Applicant. Note that the analyses of DOR and RFS were exploratory without pre-specified statistical test(s).

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Data:

In addition to the clinical endpoints, Study AC220-A-U302 was also designed to collect patient-reported outcomes (PRO) as exploratory endpoints. Assessments were conducted using two PRO scales: European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) and EuroQol 5 Dimension 5 Level (EQ-5D-5L). EORTC QLQ-C30 is a self-administered, cancer-specific 30-item questionnaire and incorporates scales for global health status/quality of life (QoL), functional status, symptoms, and perceived financial impact of the disease. EQ-5D-5L is a generic and preference-weighted measure for capturing QoL on the day of the assessment. Among the 539 subjects who were included in the ITT Analysis Set, 509 (94.4%) were included in the PRO Analysis Set (N = 254 for quizartinib and N = 255 for placebo).

Table 45 – EORTC QLQ-C30 Compliance Rate in Study AC220-A-U302 by Visit (EORTC QLQ-C30 Global Health Status/QoL Analysis Set)

Visit	Global Health Status/Quality of Life			All Other Scales
	Overall n/N (%)	Quizartinib n/N (%)	Placebo n/N (%)	Range of Compliance Rates (%)
Induction Phase				
Cycle 1 Day 8 (Baseline)	505/509 (99.2)	252/254 (99.2)	253/255 (99.2)	98.2 - 99.2
Cycle 1 Day 28	396/458 (86.5)	199/231 (86.1)	197/227 (86.8)	85.4 - 86.7
Cycle 2 Day 28	76/93 (81.7)	36/45 (80.0)	40/48 (83.3)	80.6 - 81.7
Consolidation Phase				
Cycle 1 Day 6	306/321 (95.3)	153/158 (96.8)	153/163 (93.9)	94.1 - 95.3
Cycle 1 Day 28	210/289 (72.7)	103/144 (71.5)	107/145 (73.8)	72.0 - 72.7
Cycle 2 Day 6	142/205 (69.3)	71/102 (69.6)	71/103 (68.9)	68.8 - 70.2
Cycle 2 Day 28	119/173 (68.8)	55/86 (64.0)	64/87 (73.6)	67.6 - 68.8
Cycle 3 Day 6	82/116 (70.7)	35/54 (64.8)	47/62 (75.8)	69.8 - 70.7
Cycle 3 Day 28	75/99 (75.8)	32/46 (69.6)	43/53 (81.1)	74.7 - 75.8
Cycle 4 Day 6	35/45 (77.8)	18/24 (75.0)	17/21 (81.0)	75.6 - 77.8
Cycle 4 Day 28	38/42 (90.5)	20/21 (95.2)	18/21 (85.7)	88.1 - 90.5
Continuation Phase				
Cycle 1 Day 1	184/197 (93.4)	100/109 (91.7)	84/88 (95.5)	92.4 - 93.9
Cycle 4 Day 1	149/167 (89.2)	79/92 (85.9)	70/75 (93.3)	86.8 - 89.2
Cycle 7 Day 1	136/149 (91.3)	74/84 (88.1)	62/65 (95.4)	89.9 - 91.3

Visit	Global Health Status/Quality of Life			All Other Scales
	Overall n/N (%)	Quizartinib n/N (%)	Placebo n/N (%)	Range of Compliance Rates (%)
Cycle 10 Day 1	121/134 (90.3)	64/72 (88.9)	57/62 (91.9)	88.1 - 90.3
Cycle 13 Day 1	104/112 (92.9)	59/64 (92.2)	45/48 (93.8)	91.1 - 92.9
Cycle 16 Day 1	90/105 (85.7)	51/59 (86.4)	39/46 (84.8)	84.8 - 85.7
Cycle 19 Day 1	85/94 (90.4)	45/50 (90.0)	40/44 (90.9)	89.4 - 90.4
Cycle 22 Day 1	73/83 (88.0)	40/45 (88.9)	33/38 (86.8)	88.0 – 88.0
Cycle 25 Day 1	62/68 (91.2)	35/37 (94.6)	27/31 (87.1)	91.2 - 92.6
Cycle 28 Day 1	55/58 (94.8)	29/30 (96.7)	26/28 (92.9)	94.8 - 94.8
Cycle 31 Day 1	42/48 (87.5)	24/26 (92.3)	18/22 (81.8)	87.5 - 87.5
Cycle 34 Day 1	33/38 (86.8)	19/20 (95.0)	14/18 (77.8)	86.8 - 89.5

N = Number of subjects at each visit; n = Number of subjects with a score completed at the visit (and having a PRO baseline result for the considered scale)

Note: % = 100 * n/N

Source: PRO Report Appendix Table 1.2.01.v2 to 1.2.15.v2

Descriptive analyses were conducted to describe the absolute scores and changes from PRO baseline (Induction Cycle 1 Day 8) for each score on the EORTC QLQ-C30 and EQ-5D-5L scales. A mixed-effects model for repeated measures (MMRM) analysis was performed to summarize the longitudinal changes in each QoL score and systematic differences in changes between the quizartinib and placebo arms. The MMRM analysis included change from PRO baseline as the response variable and QoL score at PRO baseline, time/visit, and a treatment-by-time interaction as covariates. A 10-point change in score was established as minimal clinically important difference (MCID) for EORTC QLQ-C30 scales, which is defined as “the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s disease management” (Deschler, 2010; Dimopoulos, 2013; Roussel, 2020;). A change of 0.06 was used as the MCID for EQ-5D-5L index scores, and a 7-point MCID was used for visual analog scale (VAS) (McClure, 2017).

Table 46 – Summary of Mixed-effects Model for Repeated Measures Differences in Change in Score From PRO Baseline (Quizartinib – Placebo) for EORTC QLQ-C30 and EQ-5D-5L in Study AC220-A-U302

Parameter	Difference Between Quizartinib vs Placebo (95% CI)
EORTC QLQ-C30	

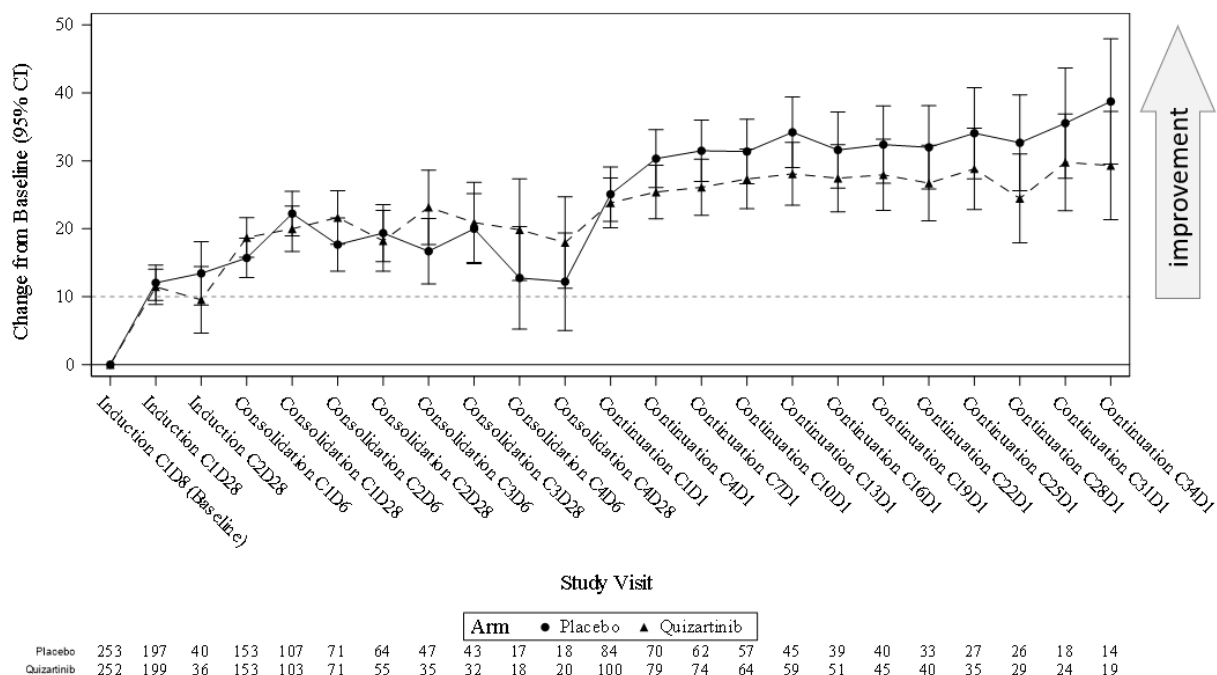
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{VANFLYTA; quizartinib}

Global Health Status/QoL	-2.0 (-4.8; 0.7)
Physical Functioning Score	-2.6 (-5.6, 0.3)
Role Functioning Score	-6.2 (-10.5, -1.9)
Emotional Functioning Score	-3.3 (-6.0, -0.7)
Cognitive Functioning Score	-0.4 (-3.0, 2.3)
Social Functioning Score	-7.0 (-11.4, -2.7)
Fatigue Score	3.0 (-0.1, 6.1)
Nausea and Vomiting Score	3.3 (1.1, 5.5)
Pain Score	1.4 (-1.4, 4.2)
Dyspnea Score	2.4 (-0.1, 4.6)
Insomnia Score	3.0 (-0.3, 6.3)
Appetite Loss Score	3.4 (-0.1, 7.0)
Constipation Score	2.5 (0.0, 4.9)
Diarrhea Score	1.3 (-0.8, 3.4)
Financial Difficulties Score	4.2 (0.1, 8.4)
EQ-5D-5L	
Index Score (US Value Set)	-0.01 (-0.03, 0.01)
VAS Score	-3.45 (-6.11, -0.79)

Note: The MMRM model included variables for baseline score, treatment, time, and treatment × time interaction. The following model specifications were applied: 1. Estimation Method: REML, 2. ESTIMATE: Least squares mean of the difference between groups (quizartinib - placebo), 3. Structure of covariance matrix: Autoregressive.
Source: PRO Report Appendix Table 1.6

Global health status/QoL, physical functioning, fatigue, and nausea/vomiting measure aspects of patient-relevant outcomes of particular importance for daily functioning and QoL and the longitudinal data are therefore provided in Figure 21, Figure 22, Figure 23, and Figure 24, respectively.

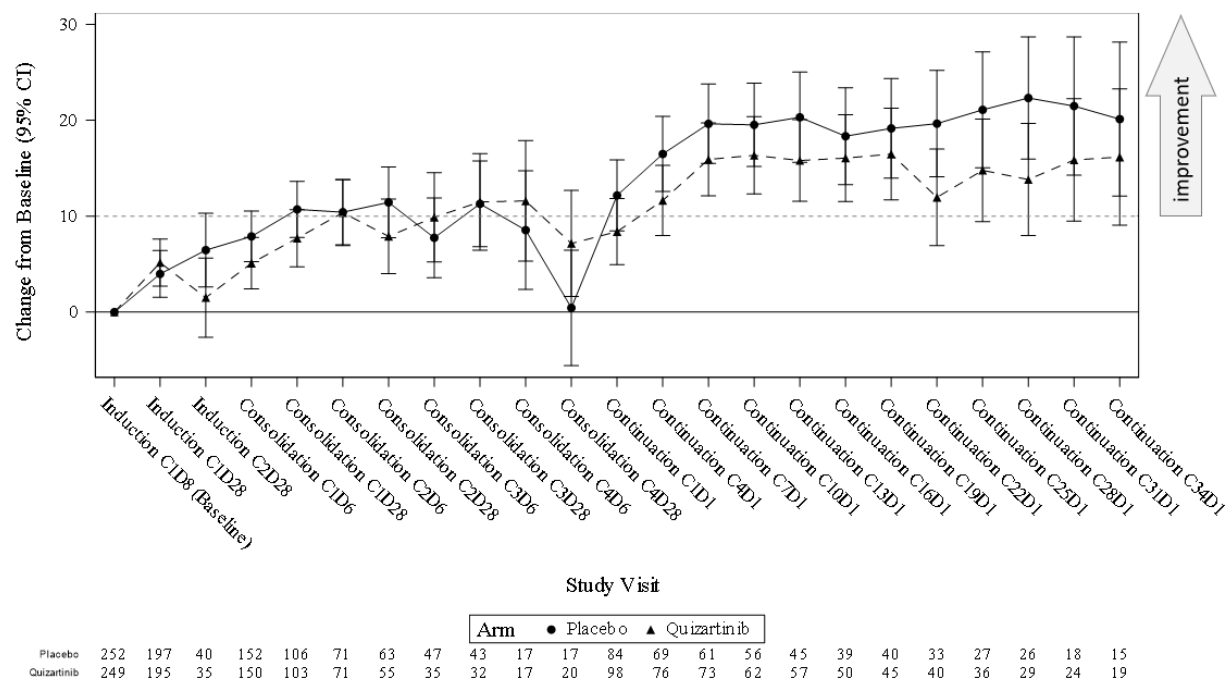
Figure 21 – EORTC QLQ-C30 Global Health Status/QoL Scale Mixed-effects Model for Repeated Measures for Change in Score From Baseline for Quizartinib vs. Placebo



Notes: The MMRM model included variables for baseline score, treatment, time, and treatment × time interaction. The following model specifications were applied: 1. Estimation Method: REML, 2. ESTIMATE: Least squares mean of the difference between groups (quizartinib - placebo), 3. Structure of covariance matrix: Autoregressive. For EORTC QLC-C30, a 10-point change in score was considered as MCID, shown as the horizontal dash line in the chart: a >10-point increase was considered 'improved', a >10-point decrease was considered 'worsened', a change between -10 and 10 (inclusive) was considered 'stable'.

Source: PRO Report Figure 2

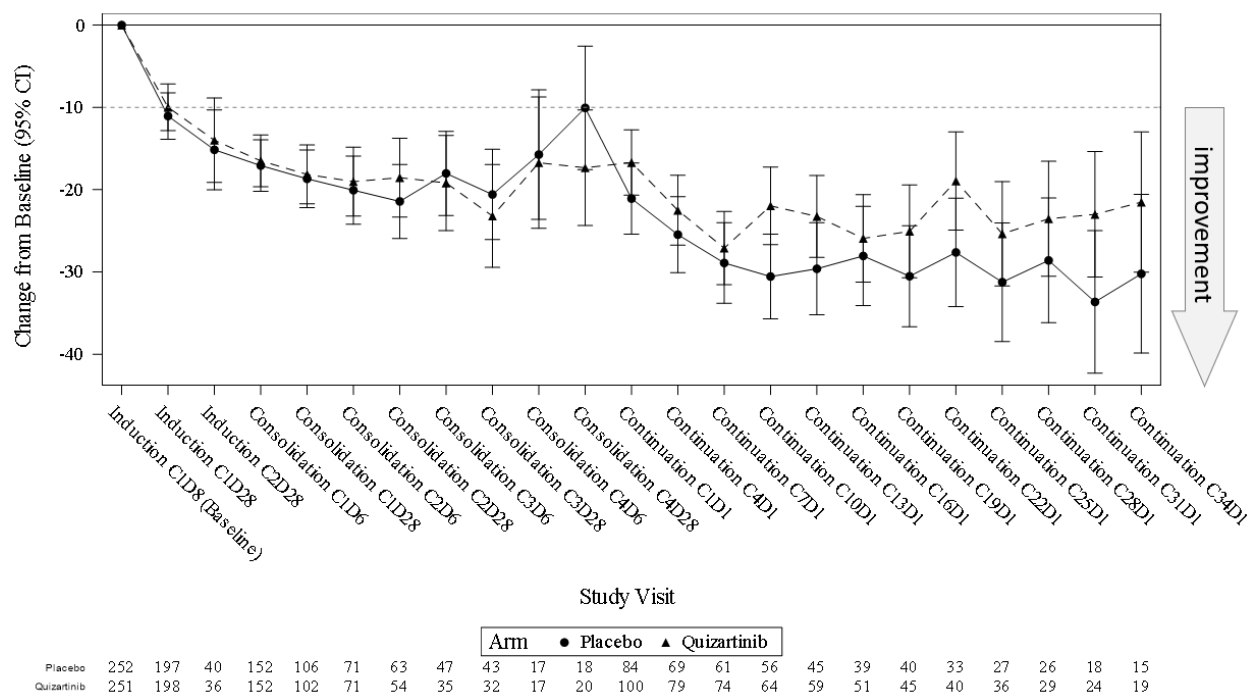
Figure 22 – EORTC QLQ-C30 Physical Functioning Scale Mixed-effects Model for Repeated Measures for Change in Score From Baseline for Quizartinib vs. Placebo



Notes: The MMRM model included variables for baseline score, treatment, time, and treatment × time interaction. The following model specifications were applied: 1. Estimation Method: REML, 2. ESTIMATE: Least squares mean of the difference between groups (quizartinib - placebo), 3. Structure of covariance matrix: Autoregressive. For EORTC QLC-C30, a 10-point change in score was considered as MCID, shown as the horizontal dash line in the chart. For the physical functioning scale, a >10-point increase was considered 'improved', a >10-point decrease was considered 'worsened', a change between -10 and 10 (inclusive) was considered 'stable'.

Source: PRO Report Figure 3

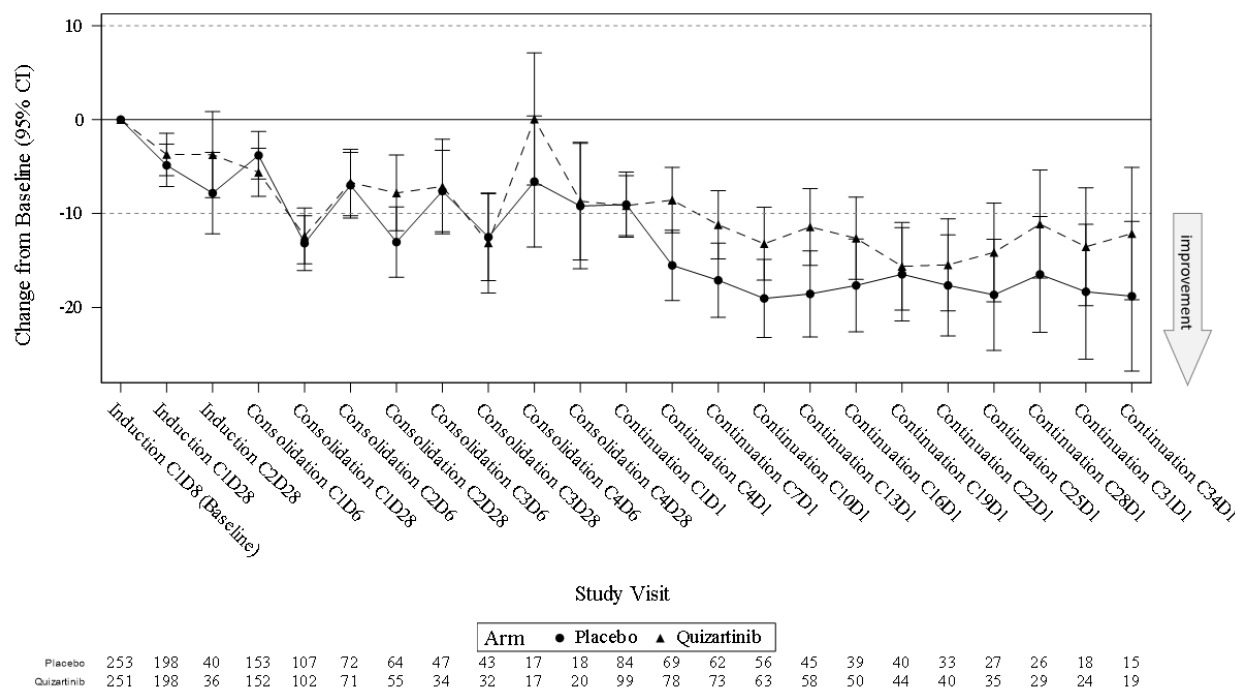
Figure 23 – EORTC QLQ-C30 Fatigue Scale Mixed-effects Model for Repeated Measures for Change in Score From Baseline for Quizartinib vs. Placebo



Note: The MMRM model included variables for baseline score, treatment, time, and treatment × time interaction. The following model specifications were applied: 1. Estimation Method: REML, 2. ESTIMATE: Least squares means of the difference between groups (quizartinib - placebo), 3. Structure of covariance matrix: Autoregressive. For EORTC QLC-C30, a 10-point change in score was considered as MCID, shown as the horizontal dash line in the chart. For the fatigue scale, a >10-point increase was considered 'worsened', a >10-point decrease was considered 'improved', a change between -10 and 10 (inclusive) was considered 'stable'.

Source: PRO Report Figure 8

Figure 24 – EORTC QLQ-C30 Nausea and Vomiting Scale Mixed-effects Model for Repeated Measures for Change in Score From Baseline for Quizartinib vs. Placebo



Note: The MMRM model included variables for baseline score, treatment, time, and treatment × time interaction. The following model specifications were applied: 1. Estimation Method: REML, 2. ESTIMATE: Least squares mean of the difference between groups (quizartinib - placebo), 3. Structure of covariance matrix: Autoregressive. For EORTC QLC-C30, a 10-point change in score was considered as minimally important difference, shown as the horizontal dash line in the chart. For the nausea and vomiting scale, a >10-point increase was considered 'worsened', a >10-point decrease was considered 'improved', a change between -10 and 10 (inclusive) was considered 'stable'.

Source: PRO Report Figure 9

The Applicant's Position:

Study AC220-A-U302 is the first study to explore the impact of quizartinib on QoL for adult patients with *FLT3*-ITD (+) AML. PRO data were collected for exploratory purposes only and the study was not designed to formally compare the treatment impact of quizartinib on PRO measures to that of placebo when combined with standard chemotherapy. A clinically meaningful improvement in QoL over time was observed in both treatment arms, albeit this observation may be confounded by potential bias introduced by attrition of subjects in later timepoints. When comparing QoL measures between treatment arms, the differences between them did not exceed the MCID of 10 points, suggesting no detrimental impact on QoL resulting from the addition of quizartinib to standard-of-care chemotherapy for newly diagnosed *FLT3*-ITD (+) AML.

The FDA's Assessment:

FDA agrees with the Applicants assessment that the PRO data above shows an improvement (> 10-point change) for both arms from the baseline measurement. However, we note that this is not necessarily surprising considering that the baseline was assessed in patients recently diagnosed with acute leukemia and after just having completed 7 days of intensive chemotherapy. We also note that later timepoints of analysis occur only in patients that live and remained on study to report their improvement from this QOL nadir at the time of the baseline measurement.

We also note that during the intensive periods of treatment (induction and consolidation) the QOL measures are almost identical between treatment arms. However, during the continuation phase, there appeared to be some separation across the selected PRO endpoints which numerically favors the placebo arm over the control arm. Of note, the interpretation should be taken with caution.

Clinical reviewer comments: This result is perhaps not surprising since the beneficial effect of quizartinib within this study design was to prevent relapse of disease. That is, the postulated benefit of quizartinib is to persist on study and be alive at the cost of added toxicity. This leads us to question the utility of QOL investigation in the setting of remission when the testing is against a placebo. Since one cannot feel better due to the benefit of the drug in this design, what in effect is being assessed is the toxicity burden of the continuation therapy against placebo treatment. If the study was assessing the toxicity burden of two comparative treatments in a continuation setting, QOL measure in addition to standard analysis of toxicity could add to our understanding of overall tolerability.

Additional Analyses Conducted on the Individual Trial

Data:

Analysis of HSCT in Study AC220-A-U302

Per protocol in Study AC220-A-U302, subjects were permitted to undergo allo-HSCT after CR or CRi was achieved. Allo-HSCT was to be performed after the Induction Phase, any time during the Consolidation Phase, or, if certain criteria were met, within the first 3 months of the Continuation Phase.

Table 47 – Post Hoc Analysis of HSCT Rate in Study AC220-A-U302 (ITT Analysis Set)

Statistics	Quizartinib (N = 268)	Placebo (N = 271)
Subjects who underwent HSCT overall ^a		
n (%)	144 (53.7)	128 (47.2)
95% CI ^b	(47.6, 59.8)	(41.2, 53.4)
Subjects who underwent HSCT in CR1 ^c		
n (%)	84 (31.3)	73 (26.9)
95% CI ^b	(25.8, 37.3)	(21.7, 32.6)
Subjects who underwent HSCT without CR		
n (%)	52 (19.4)	41 (15.1)
95% CI ^b	(14.8, 24.7)	(11.1, 20.0)
Subjects who underwent HSCT after relapse ^d		
n (%)	8 (3.0)	14 (5.2)
95% CI ^b	(1.3, 5.8)	(2.9, 8.5)

^a Includes protocol-specified HSCT and non-protocol-specified HSCT

^b Based on the Clopper-Pearson method.

^c Includes protocol-specified HSCT and non-protocol-specified HSCT that occurred after the CR1 without evidence of relapse by IRC assessment.

^d Includes protocol-specified HSCT and non-protocol-specified HSCT that occurred after relapse post CR by IRC assessment.

Note: The denominator for percentages is the number of subjects in the ITT Analysis Set. Subjects with protocol-specified HSCT are subjects who underwent allo-HSCT directly following protocol treatment, with no intervening AML therapy (excluding conditioning regimens).

Source: eCTD M5.3.5.1 AC220-A-U302 CSR Supplemental Table 14.2.6.2

The Applicant's Position:

The rates of HSCT were high in both treatment arms, which reflects the clinical practice for this subpopulation of high-risk patients with *FLT3*-ITD (+) AML. Rates of HSCT overall and during the first CR (CR1) were numerically higher with quizartinib than with placebo. Approximately 30% of subjects in the quizartinib arm and 27% in the placebo arm were transplanted in CR1, which is considered standard of care for *FLT3*-ITD (+) AML in many countries.

The FDA's Assessment:

The timing of HSCT with respect to disease status was similar on both arms, with most transplantations occurring as part of first line therapy (either during first CR or in patients who did not achieve a CR). Despite the high frequency of HSCT on the study, the OS benefit in favor

of the quizartinib arm appears consistent when OS is censored at the time of HSCT (Table 27).

Also, FDA requested the Applicant to clarify the numbers in Table 47, specifically the 157 patients receiving HSCT in first complete remission (CR) on 29 March 2023. From datasets ADRS and ADSL, FDA got 297 subjects achieving CR (only first time CR counted) by INDEPENDENT ASSESSOR, among which 179 HSCT in first CR across the arms, while 245 by INVESTIGATOR, among which 145 HSCT in first CR across the arms. The Applicant responded on 17 April 2023, clarifying that “Two-hundred and ninety-seven (297) subjects achieved CR. Of those, 179 CR patients received HSCT (157 with HSCT in CR1 and 22 with HSCT after relapse).”

Data:

Analysis of EFS and CR by NPM1 mutation status in Study AC220-A-U302

Table 48 – Analysis of Event-free Survival Based on *NPM1* Mutation Status in Study AC220-A-U302 – IRC Assessment (ITT Analysis Set)

Statistics	NPM1 Mutation Status			
	Yes		No	
	Quizartinib (n = 142)	Placebo (n = 140)	Quizartinib (n = 116)	Placebo (n = 120)
Primary analysis: ITF definition: Not achieving CR by Day 42 from the start of the last induction cycle				
Subjects with events, n*	95	104	94	101
Median EFS ^a (95% CI) (months)	6.14 (0.23, 13.86)	5.59 (2.86, 6.34)	0.03 (NE, NE)	0.03 (NE, NE)
HR ^b relative to placebo (95% CI)	0.856 (0.647, 1.131)		0.959 (0.724, 1.271)	
Sensitivity analysis: ITF definition: Not achieving CR by the end of the Induction Phase				
Subjects with events, n*	86	100	91	101
Median EFS ^a (95% CI) (months)	13.86 (8.54, 25.82)	6.14 (5.13, 8.41)	0.03 (NE, NE)	0.03 (NE, NE)
HR ^b relative to placebo (95% CI)	0.734 (0.550, 0.980)		0.890 (0.670, 1.182)	
Sensitivity analysis: ITF definition: Not achieving CR _c by the end of the Induction Phase				
Subjects with events, n*	78	92	85	97
Median EFS ^a (95% CI) (months)	19.78 (12.68, NE)	6.97 (6.01, 10.58)	4.34 (0.03, 8.15)	0.03 (0.03, 2.86)
HR ^b relative to placebo (95% CI)	0.696 (0.514, 0.942)		0.760 (0.568, 1.018)	

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^a The median EFS is from a Kaplan-Meier analysis. The CI for the median is computed using the Brookmeyer-Crowley method.

^b The Cox PH model is not adjusted for stratification factors.

Note: EFS is defined as the time from the date of randomization to the date of refractory disease, relapse, or death from any cause, whichever occurred first. n* includes subjects with an EFS event and n represents the number of subjects in each *NPM1* mutation status subgroup.

Source: eCTD M5.3.5.1 AC220-A-U302 CSR Supplemental Tables 14.2.2.4.1, 14.2.2.4.2 and 14.2.2.4.3

Table 49 – Analysis of Response Rate Based on *NPM1* Mutation Status in Study AC220-A-U302 – IRC Assessment (ITT Analysis Set)

Statistics	<i>NPM1</i> Mutation Status			
	Yes		No	
	Quizartinib (N=268)	Placebo (N=271)	Quizartinib (N=268)	Placebo (N=271)
CR by IRC				
n*/n (%)	98/142 (69.0)	97/140 (69.3)	44/116 (37.9)	44/120 (36.7)
95% CI ^a	(60.7, 76.5)	(60.9, 76.8)	(29.1, 47.4)	(28.1, 45.9)
CRc by IRC				
n/n* (%)	120/142 (84.5)	115/140 (82.1)	65/116 (56.0)	52/120 (43.3)
95% CI ^a	(77.5, 90.0)	(74.8, 88.1)	(46.5, 65.2)	(34.3, 52.7)

^a Based on the Clopper-Pearson method. n* includes subjects with a response and n represents the number of subjects in each *NPM1* mutation status subgroup.

Source: eCTD M5.3.5.1 AC220-A-U302 CSR Supplemental Tables 14.2.3.5 and 14.2.3.6

The Applicant's Position:

Although the study was not designed to assess the impact of *NPM1* mutation status on treatment outcomes, the results seen in the mutant *NPM1* (*NPM1*^{mut}) and WT *NPM1* (*NPM1*^{wt}) subgroups are consistent with the EFS and CR/CRc analyses in the overall study population. Consistent with the well-established role of *NPM1*^{wt} as an adverse prognostic factor (Pollyea, 2021; Döhner, 2017), better outcomes were observed in *NPM1*^{mut} subjects compared to *NPM1*^{wt} subjects, including the longer median EFS based on the primary and 2 sensitivity EFS analyses, as well as the higher rates of CR and CRc in *NPM1*^{mut} subjects versus *NPM1*^{wt} subjects.

No differences were seen when comparing the rates of CR or CRc for quizartinib and placebo in both the *NPM1*^{mut} and *NPM1*^{wt} subgroups, which is consistent with the results seen in the overall population. Similarly, when comparing the treatment effect of quizartinib versus placebo based on EFS in both the *NPM1*^{mut} and *NPM1*^{wt} subgroups the results are consistent with the trends in the overall population. When considering the protocol-defined EFS based on ITF as not achieving CRc by the end of the Induction Phase, HRs of 0.760 in the *NPM1*^{wt} subgroup and 0.696 in the *NPM1*^{mut} subgroup were observed, suggesting there may be a

benefit of quizartinib in both *NPM1* subgroups. It is important to recognize the high unmet medical need in the high-risk *FLT3*-ITD (+) *NPM1*^{wt} population where treatment outcomes associated with available therapies remain unsatisfactory.

The FDA's Assessment:

FDA agrees with the Applicant's assessment except a few numbers as follows:

In Table 48, Sensitivity analysis: ITF definition: Not achieving CRc by the end of the Induction Phase, under *NPM1* wild-type columns, 1) the lower boundary of 95% CI of median EFS for quizartinib arm was 2.83, not 0.03; 2) the median EFS (95% CI) for placebo arm were 2.10 (1.64, 3.25), not 0.03 (0.03, 2.86) based on FDA analyses.

The effect of *NPM1* mutation status on EFS and CR endpoints showed similar trends to those in the OS analysis above. Specifically, that *NPM1* mutated patients treated with quizartinib had the longest median EFS, at least with the censoring rules used for the EFS sensitivity analysis. This same group, *NPM1* mutated quizartinib-treated, had the longest median OS estimate above.

Clinical reviewer comment: Perhaps the most striking finding is derived from a look at the control arm. Despite a large difference in CR rate for NPM1 mutant versus NPM1 Wt (69.3% mutant vs 36.7% Wt), median OS was inferior in the placebo treated NPM1 mutated patient than in NPM1 Wt (Median OS 15.1 months NPM1 mutated vs 17.3 months NPM1 Wt). As mentioned above, this result agrees with the recent 2022 ELN risk groups that place all NPM1 mutant patients with FLT3-ITD in the intermediate risk group. This essentially means that within the context of FLT3-ITD, NPM1 status does not improve long term outcomes. Lastly, it also points to at least one genetic subtype of AML where there is a strong disconnect between initial response rate and OS. A similar trend between response and OS has been reported in the relapsed setting for NPM1 mutant AML.

8.1.3. Supportive Studies in Newly Diagnosed AML

The Applicant's Position:

The three Phase 1 studies provide supplemental data for the safety and preliminary efficacy of quizartinib in this indication: 2 studies in combination with chemotherapy in newly diagnosed AML (2689-CL-0005 [N=18] and AC220-A-J102 [N=7]) and 1 study as maintenance monotherapy in patients with AML after HSCT (2689-CL-0011 [N=13]). The efficacy results of these studies are summarized below.

Study 2689-CL-0005 was a Phase 1, open-label, multiple-dose, dose-escalation study in subjects with newly diagnosed AML (*FLT3*-ITD [+] or *FLT3*-ITD [-]) receiving standard induction and

consolidation chemotherapy. Induction (1 or 2 cycles) consisted of daunorubicin (60 mg/m²/day) on Days 1, 2, and 3; cytarabine (200 mg/m²/day) on Days 1 to 7; and quizartinib (40 or 60 mg/day) on Days 4 to 10 or 4 to 17. A total of 19 subjects were enrolled (18 treated with quizartinib). Subjects were mostly white (78.9%), female (57.9%), with a median age of 43.0 years (between 22 and 60 years). Overall, 16 subjects (84%) achieved some degree of response, and 9 subjects (47%) achieved CR (2689-CL-0005 clinical study report [CSR]).

Study AC220-A-J102 was a multicenter, open-label, Phase 1b clinical study of quizartinib administered in combination with chemotherapy in Japanese subjects with newly diagnosed AML. Subjects were enrolled in the study irrespective of *FLT3* mutation status (*FLT3*-ITD [+] or *FLT3*-ITD [-]). Quizartinib was administered at a dose of 20 mg/day at Level 1 and 40 mg/day at Level 2. Dose escalation for a single subject was not allowed. The primary objectives of this study were to evaluate the safety and PK of quizartinib when used with standard induction and consolidation therapy in Japanese subjects with newly diagnosed AML, and to determine the recommended dose of quizartinib for Japanese subjects in subsequent phases of development. This study demonstrated that doses of 20 or 40 mg QD quizartinib in combination with standard chemotherapy are generally well tolerated. A total of 7 subjects were enrolled. Subjects were mostly female (57.1%), with a median age of 62 years (between 34 and 68 years). Overall, the response rate was 85.7% (6 subjects), and 5 subjects (71.4%) achieved CRi (AC220-A-J102 CSR).

Study 2689-CL-0011 was a Phase 1 study that examined maintenance monotherapy with quizartinib in subjects (aged ≥18 years) with AML in remission after receipt of an allo-HSCT. Subject dose was assigned manually by using a modified rolling 6 design. Two dose levels were tested, given daily in continuous 28-day cycles: dose level 1 at 40 mg and dose level 2 at 60 mg. Dose limiting toxicities (DLTs) were assessed for the first 2 cycles, and subjects were allowed to continue up to a maximum of 24 cycles. Thirteen subjects were enrolled, including 1 subject who had previously received quizartinib as a part of Study 2689-CL-0005. All subjects had received a human leukocyte antigen-matched allo-HSCT (4 related stem cell donors and 9 not related stem cell donors), with a median of 56 days (range: 41 to 70 days) before study enrollment. All subjects were *FLT3*-ITD (+) by local testing at the time of diagnosis. The majority of subjects were male (53.8%), and all were white (100%). The median age was 43.0 years (range: 23 to 61 years). Of the 13 total subjects, 10 (77%) received quizartinib for more than a year and 6 subjects (46%) completed 24 cycles. No maximum tolerated dose (MTD) was identified, but 60-mg QD dose was selected as the highest dose for continuous daily administration based on randomized comparison of daily 30 and 60 mg doses in R/R AML. OS ranged from approximately 13 to 142 weeks, with 9 subjects (69%) surviving ≥50 weeks and 4 subjects (31%) surviving >2 years (104 weeks) (2689-CL-0011 CSR).

The FDA's Assessment:

FDA agrees with the Applicant's position. These small pilot studies showed that quizartinib could be tolerated when combined with induction chemotherapy and as remission

maintenance monotherapy for extended periods of time. Due to the small size, heterogenous treatments given (variation on dose and timing were given), and single arm nature of these trials, conclusions from these studies are limited to claims of tolerability and pooling of overall safety information.

8.1.4. Supportive Studies in Relapsed/Refractory AML

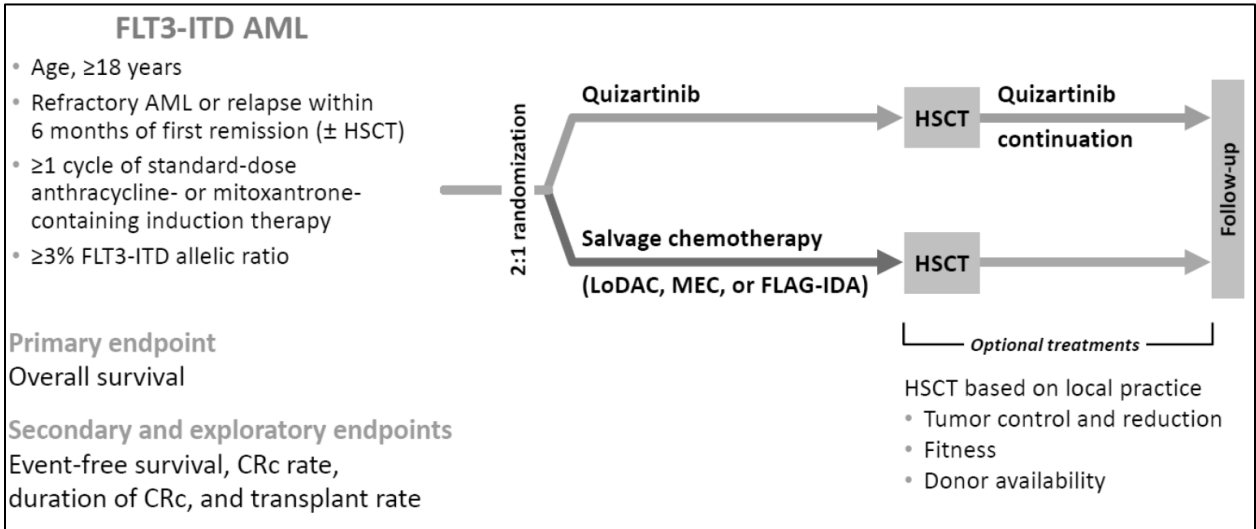
8.1.4.1. Pivotal Study in Relapsed/Refractory FLT3-ITD (+) AML – Study AC220-007 (QuANTUM-R)

Trial Design

The Applicant’s Description:

Study AC220-007 was a global, randomized, open-label, active-controlled, Phase 3 study that evaluated the efficacy and safety of quizartinib monotherapy compared with salvage chemotherapy in subjects with FLT3-ITD (+) AML who were in first relapse within 6 months of first remission or who were refractory after prior therapy, with or without prior HSCT. The study design from the Screening Visit through the Treatment Period is shown in Figure 25.

Figure 25 – Study Design Schematic (Screening to Treatment Period) for Study AC220-007



Notes: Subjects could continue quizartinib or LoDAC until HSCT, determination by the investigator of no clinical benefit, or unacceptable toxicity.

Subjects who received MEC or FLAG-IDA were to receive 1 cycle of therapy and could receive a second cycle of the same therapy at the investigator’s discretion.

FLT3-ITD mutation status was assessed using a companion diagnostic within 14 days of randomization.

Trial location: This study was conducted at 114 sites across 18 countries in North America, Europe, Australia, and Asia.

Treatment assignment: 367 patients were enrolled and randomized in a 2:1 ratio using a permuted block size of 6 to one of the 2 treatment arms: quizartinib arm (245 patients) or salvage chemotherapy arm (122 patients). Randomization was stratified by prior therapy and response and preselected salvage chemotherapy, without regard to investigative site. The chemotherapy agent and regimen were preselected by investigators prior to randomization.

Blinding: This was an open-label study.

Study treatment: Patients were randomized to receive either quizartinib monotherapy (20- or 30-mg tablets administered orally QD) or salvage chemotherapy (administered subcutaneously [low-dose cytarabine (LoDAC)] or IV [mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC) and fludarabine, cytarabine, and granulocyte-colony stimulating factor (G-CSF) with idarubicin (FLAG-IDA)]).

For patients randomized to quizartinib, the starting dose was 30 mg/day, unless the patient was receiving concurrent therapy with a strong CYP3A inhibitor, in which case the starting dose was 20 mg/day. For those not taking a strong CYP3A inhibitor, the dose of quizartinib was increased from 30 to 60 mg/day starting on Day 16 (± 1 day) if the subject's average QTcF, based on triplicate reading, was ≤ 450 ms on and before Day 15 (± 1 day). For subjects taking a strong CYP3A inhibitor, the dose of quizartinib was increased from 20 to 30 mg/day if they met the above QTcF requirements.

The investigator preselected the specific salvage chemotherapy regimen before randomization. All salvage chemotherapy was administered during 28-day cycles. The start of cycle 2 (MEC, FLAG-IDA, or LoDAC) and subsequent cycles (LoDAC) could be delayed for up to 14 days to allow for recovery from toxicity. Dose reductions were allowed for toxicity and were documented in the source record. Patients receiving salvage chemotherapy, including those who underwent HSCT, were followed on study and no crossover to investigational study drug was planned or allowed.

Duration of treatment: Total duration of treatment with study drug was until HSCT, lack of clinical benefit, or unacceptable toxicity.

Choice of control arm: At the time Study AC220-007 was implemented, guideline-recommended chemotherapy regimens for R/R AML include intensive ('aggressive') cytotoxic regimens for appropriate patients ('fit patients') or low-dose ('less aggressive') regimens for unfit patients. Intensive combinations include cladribine, cytarabine, and G-CSF with or without mitoxantrone or idarubicin; fludarabine, cytarabine, idarubicin, and G-CSF (FLAG) with or without idarubicin (IDA); MEC; and clofarabine, cytarabine, and G-CSF. Therefore, salvage chemotherapy, which may have included high-intensity chemotherapy (MEC or FLAG-IDA) or low-intensity chemotherapy (LoDAC), was chosen as the active comparator for Study AC220-007.

Dose modification/dose discontinuation: Guidelines for dose modification and treatment discontinuation were the same as those in Study AC220-A-U302 (Sections 6.2.2.1 and 8.1.1). For patients randomized to quizartinib in Study AC220-007 who underwent HSCT, quizartinib was to be discontinued 7 days before initiation of a conditioning regimen. Following HSCT, treatment with quizartinib was allowed by the protocol, provided that patients met protocol-specified criteria that were intended to ensure recovery from the effects of HSCT and were able to tolerate continued quizartinib administration.

Concomitant medications: The prohibited concomitant medications and those that were to be avoided were the same as Study AC220-A-U302 (see Section 8.1.1).

Diagnostic criteria: Subjects were enrolled based on *FLT3*-ITD (+) status as determined centrally using the (b) (4) *FLT3*-ITD CTA for the determination of *FLT3*-ITD mutation status from bone marrow and/or blood samples. This CTA is a molecular assay that employs PCR and capillary electrophoresis technology.

Inclusion/exclusion criteria: The study enrolled subjects with R/R *FLT3*-ITD (+) AML.

Key inclusion criteria:

- Morphologically documented primary AML or AML secondary to myelodysplastic syndrome (MDS), as defined by WHO criteria
- In first relapse (with duration of remission of 6 months or less) or refractory after prior therapy (at least 1 cycle of anthracycline- or mitoxantrone-containing induction chemotherapy), with or without HSCT
- Presence of the *FLT3*-ITD activating mutation in bone marrow or peripheral blood (AR as determined by a central laboratory with a cutoff of $\geq 3\%$ *FLT3*-ITD/total *FLT3*)
- Eligible for preselected salvage chemotherapy, according to the investigator's assessment
- Discontinuation of prior AML treatment before the start of study drug administration
- Total serum bilirubin $\leq 1.5 \times$ ULN
- Serum AST and/or ALT $\leq 2.5 \times$ ULN

Key exclusion criteria:

- APL
- AML secondary to prior chemotherapy for other neoplasms, except AML secondary to prior MDS
- History of another malignancy, unless the candidate had been disease-free for ≥ 5 years
- Persistent, clinically significant $>$ Grade 1 nonhematologic toxicity from prior AML therapy

- Clinically significant graft-versus-host disease (GVHD) or GVHD requiring initiation of treatment or treatment escalation within 21 days, and/or greater than Grade 1 persistent or clinically significant nonhematologic toxicity related to HSCT
- History of or current CNS involvement with AML
- Prior treatment with quizartinib or participation in a prior quizartinib study
- Prior treatment with a FLT3-targeted therapy including sorafenib or investigational FLT3 inhibitors
- Uncontrolled or significant cardiovascular disease, including the following:
 - QTcF >450 ms (average of triplicate determinations)
 - Diagnosed or suspected long interval between the start of the Q wave and the end of the T wave (LQTS), or known family history of LQTS
 - History of clinically relevant ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or TdP
 - Myocardial infarction within 6 months prior to screening
 - Uncontrolled angina pectoris within 6 months prior to screening
 - New York Heart Association Class 3 or 4 CHF
 - Uncontrolled hypertension

Study assessments: For subjects receiving quizartinib, bone marrow assessments were performed at screening and on Day 1 of Cycle 2 and Cycle 3. Bone marrow assessments were also performed on Day 1 of each subsequent cycle unless the subject had already achieved CR, complete remission with incomplete platelet recovery (CRp), or CRi. In that event, bone marrow testing was repeated after every 3 subsequent cycles, unless there was evidence of relapse. Bone marrow assessments were also performed at the Early Termination/End-of-treatment Visit, and as clinically indicated. Following HSCT, bone marrow assessments were required on Day 1 of post-HSCT Cycle 1, on Day 1 of Cycle 4 and every 3 cycles subsequently, at the Early Termination/End-of-treatment Visit, and as clinically indicated.

For subjects receiving salvage chemotherapy, bone marrow assessments were required at screening. For high-intensity chemotherapy (MEC or FLAG-IDA), bone marrow assessments were also required on Day 29 (± 14 days) of each cycle of therapy, and at the early termination/End-of-treatment Visit, and as clinically indicated. For LoDAC, bone marrow assessments were also required on Day 1 of Cycle 2 and Day 1 of Cycle 3. If a subject continued to receive LoDAC past Cycle 2, bone marrow assessments were repeated on Day 1 of each subsequent cycle unless the subject had already achieved a CR, CRp, or CRi. In that event, bone marrow testing was repeated after every 3 subsequent cycles, unless there was evidence of relapse. Also for LoDAC, bone marrow samples were required at the Early Termination/End-of-treatment Visit, and as clinically indicated.

Response to treatment was defined per Sponsor-modified Cheson criteria ([Cheson, 2003](#)). CR was defined as <5% bone marrow blasts, no blasts with Auer rods, no persistence of

extramedullary disease, ANC $>1 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, and RBC and platelet transfusion independence (defined as 4 weeks without RBC transfusions and 1 week without platelet transfusion). CRp was defined as meeting all criteria for CR except with incomplete platelet recovery ($<100 \times 10^9/L$). CRi was defined as meeting all criteria for CR except with incomplete hematological recovery with residual neutropenia $<1 \times 10^9/L$ and/or platelet count $<100 \times 10^9/L$. RBC and platelet transfusion independence was not required for CRi.

During study treatment (quizartinib or salvage chemotherapy), subjects were monitored regularly for toxicities with ECGs, physical examinations, and laboratory tests (hematology, chemistry and urinalysis) at the visits specified in the study protocol.

Quizartinib dose modifications were required if the subject experienced QTcF prolongation, other nonhematologic toxicities, or myelosuppression, or were receiving concomitant strong CYP3A inhibitors.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the study design. We note the following specific components of the salvage chemotherapy arm.

- LDAC: 20 mg subcutaneously twice daily on days 1-10 of each 28-day cycle; treatment could continue until PD or unacceptable toxicity
- Intensive chemotherapy:
 - o MEC:
 - Mitoxantrone (8 mg/m²/day) by intravenous (IV) on days 1-5
 - Etoposide (100 mg/m²/day) by IV infusion immediately after mitoxantrone on days 1-5
 - Cytarabine (1000 mg/m²/day) by IV infusion immediately after etoposide on days 1-5
 - o FLAG-IDA:
 - G-CSF (300 µg/m²/day) by IV infusion OR (5 µg/kg/day) on days 1-5
 - Additional G-CSF recommended 7 days post completion of chemotherapy, until recovery of ANC to $>0.5 \times 10^9/L$
 - Fludarabine (30 mg/m²/day) by IV infusion on days 2 – 6
 - Cytarabine (2000 mg/m²/day) by IV infusion, beginning 4 hours after the fludarabine infusion, on days 2 – 6
 - Idarubicin (10 mg/m²/day) IV on days 2-4

Up to 2 cycles of induction could be given to patients receiving MEC or FLAG-IDA.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint was OS, defined as the time between the date of randomization and the date of death from any cause. The secondary efficacy endpoint was EFS, defined as the time from randomization until documented refractory disease, relapse after CRc, or death from any cause, whichever occurred first.

Exploratory efficacy endpoints included CRc rate, CR rate, duration of CRc, duration of CR, and transplant rate.

- CRc rate, which is the percentage of subjects achieving a best response of CR, CRp, or CRi
- CR rate, which is the percentage of subjects achieving a best response of CR
- Duration of CRc and CR, which is the time from the first documented response until the date of documented relapse
- Transplant rate (bridge to transplant), which is the percentage of subjects undergoing allo-HSCT directly following protocol-specified treatment with no intervening AML therapy

The FDA's Assessment:

FDA agrees with the Applicant's description of the study endpoints and notes that the protocol did not specifically define induction failure in the definition of EFS.

Statistical Analysis Plan and Amendments

The Applicant's Description:

All efficacy analyses were performed according to treatment assigned at randomization. All safety analyses were based on actual treatment received. The ITT Analysis Set included all subjects who were randomized. The Safety Analysis Set included all subjects who received at least 1 dose of the study drug. The Per-protocol Set (PPS) included all subjects in the ITT Analysis Set who had no major protocol deviations that would affect assessment of efficacy endpoints. Subjects who were randomized but did not receive any dose of study drug and those who had negative *FLT3*-ITD test results based on central testing were excluded from the PPS.

The ITT Analysis Set was used for the analysis of all efficacy endpoints. Supporting analyses were also conducted with the PPS. There were 2 planned cutoff dates for efficacy analyses: 1 interim analysis, when approximately 50% (140 of 280) of the expected number of events (deaths) had occurred, and a final analysis at 280 OS events. EFS was to be analyzed only if the OS result was positive. The actual interim analysis was performed when 153 (55%) OS events were reported. The interim stopping boundary for OS was not crossed at that time, and the data monitoring committee recommended for the study to continue without modification.

Calculation of sample size was based on comparison of OS, in the 2 treatment groups (quizartinib and salvage chemotherapy) at a 2-sided significance level of 0.05, assuming that

median survival is 3.9 months in the salvage chemotherapy arm with an increase to 6 months, in the quizartinib arm (HR 0.65). As of the defined data cutoff of 22 Feb 2018, there were 276 deaths to support the primary ITT analysis.

Analysis of OS and EFS were conducted for the prespecified subgroups including: age; sex; race; geographic region; stratification factors from randomization (prior therapy and response and preselected salvage chemotherapy); *FLT3*-ITD AR at randomization; AML history; prior allo-HSCT; AML cytogenetic risk score; and baseline blast count.

Safety and tolerability were assessed by incidence, severity, and changes from baseline of all relevant parameters including TEAEs, clinical laboratory values, vital signs, and ECG parameters. Unless otherwise specified, all safety analyses were performed on the Safety Analysis Set and grouped by actual treatment received. AEs to be included were restricted to TEAEs. Death, other serious AEs (SAEs), and AEs associated with dose reduction, dose interruption, and premature discontinuation of study drug were summarized by treatment arm. AEs of special interest (AESIs) in this study were TdP/QT prolongation, hepatic disorders, cardiac failure, cardiac arrhythmias; and sequelae of cytopenias, such as infections and bleeding.

The FDA's Assessment:

We agree with the Applicant's assessment of the SAP. The primary efficacy analyses were to be performed on the intent-to-treat (ITT) population, consisting of all patients randomized. For OS, patients were not censored at the time of subsequent non-protocol AML therapy, including HSCT.

The study planned to accrue 363 patients and assumed a 10% drop out rate. With 280 deaths and assuming a median OS of 3.9 months in the control arm and 6 months in the quizartinib arm, the study had 90% power and a 2-sided significance level alpha of 0.05 to detect a hazard ratio of 0.65 in OS. The primary analysis was to take place when 280 events occurred.

The primary efficacy endpoint OS was to be analyzed by the stratified log-rank test. The stratification factors were to be those used for randomization. A non-stratified log-rank test was to be used as supportive evidence of efficacy.

The key secondary endpoint EFS was to be analyzed by the stratified log-rank test with covariates to control for response to first-line AML therapy and pre-selected salvage chemotherapy in the ITT. To maintain the overall type 1 error rate at the 0.05 significance level, hypothesis testing in the secondary analysis was to be performed only if the null hypothesis in the primary analysis was rejected at the overall two-sided 0.05 significance level.

Sensitivity analyses for OS were to include an analysis where patients were censored at the date of HSCT, and an analysis of OS on the PPS, of all patients randomized and without major protocol deviations.

Sensitivity analyses for EFS were to include an analysis on the PPS.

One interim analysis was planned at 140 events with an O'Brien-Fleming boundary for superior efficacy and a conditional power (CP) of 10% for futility. The Lan-DeMets spending function was to be employed to control the overall Type I error of 1-sided 0.025 for the primary efficacy analysis of OS such that the nominal Type I error was to be 0.001525 at interim analysis and 0.0245 at the final analysis. For the secondary endpoint EFS, the analysis plan employed a hierarchical ("gatekeeping") testing procedure to ensure a study-wise 1-sided Type 1 error rate of 0.025, such that EFS would be analyzed using the same boundaries and nominal Type 1 error for the primary analysis at the interim or final analysis.

Protocol Amendments

The Applicant's Description:

The clinical Study Protocol AC220-007 was revised 7 times over the course of study conduct as summarized in Table 50.

Table 50 – AC220-007 Clinical Study Protocol and Amendments

Amendment	Date	Key Revisions
0.0	18 Nov 2013	Initial version
1.0	24 Dec 2013	Incorporation of the FDA's concurrence of proposed dosing regimen prior the submission of the IND.
2.0	26 May 2015	Clarified the <i>FLT3</i> -ITD AR cutoff from 3% to $\geq 3\%$ and the 6-month duration of remission was modified to allow the enrollment of subjects who relapsed within 6 months after allo-HSCT
3.0	06 Oct 2015	Changed sponsorship from Ambit Biosciences to Daiichi Sankyo, Inc. and to Daiichi Sankyo Development Limited in Europe
3.1	19 Nov 2015	Allowed for the prior use of midostaurin, a multikinase inhibitor which has low activity against <i>FLT3</i> and there are no reports of development of D835 TKD mutations which could lead to cross-resistance to quizartinib
4.0	04 May 2016	Sponsorship in Europe was transferred from Daiichi Sankyo Development Limited to Daiichi Sankyo, Inc.
5.0	15 Aug 2016	Removed the adaptive design feature and changed the design to a traditional group sequential design with an interim analysis planned at 140 events (deaths) and increased planned enrollment from 326 to 363 although there was no change in the total number of planned events at 280.
6.0	30 Jun 2017	Administrative changes, added information on crossover from salvage chemotherapy to quizartinib, and other minor revisions

The FDA's Assessment:

The first patient was randomized to the study on 5/7/2014, after the first Amendment of the study was dated 12/24/2013. The data cut-off for efficacy for this NDA was 12/21/2020.

FDA notes that Amendment dated 6/3/2015 clarified timing for quizartinib, changed the dose escalation schedule and requirement of ECG monitoring post dose escalation, changed response assessment timing to allow for count recovery, and revised inclusion criteria to include patients in first relapse with DOR <6 months, including 6 months post-HSCT, and added exclusion criteria for bradycardia due to QTc prolongation. Revisions to the eligibility criteria in Amendment 2 might have contributed to some inconsistencies in prior therapies/relapse data.

Amendment 5 dated 9/2/2016 increased the planned number of subjects to 363 to reach planned number of events (280) in a "reasonable time," removed references to adaptive design that would allow for increase of sample size at the time of the interim analysis, added efficacy objectives/variables (CR, CRc, duration of CR and CRc), revised dose modifications for patients with QTcF prolongation if already at a reduced dose, added language to help minimize the number of subjects without survival information, revised censoring analysis for HSCT for the sensitivity analysis of OS, and added subgroup analyses for primary and secondary endpoints, and safety analyses. The revision in Amendment 5 with regard to follow-up raises the possibility that the potential for a high rate of early censoring was foreseen already then.

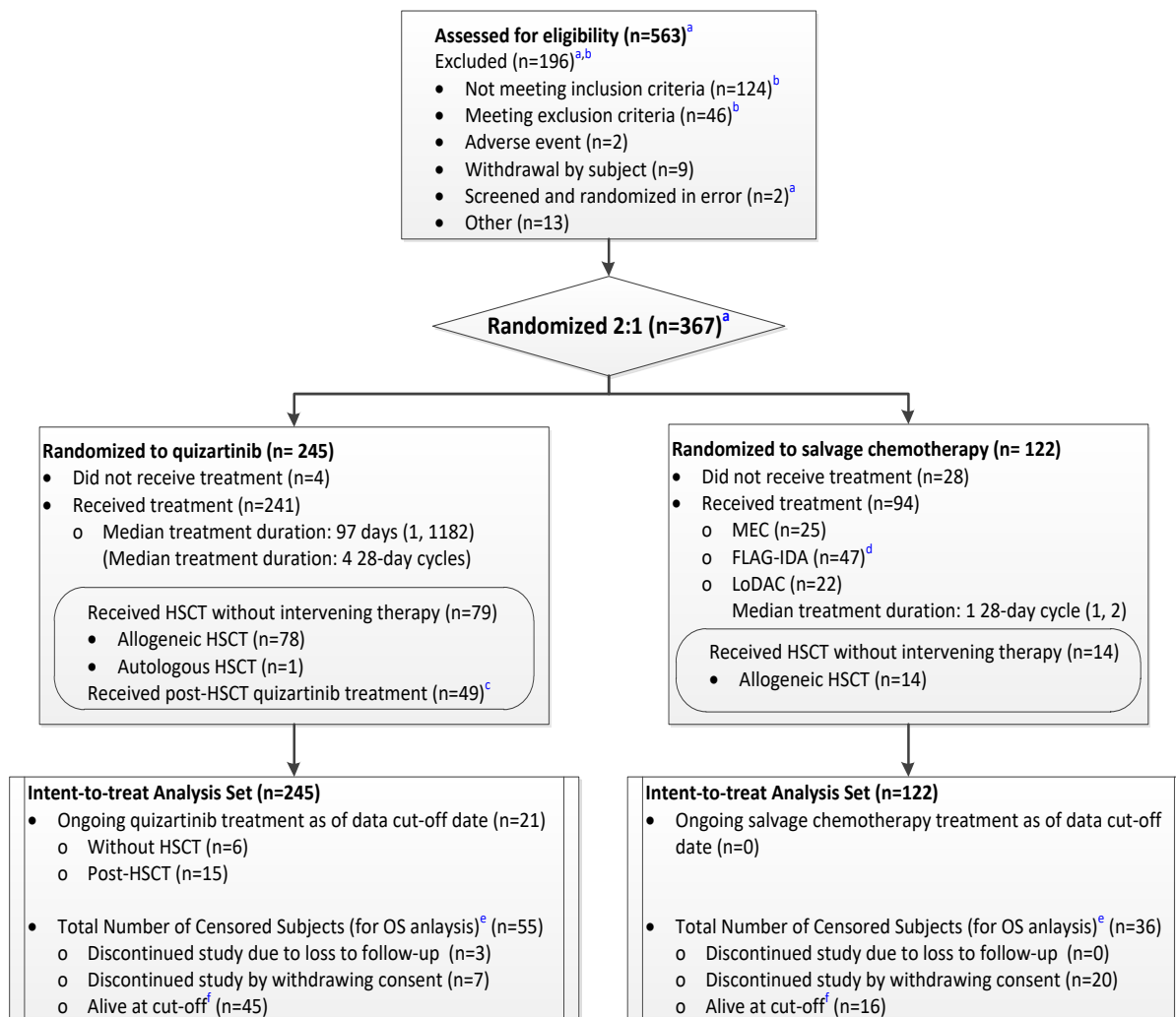
8.1.4.2. Study Results – Study AC220-007

Subject Disposition

Data and The Applicant's Position:

Overall, a total of 367 subjects were randomized (245 subjects in quizartinib arm and 122 subjects in salvage chemotherapy arm) and included in the ITT Analysis Set. Details of the subject disposition and treatment and study discontinuation are presented below.

Figure 26 – Subject Disposition in Study AC220-007



^a Two subjects were screened and randomized in error. They were randomized into the study using different subject numbers. They are counted twice in “Assessed for eligibility” category, and counted in both “Excluded” and “Randomized” categories.

^b See AC220-007 CSR Table 14.1.1.2 for the full list inclusion criteria that were not met and exclusion criteria that were met.

^c Of the 49 subjects who received post-HSCT quizartinib treatment, 1 subject had undergone autologous HSCT and 48 subjects had allo-HSCT.

^d Of the 47 subjects who received FLAG-IDA, 46 subjects received all 4 drugs (FLAG-IDA), and 1 subject did not receive G-CSF.

^e Subjects were censored at the date when they were last known to be alive. If there was no death reported for a subject before the cutoff date for OS analysis, OS was censored at the last contact date at which the subject was known to be alive. AC220-007 CSR (Appendix 16.1.9.1)

^f “Alive” means that the end of study eCRF page was not completed by the cutoff date, and the subject remains ongoing in the study.

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Sources: AC220-007 CSR Table 14.1.1.1, Table 14.1.1.2, Table 14.1.4.1, Table 14.2.1.6a, Table 14.2.4.1b, Table 14.2.4.1c, Listing 16.2.1.2, Listing 16.2.1.3, and Listing 16.2.6.1.1

Most subjects randomized to the salvage chemotherapy arm were preselected by the investigator to receive intensive chemotherapy (FLAG-IDA regimen or MEC).

Of the subjects randomized, 241 and 94 subjects received treatment with quizartinib or salvage chemotherapy, respectively. As a result there was an imbalance in the randomized not treated subjects with a larger number occurring in the salvage chemotherapy arm compared with the quizartinib arm (1.6% vs 23%, respectively).

A total of 93 subjects had an HSCT immediately following conclusion of study drug without intervening AML therapy. A higher proportion of subjects in the quizartinib arm received HSCTs (79 [32.2%]) than in the salvage chemotherapy arm (14 [11.5%]). At the time of the data cutoff, 21 subjects continued on quizartinib therapy: 6 subjects (2.4%) continued initial quizartinib without intervening HSCT and 15 (6.1%) continued on quizartinib after HSCT. All subjects in the salvage chemotherapy arm discontinued study drug and 16 (13.1%) remained in the study at the time of data cutoff.

Differences between the treatment arms in the reasons for study drug discontinuation were consistent with the treatment regimens and the longer duration of study drug for subjects on the quizartinib arm compared to the salvage chemotherapy arm. Progressive disease was the most common reason for study drug discontinuation in the salvage chemotherapy arm (40.2%) and was more frequent than in the quizartinib arm (19.2%). The most common reason for study drug discontinuation in the quizartinib arm (initial quizartinib treatment) was HSCT (32.2%).

Of the 79 subjects randomized to quizartinib who received HSCT immediately following conclusion of study drug without intervening AML therapy, 49 restarted quizartinib after HSCT. Of these 49 subjects, 34 subsequently discontinued quizartinib. The primary reasons for discontinuing quizartinib post-HSCT were relapse (17 subjects) or AEs (10 subjects).

The FDA's Assessment:

For the purposes of tabulation of early discontinuations in Table 51, the term "lack of efficacy" included events including relapse, progression, lack of efficacy, or an AE with a PT related to the underlying disease or relapse.

Table 51: FDA Adjudicated Patient Disposition for Study AC220-007, ITT Population

	Quizartinib (N=245)	Salvage (N=122)
Treated	241 (98%)	94 (77%)

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Ongoing (quizartinib arm) Or “completed tx” (salvage) ^a	20 (8%)	23 (24%)
Discontinued tx	221 (92%)	71 (76%)
Reason for early discontinuation		
Lack of efficacy	129 (54%)	52 (55%)
HSCT ^b	31 (13%)	3 (3%)
AE	37 (15%)	3 (3%)
Death	14 (6%)	10 (11%)
Consent withdrawal	2 (1%)	1 (1%)
Unknown	4 (4%)	-
Other	4 (4%)	2 (2%)
Source: FDA clinical review of data cutoff of 1/31/2019; ^aSince quizartinib (and LDAC in the salvage arm) is administered daily, continuously, and the high intensity salvage regimens are administered as 5-7 cycles, with a maximum of 2 cycles per protocol, the reporting of early discontinuation between the arms is inherently biased; ^bAlthough the applicant used the term “HSCT” for treatment discontinuation for any patient who discontinued initial quizartinib therapy, even those who had therapy interrupted for HSCT and restarted therapy post-HSCT, FDA used this disposition term only for patients who had quizartinib permanently discontinued for HSCT. Note that of 12/21/2020 all patients had discontinued treatment due to Study AC220-007 study closure.		

Notably, there was an imbalance in the number of patients randomized but not treated, consisting of only 4 patients (2%) on the quizartinib arm compared to 28 patients (23%) on the salvage arm. Further, while all 4 patients on the quizartinib continued to be followed on study, and reason for discontinuation was death, of the 28 patients in the salvage arm, 17 withdrew from the study, including 15 in whom this happened within a week of randomization, 1 in which this happened within 10 days, and one in which this happened on day 36. With the exception of 2 patients for whom a death date was available, the remaining 15 patients were censored on the day of study discontinuation with the reason “no survival follow-up within 3 months.”

Reviewer comment: The imbalance noted above, both in terms of the patients randomized and not treated and to the early censoring for the primary endpoint that occurred almost exclusively on the control arm, introduces potential bias that raises concerns regarding the credibility of the study results. It is possible that the OS for the 15 patients censored early would improve the results for the salvage arm to an extent that the difference between the arms, which is quite small (6.5 weeks), would be rendered statistically insignificant. FDA also noted an imbalance in early censoring between treatment arms with 9 patients on the control arm censored prior to

week 8 and an additional patient on that arm was censored at exactly week 8 (day 56), while only 1 patient on the quizartinib arm was censored within the first 8 weeks. Various sensitivity analyses need to be done to assess for robustness of the study results.

Table of Demographic Characteristics

Data:

Table 52 – Select Demographic in Study AC220-007 (ITT Analysis Set)

Parameter	Quizartinib Monotherapy (N = 245)	Salvage Chemotherapy (N = 122)
Age (years)		
Median (Min, Max)	55.0 (19, 81)	57.5 (18, 78)
Age category, n (%)		
<65 years	180 (73.5)	89 (73.0)
≥65 years to <75 years	53 (21.6)	30 (24.6)
≥75 years	12 (4.9)	3 (2.5)
Sex at birth, n (%)		
Male	113 (46.1)	64 (52.5)
Female	132 (53.9)	58 (47.5)
Race, n (%)		
White	184 (75.1)	93 (76.2)
Black or African American	9 (3.7)	3 (2.5)
Asian	24 (9.8)	16 (13.1)
ECOG PS at baseline, n (%)		
0	87 (35.5)	47 (38.5)
1	131 (53.5)	54 (44.3)
≥2	27 (11.0)	21 (17.2)
Geographic region, n (%)		
North America	100 (40.8)	41 (33.6)
US	82 (33.5)	36 (29.5)
Canada	18 (7.3)	5 (4.1)
Europe + Australia	127 (51.8)	68 (55.7)
Asia	18 (7.3)	13 (10.7)

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Note: Age in years is calculated as integer of (informed consent date - birth date)/365.25. Denominator for percentages is the number of subjects in the ITT Analysis Set.
Source: AC220-007 Tables 14.1.2.1 and 14.1.1.3

The Applicant's Position:

Demographic and baseline characteristics for subjects in the ITT Analysis Set were consistent with a R/R *FLT3*-ITD (+) AML population and similar between treatment arms.

The FDA's Assessment:

Demographic information for the patients on Study AC220-007 are summarized in Table 52. The median age was slightly younger in the quizartinib arm, but the range was wider, including a patient who was 81 years old. The majority of the patients were females on the quizartinib arm and males on the control arm. Approximately one-third of the patients on each arm were treated in the US. The slightly higher percentage of patients on the salvage arm with an ECOG PS of 2 may bias the study results in favor of the quizartinib arm.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 53 – AML History and Disease Characteristics in Study AC220-007 (ITT Analysis Set)

Parameter	Quizartinib Monotherapy (N = 245)	Salvage Chemotherapy (N = 122)
Time from diagnosis to randomization (weeks)		
Median (min, max)	23.43 (3.7, 73.1)	23.21 (3.3, 312.3)
Antecedent hematologic disorders, n (%)	16 (6.5)	9 (7.4)
MDS	15 (6.1)	7 (5.7)
Blast count (bone marrow) at baseline (%)		
Median (min, max)	66.4 (5, 99)	70.0 (6, 100)
WHO classification of AML with recurrent genetic abnormalities, n (%)		
AML with mutated <i>NPM1</i>	115 (46.9)	57 (46.7)
AML with mutated <i>CEBPA</i>	5 (2.0)	5 (4.1)
Risk status with specific cytogenetic patterns^a, n (%)		
Intermediate: normal, +8, +6, -y	191 (78.0)	81 (66.4)
Unknown risk	19 (7.8)	19 (15.6)
Unfavorable: de15q, -5, or del7q, -7, complex	23 (9.4)	14 (11.5)

Parameter	Quizartinib Monotherapy (N = 245)	Salvage Chemotherapy (N = 122)
Favorable: inv(16), t(16;16), or t(8;21), t(15;17)	12 (4.9)	8 (6.6)
Randomization stratification factors		
Prior therapy and response, n (%)		
Relapsed within 6 months not post-HSCT	109 (44.5)	54 (44.3)
Refractory	80 (32.7)	41 (33.6)
Relapsed within 6 months post-HSCT	56 (22.9)	27 (22.1)
Preselected salvage chemotherapy regimen, n (%)		
Low intensity (LoDAC)	57 (23.3)	29 (23.8)
High intensity (MEC or FLAG-IDA)	188 (76.7)	93 (76.2)
FLT3-ITD VAF by central testing (max AR FLT3-ITD/total FLT3), n(%)		
>50%	90 (36.7)	43 (35.2)
>25% to ≤50%	86 (35.1)	42 (34.4)
3% to ≤25%	66 (26.9)	37 (30.3)
<3% ^b	3 (1.2)	0

^a The predictive value of hierarchical cytogenetic classification in older adults with AML: analysis of 1065 subjects entered into the UK Medical Research Council AML11 Trial72.

^b <3% FLT3-ITD was considered negative and are excluded from the PPS

Note: Denominator for percentages is the number of subjects in the ITT Analysis Set.

NPM1 and CEBPA status were determined on the basis of local testing.

Source: AC220-007 CSR Table 14.1.2.1, Table 14.1.2.4, and Table 14.1.2.7

The Applicant's Position:

Baseline AML characteristics were generally similar between treatment arms.

The FDA's Assessment:

The higher rate of unknown cytogenetics for the salvage arm raises concerns regarding an imbalance in expected outcomes between the arms. The classification system used for cytogenetic risk relatively old and does not utilize the more modern ELN risk stratification that incorporates more abnormalities, such that the balance in cytogenetic risk may not be accurate.

Since the randomization was stratified by pre-selected chemotherapy (high vs low, investigator decision), the rates of each category were balanced between the arms.

Table 54: Demographics by Pre-Selected Chemotherapy Stratum and Arm

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	High intensity		Low intensity	
	Quizartinib (N = 188) n (%)	Salvage (N=93) n (%)	Quizartinib (N =57) n (%)	Salvage (N=29) n (%)
Sex				
Male	88 (47)	47 (51)	25 (44)	17 (59)
Age				
Median, years	54	56	64	66
Range	19-79	21-74	19-81	18-78
< 65 y	151 (80)	75 (81)	29 (51)	14 (48)
>65 y	37 (20)	18 (19)	28 (49)	15 (52)
Race				
White	148 (79)	74 (80)	36 (63)	19 (66)
Region				
Europe	2 (50)	13 (46)	37 (65)	20 (69)
United States	73 (39)	33 (36)	9 (16)	3 (10)
ECOG PS baseline				
2	17 (9)	12 (13)	10 (18)	9 (31)
Prior HSCT				
Yes	72 (38)	19 (20)	13 (23)	-
FLT3 allelic ratio				
<3%	3 (2)		-	
3%-≤25%	51 (27)	31 (33)	15 (26)	6 (21)
>25%-≤50%	61 (32)	29 (31)	25 (44)	13 (45)
>50%	73 (39)	33 (36)	17 (30)	10 (35)
Cytogenetic risk category ^a				
Favorable	9 (5)	7 (8)	3 (5)	1 (3)
Intermediate	145 (77)	62 (67)	46 (81)	19 (66)
Unfavorable	19 (10)	10 (11)	4 (7)	4 (14)
Unknown	15 (8)	14 (15)	4 (7)	5 (17)

Source: FDA reviewer; ^ausing the 2001 risk stratification system from Grimwade, Blood 2001, based on the following categories: Favorable: inv(16), t(16;16), or t(8;21), t(15;17); Unfavorable: de15q, -5, or del7q, -7, complex karyotype; Intermediate: normal, +8, +6, -y.

As expected, the median age in the low intensity stratum was higher than in those stratified to high intensity therapy, as was the rate of patients over 65 in that strata (50% of patients in each arm among those pre-selected for low intensity therapy compared to approximately 20% for those pre-selected for high intensity therapy). The striking imbalance between patients with an

ECOG PS of 2 between the arms in the low intensity stratify highlights the difference in the ITT population, but this is the stratum more affected by the imbalance, and may bias the study results in favor of the quizartinib treated arm. The fact that 23% of patients in the low intensity stratum had prior HSCT while none in the control arm in this stratum is also concerning for imbalance, but this can be in both directions: if it is due to the fact that the patients disease was responsive to therapy and thus allowed for achievement of CR that allowed for transplant, while patients in the salvage arm had more resistant disease, this would bias the results in favor of quizartinib; in contrast, the morbidities due to prior transplant (that might be the reason for pre-selection to this stratum by the investigators) may increase the risk of toxicities in the quizartinib arm and bias the results in favor of the control arm. Since these cannot be determined, uncertainty remains between this imbalance, and must be taken into account upon interpretation of the study results. The imbalance in cytogenetic risk in the low risk stratum (specifically unfavorable risk) also biases the results in favor of the quizartinib arm; however, since the cytogenetic risk stratification system used for definitions of these categories is fairly outdated, the impact on the study results is uncertain.

In an attempt to analyze the impact of the highly biased rate of untreated patients on the salvage arm (23%) as compared to the quizartinib arm (2%), FDA performed an analysis of demographic characteristics of the untreated patients for comparison to the ITT population, summarized in Table 55 below:

Table 55: Demographics of Patients Randomized but not Treated, AC220-007

	QUIZARTINIB (N = 4) n (%)	SALVAGE (N=28) n (%)
Sex		

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Male	1 (25)	16 (57)
Age		
Median, years	53.5	60.5
Range	46-65	18-74
< 65 y	3 (75)	19 (68)
>65 y	1 (25)	9 (32)
Race		
White	4 (100.0)	17 (60.7)
Region		
Europe	2 (50)	13 (46)
United States	2 (50)	7 (25)
Asia	-	6 (21)
Canada	-	2 (7)
ECOG PS baseline		
2	-	5 (17.9)
Stratification, salvage therapy		
High Intensity	2 (50)	21 (75)
LDAC	2 (50)	7 (25)
Prior treatment/response		
Refractory	-	15 (54)
Relapsed in <= 6 Months (no HSCT)	2 (50)	8 (29)
Relapsed in <= 6 Months (HSCT)	2 (50)	5 (18)

Source: FDA reviewer

Since only 4/245 patients randomized to the quizartinib arm were not treated, the analyses are limited and comparisons between the groups are not particularly informative.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 56 – Primary Analysis of Overall Survival in Study AC220-007 (ITT Analysis Set)

OS Analysis	Quizartinib Monotherapy (N = 245)	Salvage Chemotherapy (N = 122)
Subjects (%) with Events	190 (77.6)	86 (70.5)
Subjects (%) without events (Censored)	55 (22.4)	36 (29.5)
Time to events (weeks) ^a		

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OS Analysis	Quizartinib Monotherapy (N = 245)	Salvage Chemotherapy (N = 122)
Median ^a (95% CI for median)	27.0 (23.1, 31.3)	20.4 (17.3, 23.7)
1 st , 3 rd quartile	15.4, 62.6	8.3, 39.6
OS Probability (95% CI)^b		
13 weeks	0.81 (0.76, 0.85)	0.65 (0.55, 0.73)
26 weeks	0.52 (0.45, 0.58)	0.39 (0.30, 0.48)
52 weeks	0.27 (0.21, 0.32)	0.20 (0.12, 0.28)
104 weeks	0.18 (0.13, 0.24)	0.15 (0.09, 0.24)
Stratified log-rank test^c		
p-value (1-sided)	—	0.0177

^a The median and quartiles are calculated using Kaplan-Meier method and CI for the median is calculated using the Brookmeyer-Crowley method.

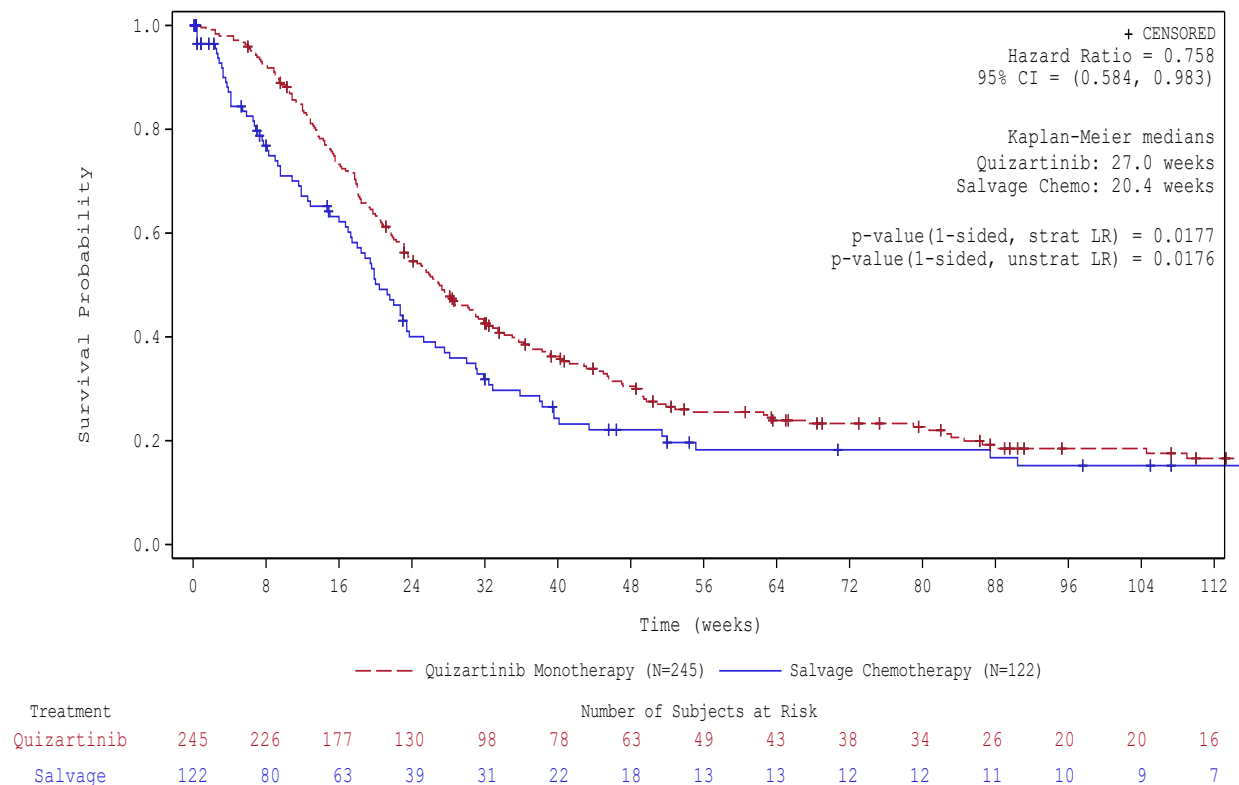
^b Survival probability and CI are calculated based on Kaplan-Meier product-limit method and Greenwood's formula.

^c Stratification factors at randomization include prior therapy and response (relapsed within ≤6 months [not post-HSCT], refractory, or relapsed within ≤6 months after allo-HSCT), and preselected salvage chemotherapy (high-intensity chemotherapy [MEC or FLAG-IDA], or low-intensity chemotherapy [LoDAC]).

Notes: The denominator for percentages is the number of subjects in the ITT Analysis Set. OS is defined as the time from the date of randomization to the date of death from any cause.

Source: AC220-007 CSR Table 14.2.1.1

Figure 27 – Kaplan-Meier Plot of Overall Survival in Study AC220-007 (ITT Analysis Set)



Note: P-values are 1-sided and based on a log-rank test. HR is obtained using an unadjusted stratified Cox PH model. Stratification factors at randomization include prior therapy and response (relapsed within ≤6 months [not post-HSCT], refractory, or relapsed within ≤6 months after allo-HSCT), and preselected salvage chemotherapy (high-intensity chemotherapy [MEC or FLAG-IDA], or low-intensity chemotherapy [LoDAC]).

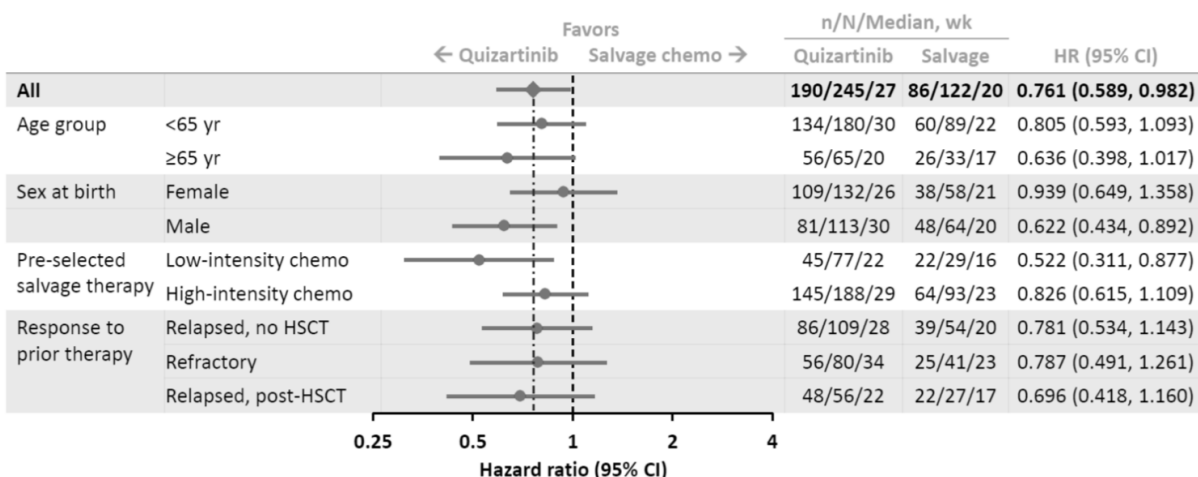
Source: AC220-007 CSR Figure 14.2.1.1.

Table 57 – Overall Survival Using Sensitivity and Supplementary Analyses in Study AC220-007 (ITT Analysis Set)

OS Analysis	Median (95% CI for Median)		HR Relative to Salvage Chemotherapy (95% CI)	Stratified p-value
	Quizartinib Monotherapy	Salvage Chemotherapy		
PPS	26.9 (23.1, 31.0)	20.0 (16.7, 25.3)	0.754 (0.567, 1.001)	0.0246
Censored for HSCT	24.6 (20.9, 27.3)	19.9 (16.7, 22.7)	0.787 (0.587, 1.054)	0.0519
Censoring at FLT3 inhibitors	28.6 (23.7, 33.4)	21.6 (17.0, 26.6)	0.740 (0.553, 0.989)	0.0203

Notes: Subjects with postrandomization HSCT were censored at the date of HSCT for OS analysis. Subjects were censored at the start of use of other FLT3 inhibitors (sorafenib [including sorafenib tosylate], lestaurinib, midostaurin, gilteritinib, quizartinib, crenolinib, ponatinib, tandutinib, and KW-2449) postrandomization.
Source: AC220-007 CSR Tables 14.2.1.2, 14.2.1.3, and 14.2.1.4

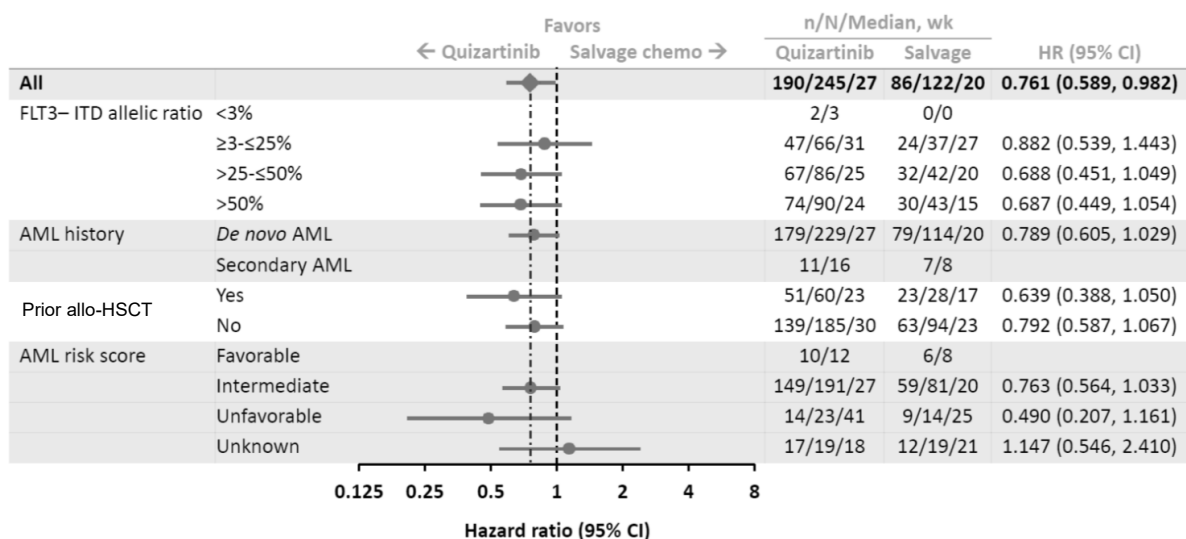
Figure 28 – Forest Plot of Overall Survival by Prespecified Subgroups (Age, Sex, Preselected Salvage Chemotherapy, Response to Prior Therapy) in Study AC220-007 (ITT Analysis Set)



Notes: HR is obtained from unstratified Cox PH model.

Source: AC220-007 CSR Figure 14.2.1.5.

Figure 29 – Forest Plot of Overall Survival by Prespecified Subgroups (*FLT3*-ITD Allelic Ratio, AML History, Prior Allogeneic HSCT, AML Risk Score) in Study AC220-007 (ITT Analysis Set)



Notes: For subgroups with less than 30 subjects, only the number of subjects with/without events are presented. HR is obtained from unstratified Cox PH model.

Source: AC220-007 CSR Figure 14.2.1.5.

The Applicant's Position:

In Study AC220-007, treatment with quizartinib monotherapy resulted in a statistically significant and clinically meaningful improvement in OS compared with salvage chemotherapy (1-sided $P = 0.0177$ by stratified log-rank test) in a population of subjects with R/R *FLT3*-ITD (+) AML. The improvement in OS was supported by 3 preplanned and several post hoc sensitivity analyses, all of which showed treatment effects that were consistent with that of the overall ITT analysis. Despite questions raised by the FDA over the robustness of the OS data, the results nevertheless are supportive of clinical benefit of quizartinib monotherapy in *FLT3*-ITD (+) AML patients. The improvement in OS was also observed across most prespecified subgroups in favor of quizartinib, which is supportive of efficacy in the overall population enrolled in Study AC220-007.

The FDA's Assessment:

As mentioned above (disposition) the high rate of early censoring, highly imbalanced between the arms, and the relatively small difference between the median OS in each arm, raised concerns regarding the credibility of the study results for the primary endpoint. If the OS of the ITT population on the salvage arm was even slightly better than the results with this censoring, the HR and p-value might not hold up. In addition, the 6.5-week survival advantage may not be clinically meaningful given safety concerns. Thus, the benefits were previously determined by

FDA to not outweigh the risks as monotherapy in patients with R/R FLT3-ITD mutated AML. However, the OS results for quizartinib in comparison to salvage chemotherapy provide some support for the clinical activity of quizartinib in patients with FLT3-ITD mutated AML.

See also the FDA Briefing Document, 2019 for comprehensive analyses conducted by the review team at the time of the initial NDA review for quizartinib.

Data Quality and Integrity

Data:

There were 28 subjects whose last survival assessment was more than 3 months prior to the cutoff date for the study-wide, final analysis data collection. These included the subjects who were censored at less than 8 weeks (n = 18), plus an additional 10 subjects. At the FDA's request, the Applicant conducted a targeted and limited public record sweep and found data on 13 of these subjects. An updated ITT analysis including these subjects was consistent with the original ITT analysis. The median OS was 26.9 (95% CI 23.1-31.0) weeks for the quizartinib arm compared with 20.4 (95% CI 17.0-25.3) weeks for the salvage chemotherapy arm (HR 0.77 [95% CI 0.60, 0.99]; P = 0.0175).

The Applicant's Position:

The updated ITT analysis was consistent with the original ITT analysis for OS for AC220-007 and supportive of use of quizartinib in combination with standard chemotherapy in the treatment of patients with newly diagnosed *FLT3*-ITD (+) AML.

The FDA's Assessment:

Based on the updated data received, there were still 6 patients, all on the control arm, for whom censoring occurred within 16 days of randomization without any further information. An additional patient, on the quizartinib arm, was censored at exactly 6 weeks, 3 other patients on the control arm were censored between 6 and 8 weeks, and 1 patient on the control arm was censored at exactly 8 weeks. When looking at all censored patients for whom "no survival follow-up" is the reason for censoring (beyond 8 weeks), 4 patients remain, 2 on each arm. While the updated data was somewhat helpful in decreasing the amount of uncertainty with regard to the outcome for the primary endpoint, the imbalance in early censoring (9 patients on the control arm and 1 patient on the quizartinib arm censored before 8 weeks, with the all censoring within the first 16 days being on the control arm) left residual uncertainty with regard to the credibility of the study results.

Efficacy Results – Secondary and other relevant endpoints

Data:

EFS was the sole secondary endpoint for Study AC220-007 and defined as the time from randomization until documented refractory disease, relapse after CRc, or death from any cause, whichever occurred first. Details are provided in Table 58.

Table 58 – Analysis of Event-Free Survival Using Sponsor-Derived Response Criteria in Study AC220-007 (ITT Analysis Set)

Statistics	Quizartinib Monotherapy (N = 245)	Salvage Chemotherapy (N = 122)
Subjects (%) with events	216 (88.2)	92 (75.4)
Subjects (%) without events (censored)	29 (11.8)	30 (24.6)
Time to events (weeks) ^a		
Median ^a	6.0	3.7
95% CI for median	(0.1, 8.3)	(0.4, 5.9)
1 st quartile	0.1	0.1
3 rd quartile	19.7	17.0
Stratified log-rank test ^b		
p-value (1-sided)	0.1071	
Unstratified log-rank test ^c		
p-value (1-sided)	0.0695	
HR (relative to salvage chemotherapy) ^b (stratified)	0.898	
95% CI	(0.697, 1.157)	
p-value for HR=1 (1-sided)	0.2034	
HR (relative to salvage chemotherapy) ^c (unstratified)	0.879	
95% CI	(0.685, 1.127)	
p-value for HR=1 (1-sided)	0.1541	

^a Median and quartiles are calculated using Kaplan-Meier method and CI for median is calculated using the Brookmeyer-Crowley method.

^b Stratification factors at randomization included prior therapy and response (relapsed within ≤6 months [not post-HSCT], refractory, or relapsed within ≤6 months after allo-HSCT), and preselected salvage chemotherapy (high-intensity chemotherapy [MEC or FLAG-IDA], or low-intensity chemotherapy [LoDAC]).

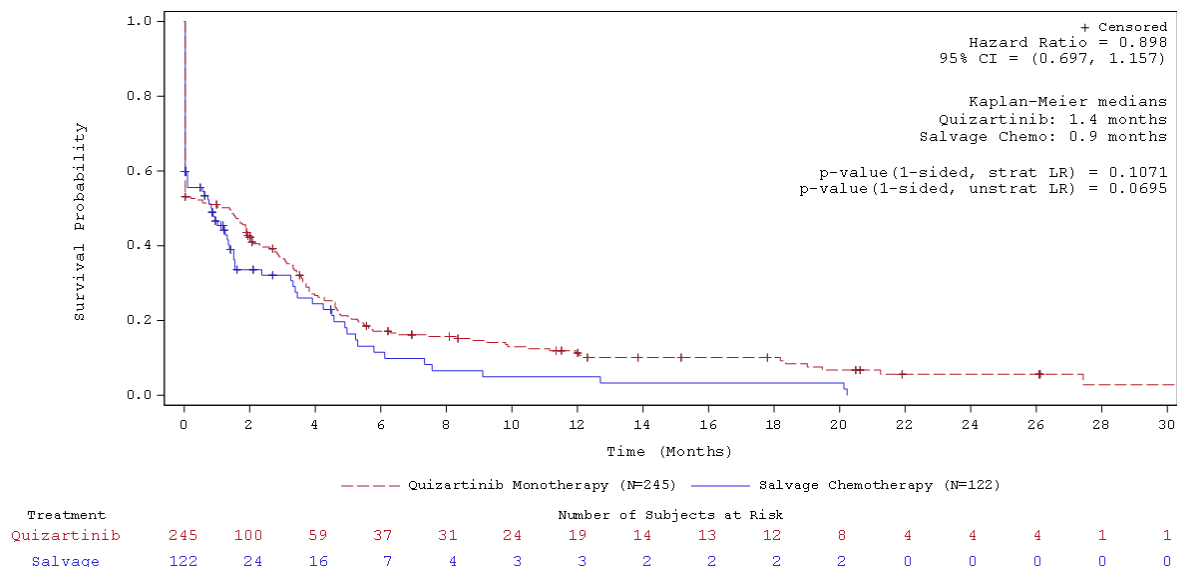
^c Unstratified analysis includes only treatment as a covariate in the Cox PH model.

Note: EFS is defined as the time from randomization until documented refractory disease, relapse after CRc, or death from any cause, whichever occurred first. For subjects who discontinued study drug without a documented response of CRc, the EFS event date is assigned to the date of randomization, and EFS is 1 day. The denominator

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for percentages is number of subjects in ITT Analysis Set. EFS was derived based on the response assessment that applies the Sponsor-modified 2003 International Working Group response criteria to the collected data.
Source: AC220-007 CSR Table 14.2.2.1

Figure 30 – Kaplan-Meier Plot of Event-Free Survival Using Sponsor-Derived Response Criteria in Study AC220-007 (ITT Analysis Set)



P-values are 1-sided and based on LR test. HR is obtained using an unadjusted stratified Cox PH model. Stratification factors at randomization included prior therapy and response (relapsed within ≤6 months [not post-HSCT], refractory, or relapsed within ≤6 months after allo-HSCT), and preselected salvage chemotherapy (high-intensity chemotherapy [MEC or FLAG-IDA], or low-intensity chemotherapy [LoDAC]). EFS was derived based on the response assessment that applies the sponsor-modified 2003 International Working Group response criteria to the collected data.

Source: AC220-007 CSR Figure 14.2.2.1

Table 59 – Summary of the Censoring Reasons for Event-Free Survival in Study AC220-007 (ITT Analysis Set)

Reason for Censoring	Quizartinib Monotherapy (N = 245) n(%)	Salvage Chemotherapy (N = 122) n(%)
Total number of censored subjects ^a	29 (11.8)	30 (24.6)
No postbaseline response assessment, no death date (censored at Day 1)	1 (3.4)	17 (56.7)

Reason for Censoring	Quizartinib Monotherapy (N = 245) n(%)	Salvage Chemotherapy (N = 122) n(%)
Had CRc, no subsequent AML therapy post-study drug, no death date without relapse	20 (69.0)	7 (23.3)
Had CRc, had subsequent AML therapy post-study drug (without relapse or before relapse)	8 (27.6)	6 (20.0)

^a Used as denominator to calculate percent rates for each censoring reason

Source: AC220-007 CSR Table 14.2.2.6

Table 60 – Exploratory Efficacy Endpoints in Study AC220-007 (ITT Analysis Set)

Statistics	Quizartinib Monotherapy (N = 245)	Salvage Chemotherapy (N = 122)
CRc rate, n (%) [95% CI] ^a	118 (48.2) [41.8, 54.6]	33 (27.0) [19.4, 35.8]
Duration of CRc (weeks), median [95% CI] ^b	12.1 [10.4, 27.1]	5.0 [3.3, 12.6]
CR rate, n (%) [95% CI] ^a	10 (4.1) [2.0, 7.4]	1 (0.8) [0.0, 4.5]
CRi rate, n (%) [95% CI] ^a	99 (40.4) [34.2, 46.8]	32 (26.2) [18.7, 35.0]
Transplant rate, n (%) [95% CI] ^c	78 (31.8) [26.1, 38.1]	14 (11.5)[6.4, 18.5]

^a Best overall response is defined as the best measured response (CR, CRp, CRi, PR, NR or Unknown) during study drug period but prior to HSCT or any other AML therapy. CRc comprises CR, CRp and CRi. Response was derived from objective criteria per Sponsor-modified Cheson criteria. Rate and 95% CI are calculated from binomial distribution.

^b Kaplan-Meier estimate. CI for median was computed using the Brookmeyer-Crowley method. The denominator for percentages is the number of subjects with CRc.

^c Transplant rate if the percentage of subjects undergoing allo-HSCT directly following the protocol treatment with no intervening AML therapy. Rate and CI are calculated based on binomial distribution.

Notes: The denominator for percentages is number of subjects in ITT Analysis Set unless otherwise specified.

Source: AC220-007 CSR Tables 14.2.3.1, 14.2.4.1, and 14.2.6.1

The Applicant's Position:

The secondary endpoint of EFS showed quizartinib was not statistically significantly different from salvage chemotherapy but did demonstrate a trend in favor of the quizartinib arm. A number of exploratory endpoints including CR rate, CRc rate, duration of CRc, and transplant rate numerically favored the quizartinib arm.

The FDA's Assessment:

One of the exploratory endpoints of the trial was CR rate, and duration of CR as well as composite complete remission (CRc) rate, as defined above. FDA considers durable CR a clinical benefit outcome in patients with relapsed/refractory AML (Jen, 2018); durable CRh (defined as

<5% bone marrow blasts by morphological examination with an ANC of >0.5 Gi/L and a platelet count of >50Gi/L, that do not meet CR requirements, in the absence of peripheral blasts or extramedullary disease) may be considered a clinical benefit endpoint in a population of patients being treated without curative intent, using agents that are relatively non-toxic and not myelosuppressive; even if achieved, it may require supporting data for transfusion independence in order to be considered a direct clinical benefit. However, CRi is not considered an endpoint equivalent to CR for regulatory decision making.

In the FDA analysis of remission rates on Study 007, FDA adjudicated each CR or CRh based on the datasets including bone marrow blast percentage and accompanying ANC and platelet counts. Since per the protocol and SAP, the CR requirements above had to be met in the absence of a RBC transfusion in the prior 4 weeks and platelet transfusion in the prior 1 week, FDA performed the per protocol analysis, but also performed a sensitivity analysis where CRs and CRhs were adjudicated solely on the basis of the bone marrow aspirate, CBC and extramedullary disease results described above. The protocol did not specify the timeframe within which the CBC results for determination of CR or CRh had to be collected in relation to the timing of the bone marrow assessment; for FDA adjudication of these outcomes, a 7-day window was used; a sensitivity analysis allowing for a window of 14 days was formed by FDA as well. The results of the applicant's analysis, as well as that of the two FDA analyses, are summarized in below; the specific patients for whom the FDA adjudicated CR or CRh rates differed from those assessed by the applicant in the sensitivity analyses are listed in the text below the table.

Table 61: CR and CRh rates, Study AC220-007

	Applicant's analysis		FDA analysis per protocol		FDA analysis independent of transfusions		FDA analysis, allowing for CBC +/- 14 days	
	Quizartinib (N = 245)	Control (N =122)	Quizartinib (N = 245)	Control (N =122)	Quizartinib (N = 245)	Control (N =122)	Quizartinib (N = 245)	Control (N =122)
CR	10 (4%)	1 (1%)	10 (4%)	1 (1%)	14 (6%)	3 (2%)	14 (6%)	4 (3%)
CRh	17 (7%)	8 (7%)	17 (7%)	3 (2%)	13 (5%)	1 (1%)	13 (5%)	1 (1%)
CR+CRh	27 (11%)	9 (7%)	27 (11%)	4 (3%)	27 (11%)	4 (3%)	27 (11%)	5 (4%)

Source: FDA clinical reviewer

To look for overall efficacy signals, FDA performed a final sensitivity analysis in which all patients with <5% blasts in their BM were considered CR if they met the peripheral count recovery criteria at any point (even beyond 14 days) after the BM assessment, and CRh if they met those criteria at any point. Using these criteria, there was no change in the results for the quizartinib arm (14 CRs and 13 CRhs), but for the control arm, there were an additional 2 CRs for a total of 6 CRs (5%) and 2 CRhs (2%), for a CR+CRh rate of 7% (8/122). The 4 additional

patients on the quizartinib arm adjudicated by FDA to have achieved CR based on the analysis independent of transfusions (all were previously assessed as CRh) are:

(b) (6)

The additional 2 patients on the control arm for whom this was the case are (b) (6) and (b) (6). The additional patient who was considered a CR based on the analysis allowing for a CBC within 14 days of the bone marrow was (b) (6) (previously considered as a non-responder).

The results of the CR and CRh analyses above raised concerns regarding the benefit of quizartinib in the population proposed in the initial NDA review. Since CR, and CR+ CRh in certain clinical settings, are endpoints representative of clinical benefit that have been used as the basis of approval of agents for the treatment of AML, a finding of high CR and/or CR+CRh rates in the quizartinib arm on Study AC220-007 would have supported the OS findings above and served as further evidence of efficacy in this population; conversely, the low CR and CRh rates described above raised further doubt regarding the results of the primary endpoint, as they were not internally consistent or robust. However, considering the results of QuANTUM-First described above, the rate of CR+CRh responses with quizartinib is reflective of measurable monotherapy activity of quizartinib in patients with FLT3-ITD mutated AML.

When CR/CRh rates have been used as the basis for marketing approval in the treatment of AML (e.g. ivosidenib, enasidenib, gilteritinib), supportive evidence for transfusion independence (TI) is necessary to strengthen the evidence of clinical benefit that CR/CRh represents (i.e., the recovery of counts to the point where transfusions are not necessary). On Study AC220-007, FDA performed an analysis of patients on the quizartinib arm who were transfusion dependent (TD) at study entry and achieved a 56-day window of transfusion independence at some point post-baseline. The denominator included 99 patients on the quizartinib arm who had documented transfusions through study day -1. In this analysis, 26 of these patients (26%; 95% CI: 19, 36) achieved TI at some point on treatment. In the context of the original NDA review, in the absence of evidence of substantial effectiveness of the drug on the underlying disease (i.e., CR and/or CR/CRh), TI alone could not be used as the sole evidence of benefit for quizartinib in patients with R/R FLT3-ITD mutated AML. However, we consider the data on TI from AC220-007 to be supportive of some monotherapy activity of quizartinib.

Dose/Dose Response

Data:

The data leading to establishing the dose and dose regimen used in Study AC220-007 are summarized in Section 6.2.2.1.

The Applicant's Position:

The efficacy, safety, and tolerability data from Study AC220-007 confirm that the dosing regimen utilized represents an appropriate balance between safety and efficacy considerations and supports the use of quizartinib in combination with standard chemotherapy for patients with *FLT3*-ITD (+) AML.

The FDA's Assessment:

On Study AC220-007, patients on the quizartinib arm were treated with different starting doses depending on whether they were on concomitant CYP3A4 inhibitor (20 mg) or not (30 mg), and dose escalation on day 16 was dependent on this factor (to 30 mg or 60 mg) as well as the QTc value on day 15, such that a dose- and exposure- response analysis would be appropriate. However, given the issues with regard to reliability of the study results as pertaining to the primary endpoint, interpretability of these analyses are subject to the same limitations as those described above with regard to interpretation of the overall study results, and are not further described here.

Due to the small numbers of CR/CRhs on Study AC220-007, response cannot be used as a clinical benefit endpoint that would allow for these analyses by dose either.

Durability of Response

Data:

See Table 60.

The Applicant's Position:

Overall, the responses are durable with observation of longer median duration of remission for CRc and CR.

The FDA's Assessment:

An analysis of durability of response was not performed due to the very small numbers of patients on AC220-007 who achieved a CR/CRh, such that these would not be used as substantial evidence of effectiveness in this context.

Persistence of Effect

Data:

See Figure 27.

The Applicant's Position:

The persistence of effect of quizartinib was established by the results of Study AC220-007. For the primary analysis of OS (ITT Analysis Set), the Kaplan-Meier plot of OS demonstrated early

and clear separation between the curves that was sustained thereafter (Figure 27). At 52 weeks (1 year), the survival probability was 27% of subjects for quizartinib compared with 20% for salvage chemotherapy.

The FDA's Assessment:

See comments above regarding the analyses of the primary endpoint.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

PROs were not collected for Study AC220-007.

Applicant Position:

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.1.5. Supportive Studies in Relapsed/Refractory AML – Study AC220-002

Study AC220-002 was an open-label, Phase 2 study of the efficacy and safety of quizartinib monotherapy in subjects with R/R AML with and without *FLT3*-ITD activating mutations. The study was divided into 2 stages. The exploratory stage included the first 60 *FLT*-ITD (+) subjects to complete the first 28-day treatment cycle, and the confirmatory stage included all remaining subjects.

In each stage, subjects were divided into 2 cohorts (approximately 120 *FLT3*-ITD (+) and 30 *FLT3*-ITD (-) subjects each) as follows:

- Cohort 1: Subjects ≥60 years of age who relapsed after 1 first-line chemotherapy regimen (with or without consolidation) in <12 months after CR1 or who were primary refractory to first-line chemotherapy
- Cohort 2: Subjects ≥18 years of age (including subjects ≥60 years of age) who were relapsed or were refractory after 1 second-line (salvage) regimen or who were relapsed or were refractory after HSCT

Quizartinib was administered QD as an oral solution continuously in 28-day cycles with no breaks between cycles. Initially, the dose of quizartinib was 200 mg/day. The dose was subsequently reduced to 135 mg/day (for males) or 90 mg/day (for females), because of occurrences of QTcF prolongation with the 200 mg/day dose. Subjects received up to 3 cycles of induction with quizartinib to achieve best response, and responders continued receiving quizartinib as consolidation and maintenance therapy.

Data:

Data from the exploratory and confirmatory stages were combined for analysis (AC220-002 CSR).

A total of 333 subjects were enrolled: 157 in Cohort 1 and 176 in Cohort 2. Subjects were predominantly white (87.4%) and almost equally distributed between males (51.1%) and females (48.9%), with a median age of 63.0 years (range: 19 to 86 years). The majority (248) of subjects were *FLT3*-ITD (+), 84 subjects were *FLT3*-ITD (-), and 1 subject had unknown or indeterminate *FLT3*-ITD status.

A total of 125 *FLT3*-ITD (+) subjects (50.4%) achieved a CRc, including 63 subjects (56.3%) in Cohort 1 and 62 subjects (45.6%) in Cohort 2. In *FLT3*-ITD (+) subjects, the median duration of CRc was 12.1 weeks for Cohort 1 and 10.6 weeks for Cohort 2. Twenty-eight *FLT3*-ITD (-) subjects (33.3%) achieved a CRc, including 16 subjects (36.4%) in Cohort 1 and 12 subjects (30.0%) in Cohort 2. Subjects responded early in their treatment with quizartinib, with *FLT3*-ITD (+) subjects achieving a CRc in approximately 4 weeks. For *FLT3*-ITD (-) subjects, the time to CRc was nearly double for Cohort 1 compared with Cohort 2 (8.1 versus 4.1 weeks, respectively).

The ability to control disease and induce remissions enabled a substantial number of subjects to undergo allo-HSCT, particularly for the younger age group in Cohort 2. Of the 112 *FLT3*-ITD (+) subjects in Cohort 1, 11 subjects had HSCT and 101 subjects had no HSCT after quizartinib. Of the 136 *FLT3*-ITD (+) subjects in Cohort 2, 47 subjects were able to go on to HSCT and 89 subjects did not go onto HSCT after quizartinib.

In Study AC220-002, a threshold VAF >10% was used to determine *FLT3*-ITD positivity. Since the CRc rates were similar in subjects with *FLT3*-ITD VAF ≤10% (CRc range of 36% to 58%) and those with VAF >10% (CRc range of 38% to 72%), while subjects with no detectable ITD mutation had lower response rates, a lower cutoff of ≤3% was chosen as the threshold for later studies (AC220-007 and AC220-A-U302).

Median OS for *FLT3*-ITD (+) subjects was approximately 25 weeks for both cohorts. For the *FLT3*-ITD (-) subjects, the median OS was 19.1 weeks in Cohort 1 and 25.1 weeks in Cohort 2. The median OS was 34.1 weeks (95% CI: 26.0, 49.0) for *FLT3*-ITD (+) subjects who underwent HSCT and 18.4 weeks (95% CI: 15.0, 22.7) for subjects who did not undergo HSCT in Cohort 2.

8.1.6. Supplemental Data from Other Phase 1 and Phase 2 Clinical Studies in Relapsed/Refractory AML

Study CP0001 was a Phase 1, first-in-human, open-label, 3+3 dose-escalation study of quizartinib in subjects with R/R AML or previously untreated AML who were unsuitable for induction chemotherapy because of age, comorbidities, or other factors. Quizartinib oral solution was initially administered at a starting dose of 12 mg QD for 14 days followed by a

14-day rest period (1 cycle). Subsequently, the protocol was amended to specify a continuous dosing (CD) schedule starting at 200 mg/day for 28 days (1 cycle). Nine dose escalations (from 12 to 450 mg) were achieved by using the 14-day regimen with 3 to 8 subjects per dose level. Two CD regimens were tested with 17 subjects on 200 mg/day and 8 subjects on 300 mg/day. A total of 76 subjects received treatment in the study. Subjects were mostly white (89.5%) and male (60.5%) with a median age of 59.5 years (range: 23 years to 86 years). Seventeen subjects (22.3%) were *FLT3*-ITD (+), 37 (48.7%) were *FLT3*-ITD (-) based on a 1% ITD to WT ratio, and 22 (28.9%) had unknown or indeterminate *FLT3*-ITD status. The overall response rate in the ITT Analysis Set, *FLT3*-ITD (+), *FLT3*-ITD (-), unknown or indeterminate *FLT3*-ITD status was 30.3%, 52.9%, 13.5% and 40.9%, respectively (CP0001 CSR).

Study AC220-A-J101 was a multicenter, open-label, Phase 1 study that assessed the safety and PKs of quizartinib as multiple-dose monotherapy in Japanese subjects with R/R AML. Subjects were enrolled in the study irrespective of *FLT3* mutation status (*FLT3*-ITD [+] or *FLT3*-WT). Seventeen subjects were registered, of which 16 subjects were treated. The median age of enrolled subjects was 68 years (range: 33 to 91 years), with an almost equal proportion of males and females. Of the 17 enrolled subjects, 16 were included in the Safety Analysis Set, the Efficacy Analysis Set, and the PK/PD Analysis Sets. The subjects received a dose of 20 mg/day quizartinib for the first cohort, with doses selected from among 20, 30, and 60 mg for the second and subsequent cohorts. The efficacy evaluation showed that the overall response rate was 56.3% (9 of 16 subjects), including 5 subjects (55.6%) in the 20-mg cohort, 2 subjects (66.7%) in the 30-mg cohort, and 2 subjects (50.0%) in the 60-mg cohort. Although no CR was reported in any subject, CRc was found in 6 subjects (37.5%) in total, 2 subjects (22.2%) in the 20-mg cohort, 2 subjects (66.7%) in the 30-mg cohort, and 2 subjects (50.0%) in the 60-mg cohort. Partial remission was observed in 3 subjects (18.8%) overall, all of whom in the 20-mg cohort (3 subjects [33.3%]). CRi was observed in 5 subjects (31.3%) overall, including 2 subjects (22.2%) in the 20-mg cohort, 1 subject (33.3%) in the 30 mg cohort, and 2 subjects (50.0%) in the 60-mg cohort. CRc was reported in 5 of 7 *FLT3*-ITD (+) subjects (71.4%) overall, including 1 subject (33.3%) in the 20-mg cohort, 2 subjects (100.0%) in the 30-mg cohort, and 2 subjects (100.0%) in the 60-mg cohort (AC220-A-J101 CSR).

Study AC220-A-J201 was a multicenter, open-label, single-arm, Phase 2 clinical study to assess the efficacy and safety of quizartinib monotherapy in Japanese subjects with *FLT3*-ITD (+) AML who have relapsed or were found to be refractory within 6 months after initial remission induction therapy (without consideration of whether they had received HSCT or not). The initial dose of quizartinib was 30 mg/day. For subjects receiving strong CYP3A inhibitors, the initial dose was 20 mg/day. Subsequently, whether or not to increase the initial dose of 30 to 60 mg/day or 20 to 30 mg/day was determined on Cycle 1 Day 16 and Cycle 2 Day 1 or thereafter in accordance with criteria for dose increase as per protocol. For subjects who achieved CRc after the start of treatment of quizartinib, subsequently relapsed, and met the criteria for dose increase, the dose of quizartinib was increased in the same manner.

The dose of the study drug was reduced in accordance with each of the criteria for dose reduction as per protocol. A total of 37 subjects were enrolled by the CSR data cutoff date (26 Feb 2018) and were included in the analysis sets. All 37 subjects were included in the Safety Analysis Set, and 32 subjects were included in the Efficacy Analysis Set. Subjects were mostly female (59.5%), with a median age of 65 years (range: 31 to 81 years). Overall, the CRc rate was 53.8% (14 subjects; 90% CI: 36.2, 70.8). Although no CR was reported in any subject, CRi was achieved as a best response in 13 subjects (48.1%). CRp was achieved in 1 subject (3.7%). The response rate was 77.8% (21 subjects; 95% CI: 57.7%, 91.4%) (AC220-A-J201 CSR).

Study 2689-CL-2004 was an open-label, randomized, multiple-dose, Phase 2 study in subjects with *FLT3*-ITD (+) AML that have relapsed or were refractory after 1 salvage regimen or HSCT. Subjects were randomly assigned to 28-day cycles of either 30 or 60 mg/day quizartinib. Seventy-six subjects were randomized, of which 74 subjects received treatment with quizartinib. Subjects were mostly white (77.6%) males (57.9%) and had a median age of 54.5 years (range: 19 to 77 years). The majority of subjects (90.8%) were *FLT3*-ITD (+). In total, 36 of the 76 randomized subjects (47.4%) achieved a best response of CRc until end of treatment. Eighteen subjects in each dose group (47.4%) achieved CRc. Median OS was 20.9 weeks and 27.3 weeks with 1 and 5 long-term (≥ 52 weeks [ie, ≥ 365 days]) survivors for the 30 and 60-mg treatment arms, respectively (2689-CL-2004 CSR).

8.1.7. Integrated Review of Effectiveness

The FDA's Assessment:

Regarding the studies in patients with R/R AML presented above, we note that the studies showed low levels of CR responses. For Study AC220-002, the Applicant and investigator adjudicated CR and CRc for both the efficacy and safety populations, as depicted in Table 62 and Table 63, below, in the *FLT3*-ITD (+) and *FLT3*-ITD (-) patients, respectively.

Table 62: Efficacy Results, AC220-002, *FLT3*-ITD (+) Subjects only

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	Cohort 1 (N=112) n (%) [95% CI]		Cohort 2 (N=136) n (%) [95% CI]		Total (N=248) n (%) [95% CI]	
Assessment for Safety Population	CRc	CR	CRc	CR	CRc	CR
Derived Disease Assessment Based on Local Morphology, First 3 Cycles	61 (54.5) [44.8, 63.9]	1 (0.9) [0.0, 4.9]	61 (44.9) [36.3, 53.6]	1 (0.7) [0.0, 4.0]	122 (49.2) [42.8, 55.6]	2 (0.8) [0.1, 2.9]
Derived Disease Assessment Based on Local Morphology, All On-treatment Data	63 (56.3) [46.6, 65.6]	3 (2.7) [0.6, 7.6]	62 (45.6) [37.0, 54.3]	5 (3.7) [1.2, 8.4]	125 (50.4) [44.0, 56.8]	8 (3.2) [1.4, 6.3]
Derived Disease Assessment Based on Central Morphology, First 3 Cycles ^a	49 (43.8) [34.4, 53.4]	0 (0.0) [0.0, 3.2]	50 (36.8) [28.7, 45.5]	2 (1.5) [0.2, 5.2]	99 (39.9) [33.8, 46.3]	2 (0.8) [0.1, 2.9]
Investigator Disease Assessment, First 3 Cycles	49 (43.8) [34.4, 53.4]	5 (4.5) [1.5, 10.1]	56 (41.2) [32.8, 49.9]	6 (4.4) [1.6, 9.4]	105 (42.3) [36.1, 48.8]	11 (4.4) [2.2, 7.8]
	Cohort 1 (N=98) n (%) [95% CI]		Cohort 2 (N=121) n (%) [95% CI]		Total (N=219) n (%) [95% CI]	
Assessment for Efficacy Evaluable Population	CRc	CR	CRc	CR	CRc	CR
Derived Disease Assessment Based on Local Morphology, Efficacy Evaluable Population, First 3 Cycles	56 (57.1) [46.7, 67.1]	1 (1.0) [0.0, 5.6]	58 (47.9) [38.8, 57.2]	1 (0.8) [0.0, 4.5]	114 (52.1) [45.2, 58.8]	2 (0.9) [0.1, 3.3]

CR = complete remission; CRc = composite complete remission

^a Those subjects who did not have a derived disease assessment based on Central Morphology were treated as nonresponders.

Source: Applicant CSR, AC220-002

Table 63: Efficacy Results, AC220-002, FLT3-ITD (-) Subjects only

NDA Multi-disciplinary Review and Evaluation {NDA 216993}
{VANFLYTA; quizartinib}

	Cohort 1 (N=44) n (%) [95% CI]		Cohort 2 (N=40) n (%) [95% CI]		Total (N=84) n (%) [95% CI]	
Assessment for Safety Population	CRC	CR	CRC	CR	CRC	CR
Derived Disease Assessment Based on Local Morphology, First 3 Cycles	13 (29.5) [16.8, 45.2]	2 (4.5) [0.6, 15.5]	11 (27.5) [14.6, 43.9]	1 (2.5) [0.1, 13.2]	24 (28.6) [19.2, 39.5]	3 (3.6) [0.7, 10.1]
Derived Disease Assessment Based on Local Morphology, All On-treatment Data	16 (36.4) [22.4, 52.2]	2 (4.5) [0.6, 15.5]	12 (30.0) [16.6, 46.5]	1 (2.5) [0.1, 13.2]	28 (33.3) [23.4, 44.5]	3 (3.6) [0.7, 10.1]
Derived Disease Assessment Based on Central Morphology, First 3 Cycles ^a	14 (31.8) [18.6, 47.6]	2 (4.5) [0.6, 15.5]	8 (20.0) [9.1, 35.6]	1 (2.5) [0.1, 13.2]	22 (26.2) [17.2, 36.9]	3 (3.6) [0.7, 10.1]
Investigator Disease Assessment, First 3 Cycles	13 (29.5) [16.8, 45.2]	4 (9.1) [2.5, 21.7]	7 (17.5) [7.3, 32.8]	1 (2.5) [0.1, 13.2]	20 (23.8) [15.2, 34.3]	5 (6.0) [2.0, 13.3]
	Cohort 1 (N=35) n (%) [95% CI]		Cohort 2 (N=33) n (%) [95% CI]		Total (N=68) n (%) [95% CI]	
Assessment for Efficacy Evaluable Population	CRC	CR	CRC	CR	CRC	CR
Derived Disease Assessment Based on Local Morphology, Efficacy Evaluable Population, First 3 Cycles	11 (31.4) [16.9, 49.3]	1 (2.9) [0.1, 14.9]	10 (30.3) [15.6, 48.7]	1 (3.0) [0.1, 15.8]	21 (30.9) [20.2, 43.3]	2 (2.9) [0.4, 10.2]

Source: Applicant CSR, AC220-002

The lack of CRs in this study is consistent with the findings in the QuANTUM-R trial, and supports the concerns raised above regarding the lack of robustness and internal consistency of the efficacy findings on QuANTUM-R. The fact that the CR rate was slightly higher (although still not significantly so) in the patients who were FLT3-ITD (-) as compared to those who were FLT3-ITD (+) raises additional questions, but these are beyond the scope of this review.

Although uninterpretable in the context of this non-randomized trial, the OS for both cohorts on Study AC220-002 were similar to the outcomes for the quizartinib arm on QuANTUM-R, such that the marginal 6.5 week OS advantage on that trial (if credible; see section 8.1.4.2 for the multiple limitations to its interpretation) appears consistent with other trials using quizartinib, and the possibility that QuANTUM-R represents an under-estimation of the OS seen with this treatment is less likely.

For Study 2689-CL-2004, the Applicant assessed CR and CRC for both the efficacy and safety

populations in Table 64. These results were based on response at the end of cycle 2. When analyzed at the end of study, the CR rate in the 30 mg cohort was unchanged, but there was one additional CR in the 60 mg cohort.

Table 64: Efficacy Results, 2689-CL-2004

	Quizartinib 30 mg N=38 n (%)	Quizartinib 60 mg N=38 n (%)	Total N=76 n (%)
CRc rate	18 (48)	18 (48)	36 (48)
90% CI	33, 62	33, 62	38, 57
CR rate	2 (5)	-	2 (3)
90% CI	0.6, 18	0, 9	0.3, 9
CRp rate	-	1 (3)	1 (1)
90% CI	0, 9	0.1, 14	0, 7
CRi rate	14 (37)	14 (37)	28 (37)
90% CI	22, 54	22, 54	26, 49

Source: Applicant CSR, page 91, Table 8.1.

As mentioned above with regard to Study AC220-002, the low rate of CRs in this study is consistent with the findings in QuANTUM-R, and supports the concerns raised above regarding the lack of robustness and internal consistency of the efficacy findings on QuANTUM-R. It is clear, however, across the monotherapy studies that quizartinib does have an anti-leukemic effect on the blast cells - hence, the CRc responses. While the mostly CRi component responses, in and of themselves, do not constitute clinical benefit, they serve as evidence of quizartinib's monotherapy antileukemic activity.

For Study 2689-CL-2004, there was no active control or placebo, and cross-trial comparisons between QuANTUM-R and study 2689-CL-2004 are necessarily exploratory in nature with regard to time to event endpoints such as OS. However, as noted above for trial AC220-002, OS for both cohorts were similar to the outcomes for the quizartinib arm on QuANTUM-R, such that the marginal 6.5 week OS advantage on that trial (if credible) appears consistent with other trials using quizartinib, and the possibility that QuANTUM-R represents an under-estimation of the OS seen with this treatment is less likely.

8.1.8. Assessment of Efficacy Across Trials

Efficacy of quizartinib in combination with chemotherapy

Data:

OS was the primary endpoint for Study AC220-A-U302. The results from the other two Phase 1 studies combination of quizartinib in combination with standard chemotherapy in newly

diagnosed AML are provided only descriptively (Table 65). Due to the study phase, limited study size, differences in subject populations and study designs, efficacy data from the studies were not pooled with data from the pivotal Phase 3 study, AC220-A-U302.

Table 65 – Summary of Efficacy of Quizartinib in Combination with Standard Chemotherapy (ITT Analysis Set)

Statistics	Pivotal Phase 3 Study AC220-A-U302		Phase 1 Clinical Studies	
	Quizartinib N=268	Placebo N=271	AC220-A-J102 N=7	2689-CL-0005 N=19
OS time to event (months)^a				
Median	31.9	15.1	NA	NA
95% CI	21.0, NE	13.2, 26.2	NA	NA
EFS (primary analysis – CR within 42 days) by IRC (months)^a				
Median	0.03	0.71	NA	NA
95% CI	0.03, 0.95	0.03, 3.42	NA	NA
EFS (sensitivity analysis – CR) by IRC (months)^a				
Median	5.0	3.4	NA	NA
95% CI	1.8, 9.0	1.7, 5.5	NA	NA
EFS (sensitivity analysis – CRc) by IRC (months)^a				
Median	11.9	5.7	NA	NA
95% CI	8.1, 16.5	4.0, 6.9	NA	NA
Remission rate and duration of remission				
CRc^b				
n (%)	192 (71.6)	176 (64.9)	5 (71.4)	16 (84.2) ^c
95% CI	65.8, 77.0	58.9, 70.6	35.9, 91.8	NR
Duration of CRc^a				
Median	27.2	12.4	NR	NA
95% CI	17.7; NE	8.7; 22.7	NR	NA
CR^b				
n (%)	147 (54.9)	150 (55.4)	0 (0.0)	9 (47.4)

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Statistics	Pivotal Phase 3 Study AC220-A-U302		Phase 1 Clinical Studies	
	Quizartinib N=268	Placebo N=271	AC220-A-J102 N=7	2689-CL-0005 N=19
95% CI	48.7, 60.9	49.2, 61.4	0.0, 35.4	24.4, 71.1
Duration of CR^a				
Median	38.6	12.4	NR	NA
95% CI	21.9, NE	8.8, 22.7	NR	NA
RFS in subjects who achieved CR^a				
Median	39.3	13.6	NA	NA
95% CI	22.6, NE	9.7, 23.7	NA	NA
CIR in subjects who achieved a CR (%) (95% CI)^d – post hoc				
12 months	18.7 (12.7, 25.6)	34.9 (27.1, 42.7)	NA	NA
24 months	31.2 (23.5, 39.2)	43.3 (34.9, 51.3)	NA	NA
36 months	33.8 (25.5, 42.2)	45.1 (36.5, 53.2)	NA	NA

^a Kaplan-Meier estimate. CI for median was computed using the Brookmeyer-Crowley method.

^b CIs were calculated using Clopper-Pearson method.

^c In Study 2689-CL-0005, CRc rate includes 2 subjects with MFLS.

^d Estimated using the cumulative incidence function

Note: Percentages are based on the N in a given treatment arm for the population analyzed and on the number of subjects censored.

Source: AC220-A-U302 CSR Tables 14.2.1, 14.2.2, 14.2.2.3, 14.2.2.5, 14.2.3, 14.2.4.1, 14.2.5, and 14.2.5.1; AC220-A-J102 CSR Table 14.2-2, 2689-CL-005 CSR Table 14.8

Table 66 – Summary of Efficacy of Quizartinib Monotherapy (ITT Analysis Set)

Statistics	Phase 3		Phase 2					Phase 1		
	AC220-007		2689-CL-2004		AC220-002 ^h		AC220-A-J201	AC220-A-J101 ^e	2689-CL-0011 ^a	CP0001 ^f
	Quizartinib Monotherapy N = 245	Salvage Chemo N = 122	30 mg N = 38	60 mg N = 38	Cohort 1 N = 112	Cohort 2 N = 136	30 to 60 mg ^d N = 32 ^d	20 to 60 mg N = 17 ^e n=7 <i>FLT3</i> -ITD (+)	40 and 60 mg N = 13	60 to 450 mg N = 76 ^f n=17 <i>FLT3</i> -ITD (+)
90 to 200 mg										
OS time to event (weeks)										
Median ^b	27.0	20.4	20.9	27.3	25.4	24.0	34.1	NR	NR (range: 13-142)	18.3 ^g
95% CI ^b	23.1, 31.3	17.3, 23.7	17.7, 25.3	17.3, 34.9	21.3, 29.7	21.1, 27.1	27.1, NE	NR	NR	10.6, 27.1 ^g
Remission rate and duration of remission										
CR ^c										
n (%) ^c	118 (48.2)	33 (27.0)	18 (47.4)	18 (47.4)	63 (56.3)	62 (45.6)	14 (53.8)	NR (4 out of 7 ^e)	NR	4 (23.5) ^g
95% CI ^c	41.8, 54.6	19.4, 35.8	33.3, 61.8	33.3, 61.8	46.6, 65.6	37.0, 54.3	33.4, 73.4	NR	NR	NR
Duration of CR ^c (weeks)										
Median ^b	12.1	5.0	4.2	9.1	12.1	10.6	16.1	NR	NR	9.7 ^g
95% CI ^b	10.4, 27.1	3.3, 12.6	2.1, 9.7	4.1, 22.3	6.3, 15.7	8.1, 16.1	4.7, 24.6	NR	NR	4.1, 29.0 ^g
CR										
n (%) ^c	10 (4.1)	1 (0.8)	2 (5.3)	0	3 (2.7)	5 (3.7)	0 (0.0)	NR	NR	1 (5.9) ^g
95% CI ^c	2.0, 7.4	0.0, 4.5	0.6, 17.7	0.0, 9.3	0.6, 7.6	1.2, 8.4	NR	NR	NR	NR

^a Study 2689-CL-0011 evaluated quizartinib monotherapy after HSCT. Evaluation of efficacy of quizartinib for maintenance therapy was a secondary endpoint and assessed by treatment duration and survival status. Median duration of treatment was 24 cycles in the 40 mg QD dose cohort and 20 cycles in the 60 mg QD cohort.

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- ^b Kaplan-Meier estimate. CI for median was computed using the Brookmeyer-Crowley method.
- ^c Rate and CI are calculated based on binomial distribution. For Study 2689-CL-2004, 90% CIs are presented.
- ^d Study AC220-A-J-201 enrolled a total of 37 subjects starting at 30 mg QD with possible increase to 60 mg QD (subjects receiving strong CYP3A inhibitors [N=3] were started on 20 mg QD with escalation to 30 mg QD; 86.5% of the overall study population was *FLT3*-ITD (+) based on a $\geq 3\%$ *FLT3*-ITD/total *FLT3* cutoff with 27 response evaluable subjects.
- ^e Study AC220-A-J101 enrolled a total of 17 subjects irrespective of *FLT3* mutation status at 20 to 60 mg QD. Of the 16 efficacy evaluable subjects, 7 subjects were *FLT3*-ITD (+): 2 received quizartinib 30 mg QD and 2 received 60 mg QD during dose escalation. The remaining *FLT3*-ITD (+) subjects received 20 mg QD. For comparison purposes, only subjects receiving 30 or 60 mg QD are listed for the response assessment. Due to small numbers, only the number of responders with CRc is listed in the table: 2/2 subjects with CRc receiving 30 mg and 60 mg; 1 additional *FLT3*-ITD (+) subject who received 20 mg QD achieved a CRc. There was no subject who achieved a CR.
- ^f Study CP0001 enrolled a total of 76 subjects irrespective of *FLT3* mutation status, 17 (22.4%) of whom were *FLT3*-ITD (+). CRc were only seen at doses of ≥ 60 mg/day of intermittent dosing (14 days on treatment and 14 days off treatment) or CD at ≥ 200 mg QD. There were 1 *FLT3*-ITD (+) subject and 1 *FLT3*-ITD (indeterminate) who achieved a CR with 200 mg QD CD.
- ^g Median OS, CRc, and CRc results listed only include the 17 subjects with confirmed *FLT3*-ITD (+) status defined as $>1\%$ *FLT3*-ITD to total *FLT3* ratio.
- ^h Study AC220-002 enrolled 2 cohorts: Cohort 1 enrolled subjects ≥ 60 years of age who were relapsed within 1 year after first-line chemotherapy regimen, with or without consolidation, or were primary refractory to first-line chemotherapy and Cohort 2 enrolled subjects ≥ 18 years of age who were R/R after 1 second-line (salvage) regimen, or after HSCT. The quizartinib dose was 200 mg/day initially and later reduced to 135 mg/day for males and 90 mg/day for females.

Note: For Study AC220-007, CRc (CR+CRi+CRp), CR, and duration of CRc assessed were assessed using objective criteria per modified Cheson criteria.

Unless indicated otherwise, percentages are based on the N in a given treatment arm for the population analyzed and on the number of subjects censored.

Source: AC220-007 CSR Tables 14.2.1.1, 14.2.3.1 and 14.2.6.1; 2689-CL-2004 CSR Tables 14.2.1.1, 14.2.2.1, 14.2.3.1, and 14.2.10.1; AC220-002 CSR Tables 49, 60, and 66; AC220-A-J201 CSR Tables 14.2-1, 14.2-9, and 14.2-13; AC220-A-J101 CSR Appendix 16.2-17; 2689-CL-0011 CSR Section 4.2 and Figure 14.2.1; CP0001 CSR Tables 5.2.1.3, 7.1.1.5, and 7.3.1.4

The Applicant's Position:

The primary efficacy data supporting this application are the statistically significant and clinically meaningful results from the pivotal study, AC220-A-U302 (QuANTUM-First), which demonstrate that quizartinib added to chemotherapy improves OS of subjects with newly diagnosed *FLT3*-ITD (+) AML and supports the conclusion that quizartinib compared with placebo in combination with standard induction and consolidation chemotherapy and then as continuation monotherapy for up to 36 cycles is an effective treatment in this patient population.

The results from Study AC220-A-U302 are supported by early Phase 1 studies in newly diagnosed AML, where quizartinib was added to frontline standard chemotherapy, demonstrating promising clinical activity in a limited number of subjects with *FLT3*-ITD (+) AML.

Evidence of quizartinib monotherapy activity is provided by the randomized, active-controlled, pivotal Phase 3 study, AC220-007, in which a 24% reduction in the risk of death during the observation period compared to salvage chemotherapy in subjects with R/R *FLT3*-ITD (+) AML, with additional Phase 2 studies providing further supportive evidence of consistent clinical activity of quizartinib in *FLT3*-ITD (+) AML. Median OS estimates were consistent across the studies, with a median OS of approximately 27 weeks in subjects treated with quizartinib 60 mg. The results were also consistent across studies with respect to rates of CRc and CR and the duration of CRc.

Quizartinib consistently demonstrated a clinical benefit across the 10 clinical studies in AML, including 2 randomized controlled studies, both in combination with standard chemotherapy regimens and as a single agent, and support the conclusion that quizartinib provides a clinically meaningful improvement for patients with *FLT3*-ITD (+) AML, a fatal disease with poor prognosis and continued high unmet medical need.

The FDA's Assessment:

Methods

Issues with clinical development program

Prior to Study AC220-A-U302 (QuANTUM-First), the Applicant investigated the safety and effectiveness of quizartinib in R/R AML in Study AC220-007 (QuANTUM-R). This study was discussed at ODAC due to trial conduct and safety issues. A major limitation of this trial was that it was open-label. There were notable imbalances between the arms, calling into question the validity of the OS results. Furthermore, QT prolongation was identified as a significant safety risk.

Issues with the pivotal (QuANTUM-First) trial design

The FDA defines maintenance therapy for AML as an extended but time-limited course of treatment given after achievement of CR with the objective of reducing the risk of relapse beyond the period of treatment (Guidance for Industry: Acute Myeloid Leukemia, 2022). Presently, there are no drugs approved as maintenance therapies for AML. While Onureg was approved for continued treatment of patients with AML who achieve CR or CRi, this is not considered a maintenance indication (Jen 2022). Levis et al (2019) reviewed post-HSCT trials of FLT3 inhibitors, noting that no trial has established the necessity of maintenance therapy in this setting. QuANTUM-First did not re-randomize patients to assess the effect of maintenance therapy. Consequently, the evidence for quizartinib maintenance therapy is limited and based purely on post-hoc, non-randomized comparisons.

Patient Population and Primary Endpoints

Two randomized, controlled trials were submitted in support of this NDA, QuANTUM-First and QuANTUM-R. QuANTUM-First was a randomized, placebo-controlled, double-blind trial in newly diagnosed patients and is the only randomized trial in the population for which an indication is currently sought by the Applicant. As such, QuANTUM-First serves as an adequate and well-controlled clinical investigation into the effects of adding quizartinib to standard induction and consolidation chemotherapy followed by maintenance monotherapy. FDA analysis of the primary endpoint of OS for this study revealed a HR of 0.78 (95% CI 0.62, 0.98; $p=0.0324$) as discussed above. The median OS in the quizartinib arm was 31.9 months (95% CI 21.0, NE) and 15.1 months (95% CI 13.2, 26.2) in the control arm, for a 16.8-month difference in median OS between arms.

As discussed above, QuANTUM-R was randomized open label trial for R/R FLT3-ITD AML. FDA analysis of the primary endpoint of QuANTUM-R revealed an OS HR of 0.77 (95% CI 0.59, 0.99; $p=0.019$). The median OS in the quizartinib arm was 26.9 weeks (95% CI 23.1, 31.0) and 20.4 weeks (95% CI 17.0, 25.2) in the control arm, for a 6-week difference in median OS between the arms. The credibility of the OS results for QuANTUM-R were plagued by uncertainties that have been described above. Given these concerns and the questionable clinical utility of a 6-week extension in median OS versus salvage chemotherapy, it was not thought that QuANTUM-R represented substantial evidence of effectiveness for the treatment of patients with R/R FLT3-mutated AML.

Secondary and Other Endpoints

FDA analysis of the per protocol EFS on QuANTUM-First was not statically significant with a HR of 0.92 (95% CI 0.75, 1.11; $p=0.2371$). However, sensitivity analysis showed that the EFS analysis was highly dependent on the time window allowed for count recovery before considering a response as induction treatment failure. Review of CR rates between arms was remarkably

similar with CR rates of 55% on both treatment arms. However, the duration of CR was 38.6 and 12.4 months in the quizartinib versus placebo arms, respectively.

FDA's analysis of the key secondary endpoint of QuANTUM-R revealed a 2.3-week difference in median EFS between the quizartinib arm and control arm for a HR of 0.9 (95% CI 0.71, 1.16). This was not statistically significant, with a p-value of 0.1138. CR rates on QuANTUM-R were 4% on the quizartinib arm and 1% on the control arm, and CR/CRh rates were 11% on the quizartinib arm and 3% on the control arm. These CR rates are similar to those seen in the non-randomized earlier phase studies AC220-002 and 2689-CL-2004, with CR rates of 2 and 3% respectively.

Subpopulations

As discussed above, analysis of subpopulations for QuANTUM-First generally showed benefit with quizartinib treatment in most groups investigated. Only the small subgroup with favorable risk cytogenetics suggested better outcomes on the placebo arm. Post-hoc analyses of the effect of quizartinib in the maintenance phase suggest that patients who receive HSCT may not derive any further benefit from quizartinib maintenance therapy.

Any analysis of subgroups in QuANTUM-R is restricted by the limitations described for the primary analysis of the ITT population above. As described in detail, the OS results for QuANTUM-R appear to be driven primarily by the substratum of patients preselected for LDAC. There was a striking imbalance between the rates of subsequent HSCT in this particular stratum (23% in the quizartinib arm and none on the LDAC arm).

Dose and Dose-Response

Since the OS results on study QuANTUM-First and QuANTUM-R cannot be used as response assessment (CR rates were equivalent on treatment arms of QuANTUM-First and CR rates in the R/R trials were low across the development program), an assessment of dose-response is not possible at this time.

Onset, Duration, and Durability of Efficacy Effects

The durability of CR on QuANTUM-First is mentioned above. Since the number of patients on quizartinib arm who achieved a CR on the Study QuANTUM-R was so small (4%), an analysis of time to response and/or durability response is not informative. The same is true for CR rates across the remaining trials in the clinical development program.

Other Relevant Benefits

The applicant points to CRc, defined as CR+ CRi+ CRp as evidence of clinical benefit across multiple trials in Table 65 and Table 66 above. It is noted that CRi and CRp are not considered evidence of clinical benefit in the treatment of AML (Jen 2018). The lack of equivalency of CR as compared to CRi and CRp in the context of cytotoxic therapies was reported in a cohort of over 6000 patients with AML treated across multiple countries and centers (Walter 2010), and absent any additional data using targeted therapies specifically the equivalency of these endpoints remains unknown. However, the statistically significant OS result from QuANTUM-R, the demonstration of monotherapy activity in terms of modest CR and CRh rates across R/R AML trials (Study AC220-007, AC220-002, and 2689-CL-2004), and the demonstration of moderate CRc rates across monotherapy trials (Table 66) are sufficient to provide confirmatory evidence that quizartinib has activity in *FLT3*-ITD AML.

8.1.9. Integrated Assessment of Effectiveness

Data:

Study AC220-A-U302 provides the primary data to support efficacy claims under this NDA; see Section 8.1.2 for details. Additional studies of quizartinib in combination with chemotherapy and as monotherapy in newly diagnosed or R/R AML provide additional supportive data (see Sections 8.1.4.2, 8.1.5, and 8.1.6).

The Applicant's Position:

Study AC220-A-U302 demonstrates that selective and potent inhibition of *FLT3*-ITD mutant signaling results in a significant improvement in survival when combined with standard induction and consolidation chemotherapy, and then as continuation monotherapy for up to 36 cycles in adult *FLT3*-ITD (+) newly diagnosed AML subjects aged between 18 and 75 years old. Considering the high-risk population enrolled in Study AC220-A-U302, quizartinib is addressing a significant unmet medical need for patients with *FLT3*-ITD (+) AML. This is particularly the case for older subjects (≥60 years), notably those who are eligible for intensive therapy, for whom current treatment options remain unsatisfactory, with a lack of randomized data to inform on appropriate treatment approaches.

Study AC220-A-U302 is the first and only global, randomized, double-blind, placebo-controlled Phase 3 study that has demonstrated a survival benefit specifically in subjects with *FLT3*-ITD (+) AML, a population associated with an inferior survival with chemotherapy alone. The study compared the effect of quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as continuation monotherapy for up to 36 cycles) on the primary endpoint of OS in adult subjects with newly diagnosed *FLT3*-ITD (+) AML. At the time of initiation of this study, chemotherapy with or without allo-HSCT was the standard for the treatment of AML; hence, placebo along with standard combination chemotherapy was used as the comparator. The study population is representative of the target population of patients with newly diagnosed *FLT3*-ITD (+) AML, and demographics and

disease characteristics of subjects in Study AC220-A-U302 were well balanced between the 2 treatment arms.

The study met its primary endpoint by demonstrating a statistical significance in OS of quizartinib compared with placebo with an HR (95% CI) of 0.776 (0.615, 0.979), corresponding to an estimated reduction in the risk of death of 22.4% in favor of the quizartinib arm. The median OS (95% CI) was 31.9 months (21.0, not estimable [NE]) in the quizartinib arm versus 15.1 months (13.2, 26.2) in the placebo arm, resulting in prolongation of median OS by 16.8 months compared with standard chemotherapy (Table 26). The survival rates at 1 year (67.4% versus 57.7%) and 2 years (54.7% versus 44.7%) also favored the quizartinib arm. The results of the preplanned supplemental and sensitivity analyses of OS were consistent with those of the primary OS analysis, showing a benefit of quizartinib, as demonstrated by consistent HRs (95% CI) of 0.774 (0.614, 0.975) for the unstratified OS analysis and 0.752 (0.562, 1.008) for the OS analysis censored at the start date of the conditioning regimen for allo-HSCT (Table 27). An improvement in OS was observed across most prespecified subgroups in favor of quizartinib. These results are considered clinically meaningful improvements, given the poor prognosis and the high unmet medical need. Furthermore, the E-R analysis indicated that the proposed dosing regimen in Study AC220-A-U302 is appropriate.

With regard to the secondary endpoint, EFS, although the primary analysis of EFS based on the definition of ITF as failure to achieve CR within 42 days of the start of the last cycle of induction chemotherapy (FDA, 2020) was not statistically significant, the sensitivity analysis based on CR in the Induction Phase using the protocol-defined 56-day window showed a clear benefit in favor of quizartinib as demonstrated by an HR (95%CI) of 0.818 (0.669, 0.999)(Table 37). Given that the protocol was designed to assess ITF up to 56 days from the start of the last induction cycle, the sensitivity analysis is consistent with the OS result and supports the overall conclusion on the efficacy of quizartinib.

Because the primary analysis for EFS was not significant, further statistical testing of other secondary endpoints was stopped. Analyses of secondary and exploratory endpoints showed that while the rates of CR were similar between treatment arms, a prespecified exploratory analysis of RFS in subjects who achieved a CR at the end of Induction Phase showed that subjects in the quizartinib arm had 3 times longer median RFS (39.3 months) than those in the placebo arm (13.6 months), resulting in a 38.7% relative risk reduction of relapse or death (Table 65). This benefit in RFS was maintained over time, and RFS rates are higher in the quizartinib arm compared with the placebo arm (73.4% versus 52.4% at 12 months and 57.8% versus 40.9% at 24 months, respectively). Furthermore, in a post hoc analysis in subjects who achieved a CR, quizartinib delayed relapse compared to placebo with lower CIR at 24 months (31.2% vs. 43.3%, respectively) and at 36 months (33.8% vs. 45.1%, respectively) from randomization (Figure 18). Additional exploratory analyses showed that the median (95% CI) duration of CR was approximately 3 times longer in subjects in the quizartinib arm (38.6 [21.9, NE] months) versus the placebo arm (12.4 [8.8, 22.7] months). The Kaplan-Meier plot of the duration of CR shows sustained separation of the curves for up to 3 years. There were no

notable differences in the demographics and baseline disease characteristics of subjects who achieved a CR between the 2 treatment arms (eCTD M2.7.3 Tables 14.1.2.1.2 and 14.1.3.1.1.3).

Taken together, these data demonstrated that quizartinib combined with chemotherapy followed by continuation monotherapy improves the OS of newly diagnosed subjects with *FLT3*-ITD (+) AML. The benefit in OS is further supported by clinically meaningful improvement in RFS, the longer duration of remission, and the lower CIR in CR subjects treated with quizartinib.

The FDA's Assessment:

We agree with the Applicant's assessment. QuANTUM-First demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of overall survival. This endpoint reflects both the long-term safety and efficacy of quizartinib treatment in newly diagnosed *FLT3*-ITD AML. Moreover, the KM plot of OS in Figure 2 above shows the treatment arms plateauing with a persistent difference, suggesting that the benefit to OS demonstrated during the Study has a continuing effect on long-term survival. While the per protocol EFS analysis was not statistically significant, sensitivity analyses conducted with an induction assessment window in line with study conduct did show benefit. Analysis of other secondary and exploratory endpoints showed a consistent effect whereby the addition of quizartinib treatment to standard therapy extended the duration of CR responses and improved RFS.

The results of FDA analyses of data from QuANTUM-First, including unadjusted and adjusted analyses of OS and RFS, suggest inconclusive evidence regarding use of quizartinib as maintenance therapy after HSCT. Note that this conclusion is based on exploratory post-hoc analyses; a more formal analysis is not possible since QuANTUM-First was inadequately designed to isolate the effect of maintenance therapy. Thus, the evidence was inadequate to support positive benefit-risk for patients post-HSCT. According to Levis et al, no *FLT3* TKI has definitively demonstrated improved efficacy for continued treatment following HSCT (Levis, 2019). Based on the lack of a demonstrated improvement in OS in patients post-HSCT, and the potential for harm (HR > 1), we recommend a Limitation of Use in the prescribing information stating that quizartinib is not indicated as maintenance monotherapy following allogeneic HSCT. Although evaluations of maintenance post-consolidation chemotherapy are also limited by the exploratory post-hoc nature of the analyses, the results are compelling enough clinically (HR 0.4 for non-HSCT patients) that we recommend inclusion of maintenance monotherapy following consolidation chemotherapy in the indication statement.

8.2. Review of Safety

Data:

Table 67 – Safety Population included in the All AML Pool

Study (Phase)	Number of Subjects Treated with Quizartinib (dose)

	and Comparator
Controlled studies conducted for this indication	
AC220-A-U302 (Phase 3)	Quizartinib 265 (40 mg/day and 30 to 60 mg/day)/ Placebo 268
Uncontrolled studies conducted in newly diagnosed AML	
2689-CL-0005 (Phase 1)	Quizartinib 18 (40 and 60 mg/day)
AC220-A-J102 (Phase 1b)	Quizartinib 7 (20 and 40 mg/day)
2689-CL-0011 (Phase 1)	Quizartinib 13 (40 and 60 mg/day)
Controlled studies conducted in R/R AML	
AC220-007 (Phase 3)	Quizartinib 241 (30 to 60 mg/day) Salvage chemotherapy 94
Uncontrolled studies conducted in R/R AML	
AC220-002 (Phase 2)	Quizartinib 333 (90 to 200 mg/day)
2689-CL-2004 (Phase 2b)	Quizartinib 74 (30 and 60 mg/day)
CP0001 (Phase 1)	Quizartinib 76 (12 to 450 mg/day)
AC220-A-J101 (Phase 1)	Quizartinib 16 (20, 30 and 60 mg/day)
AC220-A-J201 (Phase 2)	Quizartinib 38 (30 to 60 mg/day)
Total Pooled Safety Data (including Study AC220-A-U302)	
All AML Pool	Quizartinib Overall: 1081 669 (30 to 60 mg/day) Monotherapy: 791 Chemotherapy combination: 290 Comparator: 362

Source: eCTD 2.7.4, Table 1.1

Table 68 – Safety Population in Studies in Solid Tumors and Healthy Volunteers

Study (Phase)	Number of subjects treated with Quizartinib (dose)
Solid tumor	
AC220-004 (Phase 1)	13 (90 mg/day and 135 mg/day)
Healthy volunteers studies	
AC220-006 (Phase 1)	6 (60 mg single dose)
AC220-008 (Phase 1)	58 (20 or 60 mg single dose)
AC220-012 (Phase 1)	77 (60 mg single dose)

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AC220-014 (Phase 1)	80 (30, 60, or 90 mg single dose)
AC220-015 (Phase 1)	89 (30 mg single dose)
AC220-016 (Phase 1)	30 (30 mg single dose)
AC220-018 (Phase 1)	62 (30 mg single dose)
AC220-019 (Phase 1)	64 (30 mg single dose)
AC220-A-U104 (Phase 1)	20 (60 mg single dose)
AC220-A-U105 (Phase 1)	12 (30 mg single dose)
AC220-A-U106 (Phase 1)	31 (60 mg single dose)
AC220-A-U107 (Phase 1)	8 (60 mg single dose [tablets]; 50 µg single dose [infusion])
Total healthy volunteers	537

Source: eCTD 2.7.4, Table 7.1

The Applicant's Position:

The characterization of the safety profile of quizartinib in adult subjects with *FLT3*-ITD (+) newly diagnosed AML is primarily based on data from Study AC220-A-U302. Since this is a placebo-controlled study, the results allow for an unbiased comparison of the safety profile of quizartinib in combination with standard chemotherapy with that of chemotherapy alone. The safety database is further augmented by inclusion of an All AML Pool that provides an additional 816 subjects with AML that were treated with quizartinib, of whom 404 subjects also received quizartinib at doses in the range of 30 to 60 mg QD. Studies in healthy volunteers and subjects with hepatic impairment provide supporting information for the assessment of safety profile of quizartinib. As such, the safety database allows for a comprehensive assessment of the safety profile of quizartinib at the recommended dosing regimen and at higher quizartinib doses, including detection and characterization of common AEs, to adequately inform on appropriate toxicity management, and the evaluation of the overall benefit-risk in the proposed indication.

The FDA's Assessment:

FDA agrees with the Applicant's approach to safety data. As stated above, the characterization of common AEs for the proposed indication is based on Study AC220-A-U302 (QuANTUM-First). This study is a double-blind, placebo-controlled study that allows for assessment of AEs that develop with quizartinib use in the context of intensive induction and consolidation chemotherapy. The Applicant also notes that their development program and safety database include a total of 1081 patients with AML that were treated quizartinib at various dose levels,

alone and in combination with chemotherapy, to further inform the incidence of severe but less frequently seen AEs.

The efficacy evaluation for QuANTUM-First in the USPI will be presented at the time of the protocol specified final analysis (August 13, 2021); therefore, the safety analysis for purposes of the USPI will also be presented from that timepoint. The Applicant submitted an updated safety dataset using a data cutoff date of (April 13, 2022). The updated dataset did not contribute significant differences in adverse events, AEs resulting in death, dose reductions or interruptions, or dose discontinuations due to AEs.

8.2.1. Safety Review Approach

Data:

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0 and were assigned grades (severity) based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03. The lower-level terms from each study's database were mapped in the integrated database to the MedDRA hierarchy. A TEAE was defined as a new AE or an AE with worsening grade occurring on or after Day 1 of study drug treatment until 30 days after the last dose of study drug. Related AEs occurring more than 30 days after the last dose of study drug were also considered TEAEs. AEs collected before the start of study drug treatment were not considered TEAEs.

Different categories of TEAE (eg, all grade and Grade 3 /4 TEAE, related TEAE, serious TEAE, TEAE associated with fatal outcome, quizartinib discontinuation and interruption) were evaluated for the pivotal study AC220-A-U302 and the All AML Pool, with focus on the 30 to 60 mg quizartinib dose group.

For the comprehensive evaluation of the safety profile of quizartinib, predefined MedDRA searches for specific categories of events of interest were conducted. The searches, defined in Table 69, were selected based on the quizartinib safety experience in previous studies, TEAEs/ treatment-emergent serious AEs (TESAEs) expected to occur with treatment with the chemotherapeutic agents used during the Induction and Consolidation Phases of Study AC220-A-U302 and certain other studies, and the reported AEs associated with treatment using other FLT3 inhibitors.

In addition to TEAEs, safety laboratory, vital signs and ECG data were evaluated. Subgroup analyses of TEAE and ECG data according to age, sex, race, ethnic origin, geographic region, duration of exposure, and concomitant use of strong CYP3A inhibitors and QT-prolonging medications were done, to evaluate the safety of quizartinib in specific subject subpopulations. Mild or moderate hepatic impairment and renal impairment were not associated with significant effect on quizartinib exposure (see Table 11); therefore analysis of safety data in subgroups of subjects with hepatic and renal impairment was not performed.

Table 69 – Predefined MedDRA Search Criteria for Specific Events of Interest

Event	Definition
QT prolongation and potentially associated events	All PTs from TdP/QT prolongation SMQ (broad) plus PTs fall, presyncope, agonal rhythm, arrhythmia, cardiac flutter, paroxysmal arrhythmia, and death
Cardiac failure	All PTs from Cardiac failure SMQ (narrow) plus PTs cardiomegaly, diastolic dysfunction, left ventricular dysfunction, cardiomyopathy, cardiotoxicity, cytotoxic cardiomyopathy, and ejection fraction decreased
IHD	All PTs from Myocardial infarction SMQ (narrow) Other ischaemic heart disease SMQ (narrow)
Hepatotoxicity	All PTs from: Cholestasis and jaundice of hepatic origin SMQ (narrow) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (narrow) Hepatitis, non-infectious SMQ (narrow) Liver related investigations, signs, and symptoms SMQ (narrow)

Source: eCTD 2.7.4 Table 2.1.

The Applicant's Position:

The safety review approach is considered comprehensive and appropriate to identify and quantify the safety profile of quizartinib in subjects with newly diagnosed AML at the proposed dosing regimen.

The FDA's Assessment:

The FDA agrees with the Applicant's safety review approach. We again note that TEAEs from Study AC220-A-U302 will form the basis for assessment of common AEs for the proposed indication. Study AC220-A-U302 was a randomized placebo-controlled trial and contained 87% (265/303) of all frontline AML patients from the total safety pool. The pooled analyses are used for signal seeking for other important AEs.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 70 – Summary of Study Drug Exposure in the All AML Pool (Safety Analysis Set)

Statistics	Study AC220-A-U302		All AML Pool			
	Quizartinib N = 265	Placebo N = 268	Quizartinib <30 mg N = 30	Quizartinib 30 to 60 mg N = 669	Quizartinib >60 mg N = 382	Total Quizartinib N = 1081
Treatment duration^a (days)						
Mean (SD)	286.9 (367.90)	237.7 (343.94)	81.6 (119.89)	209.7 (308.43)	104.0 (118.15)	168.8 (258.62)
Median	75.0	66.5	53.5	84.0	69.0	74.0
Min, max	1, 1289	3, 1273	7, 645	1, 1689	2, 1126	1, 1689
Total subject- years of exposure	208.2	174.4	6.7	384.1	108.7	499.5
Treatment duration group (days), n (%)						
0 – 30	82 (30.9)	95 (35.4)	9 (30.0)	127 (19.0)	72 (18.8)	208 (19.2)
31 – 90	60 (22.6)	65 (24.3)	13 (43.3)	229 (34.2)	165 (43.2)	407 (37.7)
91 – 180	22 (8.3)	25 (9.3)	6 (20.0)	140 (20.9)	93 (24.3)	239 (22.1)
181 – 365	22 (8.3)	24 (9.0)	1 (3.3)	58 (8.7)	35 (9.2)	94 (8.7)
366 – 730	31 (11.7)	23 (8.6)	1 (3.3)	54 (8.1)	15 (3.9)	70 (6.5)
≥731	48 (18.1)	36 (13.4)	0	61 (9.1)	2 (0.5)	63 (5.8)

^a Treatment duration (days) = date of last dose - date of first dose + 1.

Source: ISS Table 2.1.1

The Applicant's Position:

The size and composition of the safety database allows for a comprehensive assessment of safety in AML subjects in general and specifically in the intended population of newly diagnosed AML subjects that are *FLT3*-ITD (+). In Study AC220-A-U302 the total subject exposure was longer in the quizartinib compared to the placebo arm. In addition, it is noteworthy that a sizeable proportion of subjects in the quizartinib arm of Study AC220-A-U302 and the 30 to 60 mg dose group of the All AML Pool (30% and 17%, respectively) remained on treatment for >1 year, which allowed for appropriate assessment of the long-term safety of quizartinib in this subject population.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position that exposure in the newly diagnosed AML subjects allowed for a comprehensive assessment of safety. The Applicant notes and we concur that the median exposure was longer in the quizartinib arm of the trial. This is also reflected by a higher percentage of quizartinib patients being exposed for over 365 days and in quizartinib patients have higher mean days of treatment. This longer exposure is reflective of quizartinib patients remaining in remission longer than the placebo-treated patients and

therefore being eligible for later phases of on-study treatment. The Applicant notes that 79 subjects on the quizartinib arm of Study AC220-A-U302 and an additional 36 from the All-AML pool were exposed to 30 to 60 mg quizartinib for over 365 days. This permits for an initial assessment of the long-term safety of quizartinib. However, whether this allows for complete assessment of long-term safety is a matter of analysis of the safety signals derived from these subjects. Additionally, as was noted in the clinical pharmacology section, the appropriate dose for maintenance phase of treatment was not systemically investigated.

Relevant characteristics of the safety population:

Data:

Table 71 – Summary of Demographics, Baseline Characteristics, and Dosing Information (Safety Analysis Set)

Parameter	Study AC220-A-U302		All AML Pool				Healthy volunteers
	Quizartinib N = 265	Placebo N = 268	Quizartinib <30 mg N = 30	Quizartinib 30 to 60 mg N = 669	Quizartinib >60 mg N = 382	Total Quizartinib N = 1081	Total Quizartinib ^a N=537
Age (years)							
Mean (SD)	53.6 (13.12)	54.3 (12.83)	62.4 (14.85)	53.8 (14.22)	57.7 (15.06)	55.4 (14.69)	35.1 (11.13)
Median	56.0	56.0	66.5	56.0	62.0	58.0	33.0
Minimum, max	23, 75	20, 75	27, 86	19, 91	19, 86	19, 91	18, 66
Age (years), n (%)							
<60	159 (60.0)	160 (59.7)	12 (40.0)	401 (59.9)	164 (42.9)	577 (53.4)	531 (98.9)
≥60 to <65	37 (14.0)	43 (16.0)	2 (6.7)	81 (12.1)	57 (14.9)	140 (13.0)	3 (0.6)
≥65 to <75	68 (25.7)	64 (23.9)	9 (30.0)	164 (24.5)	131 (34.3)	304 (28.1)	3 (0.6)
≥75	1 (0.4)	1 (0.4)	7 (23.3)	23 (3.4)	30 (7.9)	60 (5.6)	0
Sex, n (%)							
Male	124 (46.8)	120 (44.8)	14 (46.7)	319 (47.7)	202 (52.9)	535 (49.5)	373 (69.5)
Female	141 (53.2)	148 (55.2)	16 (53.3)	350 (52.3)	180 (47.1)	546 (50.5)	164 (30.5)
Race, n (%)^b							
White	157 (59.2)	161 (60.1)	16 (53.3)	431 (64.4)	333 (87.2)	780 (72.2)	334 (62.2)
Black or African American	2 (0.8)	5 (1.9)	1 (3.3)	16 (2.4)	15 (3.9)	32 (3.0)	166 (30.9)
Asian	79 (29.8)	77 (28.7)	13 (43.3)	154 (23.0)	9 (2.4)	176 (16.3)	10 (1.9)
Other	27 (10.2)	25 (9.3)	0	36 (5.4)	9 (2.4)	45 (4.2)	27 (5.0)
Unknown	0	0	0	32 (4.8)	16 (4.2)	48 (4.4)	0

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Parameter	Study AC220-A-U302		All AML Pool				Healthy volunteers
	Quizartinib N = 265	Placebo N = 268	Quizartinib <30 mg N = 30	Quizartinib 30 to 60 mg N = 669	Quizartinib >60 mg N = 382	Total Quizartinib N = 1081	Total Quizartinib ^a N=537
Ethnicity, n (%)^b							
Hispanic/ Latino	6 (2.3)	15 (5.6)	0	25 (3.7)	15 (3.9)	40 (3.7)	73 (13.6)
Not Hispanic/ Latino	234 (88.3)	231 (86.2)	17 (56.7)	538 (80.4)	320 (83.8)	875 (80.9)	464 (86.4)
Not reported	0	0	0	0	39 (10.2)	39 (3.6)	0
Unknown	25 (9.4)	22 (8.2)	13 (43.3)	106 (15.8)	8 (2.1)	127 (11.7)	0
Geographic region, n (%)							
North America	16 (6.0)	18 (6.7)	17 (56.7)	211 (31.5)	198 (51.8)	426 (39.4)	529 (98.5)
US	8 (3.0)	13 (4.9)	17 (56.7)	185 (27.7)	194 (50.8)	396 (36.6)	529 (98.5)
Canada	8 (3.0)	5 (1.9)	0	26 (3.9)	4 (1.0)	30 (2.8)	0
Europe	161 (60.8)	161 (60.1)	0	301 (45.0)	184 (48.2)	485 (44.9)	8 (1.5)
Asia and Other regions	88 (33.2)	89 (33.2)	13 (43.3)	157 (23.5)	0	170 (15.7)	0
12-lead ECG at baseline, n (%)^c							
Normal	209 (78.9)	211 (78.7)	24 (80.0)	508 (75.9)	265 (69.4)	797 (73.7)	471 (87.7)
Abnormal	56 (21.1)	55 (20.5)	6 (20.0)	160 (23.9)	117 (30.6)	283 (26.2)	66 (12.3)
Unknown	0	2 (0.7)	0	1 (0.1)	0	1 (<0.1)	0
ECOG PS, n (%)							
0	87 (32.8)	97 (36.2)	7 (23.3)	219 (32.7)	83 (21.7)	309 (28.6)	NA
1	133 (50.2)	134 (50.0)	8 (26.7)	347 (51.9)	204 (53.4)	559 (51.7)	NA
≥2	45 (17.0)	36 (13.4)	15 (50.0)	103 (15.4)	93 (24.3)	211 (19.5)	NA

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Parameter	Study AC220-A-U302		All AML Pool				Healthy volunteers
	Quizartinib N = 265	Placebo N = 268	Quizartinib <30 mg N = 30	Quizartinib 30 to 60 mg N = 669	Quizartinib >60 mg N = 382	Total Quizartinib N = 1081	Total Quizartinib ^a N=537
Unknown	0	1 (0.4)	0	0	2 (0.5)	2 (0.2)	NA
FLT3-ITD VAF^{d,e}							
0<3%	0	0	0	4 (0.6)	71 (18.6)	75 (6.9)	NA
≥3 -25%	94 (35.5)	98 (36.6)	0	182 (27.2)	69 (18.1)	251 (23.2)	NA
>25-50%	141 (53.2)	136 (50.7)	0	276 (41.3)	114 (29.8)	390 (36.1)	NA
>50%	29 (10.9)	34 (12.7)	0	148 (22.1)	78 (20.4)	226 (20.9)	NA
Unknown	1 (0.4)	0	30 (100)	59 (8.8)	50 (13.1)	139 (12.9)	NA
Average daily dose (mg)							
Mean (SD)	36.5 (10.18)	38.4 (12.07)	18.1 (4.77)	38.9 (12.30)	119.8 (52.75)	66.9 (51.18)	NA
Median	40.0	40.0	20.0	40.0	112.1	49.6	NA
Min, max	12, 59	16, 59	8, 27	4, 80	17, 450	4, 450	NA

^a Doses tested in Healthy volunteers studies were 20 to 90 mg QD

^b Race and ethnicity were not collected in some regions.

^c Baseline 12-lead ECG is defined as the worst centrally read overall interpretation recorded on the latest date prior to initial administration of study drug. For studies in which central ECGs were not performed, the investigator assessment was used. "Normal/abnormal" ECG classification is based on the overall evaluation of the ECG by the central ECG laboratory.

^d FLT3-ITD VAF was not collected in Study 2689-CL-0005.

^e The represented FLT3-ITD VAF ranges convert to FLT3-ITD AR (FLT3-ITD/WT FLT3) ranges of 0 to <0.03, ≥0.03 to 0.33, >0.33 to 1, and >1, respectively.

Note: The denominator for percentages is the N in the corresponding Safety Analysis Set.

Source: ISS Table 1.1.1, 1.2.1, and 2.1.1

The Applicant's Position:

Relevant demographic characteristics are well balanced between the quizartinib and placebo arms in Study AC220-A-U302, providing assurance with respect to the safety conclusions and the interpretation of comparisons made between treatment arms. The pivotal study and the pooled AML dataset include a substantial proportion of subjects older than 65 years, which allowed for the assessment of the safety profile of quizartinib in older age groups. The population enrolled is sufficiently diverse and representative of a broader population of adult patients with *FLT3*-ITD (+) newly diagnosed AML.

The FDA's Assessment:

FDA agrees with the Applicant's position that Study AC220-A-U302 was well balanced between the randomized arms. The population enrolled on Study AC220-A-U302 generally reflects patients with newly diagnosed *FLT3*-ITD mutated AML that are fit for treatment with intensive chemotherapy. It is notable that the median age of subjects enrolled was 56 years for both arms and that 40% of enrolled subjects were age ≥ 60 years. The racial composition of the study was 60% white, 29% Asian, 10% other (including not collected per local regulations), and 1% Black. While this racial composition is generally consistent with the geographic regions in which the trial was conducted, it is unclear what the final breakdown might have been if country specific privacy laws had allowed for the racial reporting of all enrolled subjects. It is notable that the reported enrollment of Black/African American subjects was (1%) on study AC220-A-U302, (3%) in the total AML quizartinib safety population, and (31%) of subjects enrolled to the healthy volunteer study. The total AML quizartinib safety population demographics are similar to those of Study AC220-A-U302. Some notable features include slightly older population with median age of 58 years old and 47% of patients age ≥ 60 years, higher percentage of white subjects (72%) and a lower percentage of Asian subjects (16.3%), and wider distribution of *FLT3*-ITD VAF levels (based on inclusion of patients with *FLT3*-WT).

Adequacy of the safety database:

Data:

See preceding sections.

The Applicant's Position:

The size and composition of the safety database allows for a comprehensive assessment of the safety of quizartinib in the intended population of newly diagnosed AML patients that are *FLT3*-ITD (+) and in specific patient subgroups.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The number of patients and the duration of follow up included in the safety database is adequate to provide a reasonable estimate of

adverse reactions over time for the indicated population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The Applicant's quality control and quality assurance activities, data management, and statistical analysis of the study data were implemented per the Applicant's applicable GCP standard operating procedures. Monitors designated by the Applicant to ensure compliance of the investigators and other site staff members involved in this study were granted direct access to the source documents maintained at individual study sites and verified that CRF data were accurately reported and consistent with the source data. As applicable, CROs and central laboratories implemented data quality control activities based on their relevant in house standard operating procedures.

The Applicant's Position:

No material concerns were identified with respect to the quality and integrity of the submitted datasets or individual case narratives. Data sets and case narratives were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported in the course of site monitoring by the Applicant or its designees and data captured in CRF and AE databases were consistent.

The FDA's Assessment:

The quality of the safety data submitted was adequate to allow substantial primary review.

Categorization of Adverse Events

Data:

The safety profile observed with quizartinib was evaluated on the basis of the following:

- Frequency, type, severity, and causal relationship of TEAEs to study treatment
- Frequency of deaths, treatment-emergent SAEs, and other clinically significant TEAEs (including AEs associated with study drug discontinuation, dose reduction, and/or study drug interruption, and AESIs and other select AEs)
- AESI for the study including
 - QTcF prolongation Grade ≥ 3 , either serious or non-serious and whether or not causally related
 - Combined elevations of aminotransferases (AT) and bilirubin

- TEAEs identified based on predefined MedDRA searches for specific events of interest (Table 69)
- Frequency and type of TEAEs in subgroups according to key intrinsic and extrinsic factors (eg, age, sex, race, ethnic origin, duration of exposure, geographic region, and concomitant use of strong CYP3A inhibitors)
- Changes in laboratory variables, vital signs and ECGs, with particular attention to abnormalities of CTCAE Grade 3 or 4.

See also Section 8.2.1.

The Applicant's Position:

The categorization of AEs was considered appropriate for evaluating the safety data in patients with AML in general and specifically in the intended population with newly diagnosed *FLT3*-ITD (+) AML.

The FDA's Assessment:

FDA agreed with mapping of reported terms to preferred terms per MedDRA 24.0. Terms that referred directly to relapse, persistence of disease, or progression of AML were excluded from FDA's analyses. TEAEs were assessed by frequency (event per patient) and maximum grade reported.

FDA reviewed the Applicant's grouped terms as above but also developed a list of group terms based on PTs that were reported in the AML ISS pool (see Appendix 19.5 for a table of FDA grouped terms used throughout FDA safety analyses unless otherwise noted). FDA assessed laboratory abnormalities as both reported AEs and by shifts from baseline labs. Since all patients in Study AC220-A-U302 presented with acute leukemia, most patients had some level of abnormal baseline labs induced by the disease process. Therefore, analysis anchored from this abnormal baseline would not identify labs that normalized with control of the acute leukemia but later became abnormal again. Therefore, analysis of both lab shifts and lab abnormalities reported as TEAEs were evaluated to identify abnormal signals.

Routine Clinical Tests

Data:

Clinical tests for safety assessment included clinical laboratory evaluations (hematology, biochemistry, coagulation, and urinalysis), vital signs and ECGs. The schedule of assessments in the protocol specified the time points at which laboratory evaluations were conducted. Per protocol, abnormal laboratory, vital signs, or ECG values considered clinically significant by the investigator were to be reported as TEAEs.

ECG in the study were obtained in triplicate and average of triplicate readings were used for the central ECG analysis. The investigator could use ECG obtained from the study-supplied ECG machine to guide initial decisions regarding dose reduction, interruption, or escalation until the average analysis from the central ECG laboratory became available. Once the analysis from the central ECG laboratory had been received, it should be used to guide dosing decisions.

Monitoring for hypokalemia at least 3 times weekly was performed during the Induction and Consolidation Phases of the study.

The Applicant's Position:

The clinical monitoring of subject safety (methods and time points) described in the protocol is considered to be reasonable and adequate for the population, disease, and targeted indication being investigated.

The FDA's Assessment:

The FDA agrees with the Applicant's position. See the discussion concerning laboratory AEs versus laboratory value shift analysis in the FDA comment above.

8.2.4. Safety Results

Deaths

Data:

Table 72 – All Deaths by Primary Cause of Death, Overall Study Period of Study AC220-A-U302 (Safety Analysis Set)

Deaths	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)
Total number	130 (49.1)	156 (58.2)
Due to disease progression	68 (25.7)	94 (35.1)
Due to AE	31 (11.7)	26 (9.7)
Other	31 (11.7)	36 (13.4)
Within 60 days of study drug initiation	20 (7.5)	13 (4.9)
Due to disease progression	2 (0.8)	2 (0.7)
Due to AE	17 (6.4)	11 (4.1)
Other	1 (0.4)	0
Within 30 days of study drug initiation	15 (5.7)	9 (3.4)
Due to disease progression	0	1 (0.4)

Deaths	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)
Due to AE	14 (5.3)	8 (3.0)
Other	1 (0.4)	0
Within 30 days after last dose	32 (12.1)	25 (9.3)
During Induction Phase	20 (7.5)	13 (4.9)
During Consolidation Phase	8 (3.0)	4 (1.5)
During Continuation Phase	4 (1.5)	8 (3.0)
Due to disease progression	0	2 (0.7)
Due to AE	30 (11.3)	23 (8.6)
Other	2 (0.8)	0

Note: First dose date is the date of first dose of treatment with study drug (quizartinib or placebo).

Data cutoff date: 13 Aug 2021. Sources: AC220-A-U302 CSR Tables 10.10, 10.11 and 14.3.2.3

**Table 73 – All Deaths by Primary Cause of Death in the Quizartinib Development Program
(Safety Analysis Set)**

Primary Cause of Death	Deaths Within 30 days After Last Dose	Deaths More Than 30 Days After Last Dose
Quizartinib in combination with chemotherapy for AML (N = 290)^a		
Due to disease progression	0	68 (23.4)
Due to AE	30 (10.3)	1 (0.3)
Other/unknown/not collected	3 (1.0)	29 (10.0)
Quizartinib monotherapy for AML (N = 791)^b		
Due to disease progression	160 (20.2)	287 (36.3)
Due to AE	94 (11.9)	44 (5.6)
Other/unknown/not collected	24 (3.0)	76 (9.6)
Monotherapy for solid tumors (N = 13)^c		
Due to disease progression	0	0
Due to AE	0	0
Other/unknown/not collected	0	1 (7.7)
Healthy volunteers (N = 537)^d		
Due to disease progression	0	0
Due to AE	0	0
Other/unknown/not collected	0	0

Primary Cause of Death	Deaths Within 30 days After Last Dose	Deaths More Than 30 Days After Last Dose
Total Treated (N = 1631)		
Due to disease progression	160 (9.8)	355 (21.8)
Due to AE	124 (7.6)	45 (2.8)
Other/unknown/not collected	27 (1.7)	106 (6.5)

^a Quizartinib in combination with chemotherapy for AML includes Studies AC220-U302, 2689-CL-0005 and AC220-A-J102.

^b Quizartinib monotherapy for AML includes Studies AC220-007, AC220-002, 2689-CL-2004, CP0001, AC220-A-J101, AC220-A-J201 and 2689-CL-0011.

^c Quizartinib in solid tumors includes Study AC220-004.

^d Healthy volunteer studies include AC220-006, AC220-008, AC220-012, AC220-014, AC220-015, AC220-016, AC220-018, AC220-019, AC220-A-U104, AC220-A-U105, AC220-A-U106, AC220-A-U107.

Notes: Primary cause of death in Studies 2689-CL-0005, 2689-CL-0011 and 2689-CL-2004 were not collected and are all summarized in the Other/unknown/not collected category.

Source: M5.3.5.3 ISS Supplemental Table 4.1.26.1

Table 74 – Treatment-emergent Adverse Events Associated With Death as an Outcome in ≥3 Subjects in the Quizartinib Arm of Study AC220-A-U302 or in the 30 to 60 mg Dose Group of the All AML Pool (Safety Analysis Set)

SOC <i>PT</i>	Study AC220-A-U302		All AML Pool
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib 30 to 60 mg N = 669 n (%)
Subjects with any TEAEs associated with death as an outcome	30 (11.3)	26 (9.7)	104 (15.5)
During Induction Phase ^b	19 (7.2)	13 (4.9)	NA
During Consolidation Phase ^b	8 (4.6)	5 (2.9)	NA
During Continuation Phase ^b	3 (2.6)	7 (7.6)	NA
Infections and infestations	20 (7.5)	12 (4.5)	44 (6.6)
<i>Pneumonia</i>	1 (0.4)	4 (1.5)	13 (1.9)
<i>Sepsis</i>	4 (1.5)	2 (0.7)	7 (1.0)
<i>Septic shock</i>	8 (3.0)	3 (1.1)	11 (1.6)
<i>Klebsiella sepsis</i>	3 (1.1)	0	3 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	12 (1.8)
<i>Acute myeloid leukaemia^a</i>	0	0	10 (1.5)

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SOC <i>PT</i>	Study AC220-A-U302		All AML Pool
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib 30 to 60 mg N = 669 n (%)
General disorders and administration site conditions	1 (0.4)	5 (1.9)	14 (2.1)
<i>Disease progression^a</i>	0	0	10 (1.5)
Nervous system disorders	3 (1.1)	4 (1.5)	10 (1.5)
<i>Haemorrhage intracranial</i>	0	1 (0.4)	5 (0.7)
Immune system disorders	1 (0.4)	0	3 (0.4)
<i>GVHD in gastrointestinal tract</i>	1 (0.4)	0	3 (0.4)

^a In Study 2689-CL-2004 and AC220-002, death due to disease progression or worsening of AML was recorded as a TEAE.

^b Percentages calculated based on subjects entering each phase as listed in Table 21: Subject Disposition in Study AC220-A-U302 (induction N=265 and N=268, consolidation N=173 and N=175, continuation N=116 and N=92, for quizartinib and placebo, respectively).

Notes: Percentage was calculated using the number of subjects in the column heading as denominator. AEs were coded using MedDRA Version 24.0.

Source: ISS Table 4.1.9, AC220-A-U302 CSR Table 14.3.1.1

Table 75 – Cause of Death for Grade 5 Adverse Events Within 30 Days of Last Dose of Study Drug in Study AC220-A-U302 (Safety Analysis Set)

Subject No.	Study Arm	Age (years), Gender (M/F)	Study Phase and Study Day of Death ^a	Cause of Death		
				Proximate ^b	Primary (Investigator Reported) ^c	Primary (Sponsor Determined) ^d
(b) (6)	Quizartinib	50, F	Induction Day 5	Pneumonia	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Placebo	71, M	Induction Day 9	Sepsis	AE: related/secondary to non-HSCT therapy	ADR to chemotherapy
	Quizartinib	69, M	Induction Day 5	Septic shock	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Quizartinib	66, F	Induction Day 35	Septic shock	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Quizartinib	61, F	Induction Day 7	Septic shock	AE: related/secondary to AML disease; related/secondary to non-HSCT therapy	ADR to chemotherapy
	Quizartinib	51, M	Consolidation Day 109	Pulmonary embolism	AE: related/secondary to AML disease	Unable to judge ^f
	Quizartinib	33, F	Induction Day 68	Brain oedema	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Quizartinib	69, M	Consolidation Day 104	Death	AE: related/secondary to AML disease	Unable to judge ^f
	Quizartinib	51, F	Induction Day 21	Mucormycosis	AE: related/secondary to AML disease; related/secondary to non-HSCT therapy	AE: related/secondary to AML
	Placebo	69, M	Continuation Day 232	General physical health deterioration	AE: related/secondary to AML disease	AML disease progression

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Subject No.	Study Arm	Age (years), Gender (M/F)	Study Phase and Study Day of Death ^a	Cause of Death		
				Proximate ^b	Primary (Investigator Reported) ^c	Primary (Sponsor Determined) ^d
(b) (6)	Placebo	63, M	Induction Day 16	General physical health deterioration ^e	AML disease progression	AML disease progression
	Quizartinib	49, F	Consolidation Day 87	Mucormycosis	AE	ADR to chemotherapy
	Placebo	66, M	Continuation Day 408	General physical health deterioration	AE: related/secondary to AML disease	AML disease progression
	Placebo	63, M	Continuation Day 302	General physical health deterioration	AE: related/secondary to AML disease	AML disease progression
	Placebo	70, M	Induction Day 23	Candida sepsis	AE: related/secondary to non-HSCT therapy	AE: related/secondary to AML disease
	Placebo	69, F	Consolidation Day 117	Septic shock	AE: related/secondary to AML disease; related/secondary to non-HSCT therapy	AE: related/secondary to AML disease
	Quizartinib	73, M	Induction Day 55	Septic shock	AE: related/secondary to AML disease; related/secondary to non-HSCT therapy	ADR to chemotherapy
	Quizartinib	62, M	Consolidation Day 138	Ventricular dysfunction	AE: related/secondary to AML disease	ADR to chemotherapy
	Placebo	29, F	Induction Day 39	Septic shock	AE: related/secondary to non-HSCT therapy	AE: related/secondary to AML disease
	Placebo	54, F	Continuation Day 343	Cerebrovascular accident	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Quizartinib	57, F	Induction Day 62	Sepsis	AE	AE: related/secondary to AML disease

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Subject No.	Study Arm	Age (years), Gender (M/F)	Study Phase and Study Day of Death ^a	Cause of Death		
				Proximate ^b	Primary (Investigator Reported) ^c	Primary (Sponsor Determined) ^d
(b) (6)	Quizartinib	47, M	Induction Day 6	Sepsis	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Quizartinib	63, F	Continuation Day 193	—	Other: Unknown	AML disease progression
	Placebo	65, F	Continuation Day 221	Pneumonia	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Quizartinib	54, F	Induction Day 79	Cardiac arrest	AE	ADR to IP (quizartinib/ placebo)
	Quizartinib	65, F	Induction Day 8	Klebsiella sepsis	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Quizartinib	67, M	Induction Day 15	Klebsiella sepsis	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Quizartinib	71, M	Induction Day 9	Klebsiella sepsis	AE: related/secondary to AML disease; related/secondary to non-HSCT therapy	ADR to chemotherapy
	Quizartinib	60, F	Induction Day 28	Sepsis	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Placebo	56, M	Consolidation Day 125	Pneumonia	AE: related/secondary to AML disease	ADR to chemotherapy and IP (quizartinib/ placebo)
	Placebo	59, F	Consolidation Day 96	Haemorrhagic stroke	AE: related/secondary to AML disease; related/secondary to non-HSCT therapy	ADR to chemotherapy
	Placebo	66, F	Continuation Day 229	Rectal haemorrhage	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Quizartinib	56, M	Consolidation Day 122	Pulmonary sepsis	AE	AE: related/secondary to AML disease
	Quizartinib	38, F	Consolidation Day 72	Septic shock	AE: related/secondary to AML disease	AE: related/secondary to AML disease

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Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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Subject No.	Study Arm	Age (years), Gender (M/F)	Study Phase and Study Day of Death ^a	Cause of Death		
				Proximate ^b	Primary (Investigator Reported) ^c	Primary (Sponsor Determined) ^d
(b) (6)	Placebo	58, F	Induction Day 11	Pneumonia	AE: related/secondary to AML disease; related/secondary to non-HSCT therapy	ADR to chemotherapy
	Placebo	68, F	Induction Day 22	Haemorrhage intracranial	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Placebo	66, M	Continuation Day 294	Respiratory failure	AE	AE: related/secondary to AML disease
	Placebo	71, M	Induction Day 62	Multiple organ dysfunction syndrome	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Quizartinib	66, F	Induction Day 18	Acute respiratory distress syndrome	AE	AE: related/secondary to AML disease
	Placebo	43, F	Induction Day 36	Sepsis	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Quizartinib	43, F	Consolidation Day 170	Septic shock	AE: related/secondary to non-HSCT therapy	ADR to chemotherapy
	Quizartinib	47, M	Induction Day 2	Febrile neutropenia	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Placebo	48, F	Consolidation Day 92	Systemic mycosis	AE: related/secondary to non-HSCT therapy	ADR to chemotherapy
	Quizartinib	56, M	Induction Day 29	Brain oedema	AE: related/secondary to AML disease	AE: related/secondary to AML
	Quizartinib	69, F	Induction Day 9	Cerebral infarction	AE: related/secondary to non-HSCT therapy	ADR to chemotherapy and IP (quizartinib/ placebo)

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Subject No.	Study Arm	Age (years), Gender (M/F)	Study Phase and Study Day of Death ^a	Cause of Death		
				Proximate ^b	Primary (Investigator Reported) ^c	Primary (Sponsor Determined) ^d
(b) (6)	Quizartinib	66, M	Continuation Day 808	Septic shock	AE: related/secondary to AML disease; related/secondary to HSCT	AE: related/secondary to HSCT
	Placebo	49, F	Induction Day 14	Encephalitis	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Quizartinib	67, M	Consolidation Day 56	Septic shock	AE: related/secondary to AML disease; related/secondary to non-HSCT therapy	ADR to chemotherapy and IP (quizartinib/ placebo)
	Placebo	69, F	Continuation Day 227	—	AML disease progression	AML disease progression
	Quizartinib	62, M	Continuation Day 278	GVHD in gastrointestinal tract	AE: related/secondary to HSCT	AE: related/secondary to HSCT
	Quizartinib	54, M	Induction Day 7	—	Other: the cause of death was not known	ADR to chemotherapy
	Quizartinib	40, M	Continuation Day 653	Varicella zoster virus infection	AE	AE: related/secondary to HSCT
	Placebo	31, F	Induction Day 42	Septic shock	AE: related/secondary to AML disease	AE: related/secondary to AML disease
	Placebo	53, M	Induction Day 11	Respiratory failure	AE: related/secondary to AML disease; related/secondary to non-HSCT therapy	AE: related/secondary to AML disease
	Placebo	71, M	Induction Day 29	Cerebrovascular accident	AE	AE: related/secondary to AML disease
	Quizartinib	67, F	Induction Day 27	Sepsis	AE: related/secondary to AML disease	AE: related/secondary to AML disease

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Subject No.	Study Arm	Age (years), Gender (M/F)	Study Phase and Study Day of Death ^a	Cause of Death		
				Proximate ^b	Primary (Investigator Reported) ^c	Primary (Sponsor Determined) ^d
(b) (6)	Placebo	63, F	Induction Day 11	Pulmonary haemorrhage	AE: related/secondary to AML disease	AE: related/secondary to AML disease

^a From start date of dosing with study drug (Day 8 [+3 days] of Cycle 1 of induction)

^b From EDC; based on event term from TEAE associated with fatal outcome

^c From EDC: AML disease progression, AE (including subcategory, if applicable), or other

^d AML disease progression, AE (including subcategory), unrelated intercurrent event, or unable to judge

^e Although Subject (b) (6) had a reported AE of general physical health deterioration associated with death as outcome, the investigator specified AML disease progression as the subject's primary cause of death.

^f For additional details, please see the Death Adjudication Report.

Sources: CSR Subject Data Listing 16.2.4.1 and 16.2.1.5 and Death Adjudication Report, eCTD 5.3.5.1

Table 76 – All Deaths by Primary Cause of Death in Study AC220-007– Cumulative Data - 21 Dec 2020 Database Lock (Safety Analysis Set)

Deaths	Quizartinib Monotherapy (N = 241) n (%)	Salvage Chemotherapy ^a (N = 94) n (%)
Any death	212 (88.0)	79 (84.0)
AML disease progression	151 (62.7)	58 (61.7)
AE	53 (22.0)	20 (21.3)
Related/secondary to AML disease	31 (12.9)	13 (13.8)
Related/secondary to non-HSCT therapy	2 (0.8)	1 (1.1)
Related/secondary to HSCT	8 (3.3)	3 (3.2)
Other ^b	8 (3.3)	1 (1.1)

^a Subjects who received salvage chemotherapy received a median (min, max) of 1 cycle (1, 2) for all 3 treatment regimens (LoDAC, MEC, and FLAG-IDA).

^b Other cause includes: unknown, ventricular tachycardia heart failure, subject underwent medical assistance in dying, cause of death is sepsis, cardiogenic shock, and sepsis due to AML

Note: Subjects with an AE as the primary cause of death can be counted in 1 or more of the related/secondary columns.

Source: AC220-007 CSR Addendum Table 14.3.1.1b-II

The Applicant's Position:

AML disease progression was the most common cause of death in the quizartinib studies. Overall, 9.8% and 21.8% of subjects, respectively, died due to disease progression within 30 days and more than 30 days of last dose of quizartinib. AEs were the second most common cause of death within 30 days after last dose of quizartinib, and infections and infestations were the most frequent category of fatal AEs.

In the pivotal study, AC220-A-U302, on-treatment deaths were all deaths that occurred within 30 days of the last dose of study medication. In accordance with reporting requirements for deaths in the study, the primary cause of on-treatment death was recorded as an AE. In Study AC220-A-U302, AML disease progression was not required to be reported as an AE per protocol; therefore, the incidence of TEAE of AML progression and/or relapse is much lower than in the earlier studies in the development program. In the AC220-A-U302 study, the most frequently reported types of TEAEs with an outcome of death were infections (septic shock and sepsis). These fatal infections predominantly occurred during the Induction and Consolidation Phases when subjects were also receiving intensive chemotherapy, with low incidence of fatal infections in the Continuation Phase.

In Study AC220-A-U302, a numerically higher incidence of deaths within 30 days of the start of study drug was observed in the quizartinib arm compared with the placebo arm. The majority of these early deaths in the quizartinib arm were also due to infections (sepsis and septic shock).

The incidence of cardiac events, including cardiac arrhythmias, associated with fatal outcome was low. Two subjects from the quizartinib arm of Study AC220-A-U302 experienced cardiac arrest that were associated with recorded ventricular fibrillation on ECG (reported as a separate TEAE for one of the subjects) and occurred in the context of Grade 3 or 4 hypokalemia. One of the subjects was successfully resuscitated by cardioversion, however the second subject died as a result of the event. An additional subject in the quizartinib arm of Study AC220-A-U302 died in his sleep 10 days after the last dose of quizartinib with no cause of death identified and no significant QTcF prolongation during the study.

In addition to the cases from Study AC220-A-U302, a comprehensive review of all potential cardiac arrhythmia events from the entire quizartinib development program revealed 1 additional case of cardiac arrest, which occurred at higher quizartinib doses in subjects with some evidence of QTcF prolongation prior to the event. The event of fatal cardiac arrest occurred in a subject in the setting of sepsis 4 days after the starting quizartinib dose of 90 mg was increased to 135 mg and the subject was on a concomitant strong CYP3A inhibitor. The subject's QTcF interval 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.

Other TEAE with fatal outcome were infrequent at 30 to 60 mg dose of quizartinib, with very low incidence of major hemorrhagic events, including intracranial hemorrhage.

Early mortality is a known complication in newly diagnosed AML subjects and can be attributed to several confounding factors, such as age, frailty, organ dysfunction, underlying disease (cytogenetic abnormality), comorbidities, and complications from chemotherapy. Bleeding and infections are the most common complications of standard chemotherapy and can result in increased risk of treatment-related early mortality during or after induction therapy. In Study AC220-A-U302, the OS Kaplan-Meier (KM) curves show an early crossing attributed to early deaths. The observed incidence rate of early deaths in the study is small and in line with reported early mortality rates in patients with newly diagnosed AML receiving standard chemotherapy ([Sasaki, 2022](#)). OS captures all-cause mortality during the study and the imbalance in deaths seen early in the study does not persist over the course of quizartinib treatment.

The OS KM curves show a clear and sustained separation in favor of the quizartinib arm, with an early crossing attributed to early deaths. Early mortality is a known complication in newly diagnosed AML subjects and can be attributed to several confounding factors, such as age, frailty, organ dysfunction, underlying disease (cytogenetic abnormality), comorbidities, and complications from chemotherapy. Bleeding and infections are the most common complications of standard chemotherapy and can result in increased risk of treatment-related

early mortality during or after induction therapy. Overall survival captures all-cause mortality during the study and the quizartinib arm has demonstrated a substantial improvement in OS over the placebo arm. The early imbalance in deaths does not persist over the course of quizartinib treatment and the overall conclusion on efficacy is not impacted.

The FDA's Assessment:

FDA performed an assessment of deaths, based on review of individual patient narratives, in patients enrolled on Study AC220-A-U302 that occurred within 30 days of the last dose of study drug, either placebo or quizartinib. In comparison to the Applicant, the FDA used simplified categories for root cause of death including TEAE treatment related, AML progressive disease, and TEAE related to transplant. We would have also considered intercurrent illness/event as a root cause of death. However, we did not identify any deaths on Study AC220-A-U302 that we would have categorized as such. Table 77 below shows the summary of FDA adjudicated deaths between arms.

Table 77: FDA Root Cause of Death

FDA Root Cause of death	Quizartinib (n=265)	Placebo (n=268)
TEAE treatment related	26 (10%)	14 (5%)
AML progressive disease/Relapse	2 (0.8%)	10 (3.7%)
TEAE related to transplant	4 (1.5%)	1 (0.4%)

Source: FDA Analysis

In making root cause determination, FDA did not assign the AE to either the chemotherapy, if recently given, or study drug (placebo or quizartinib). Instead, the determination was made that the AE was related to recent protocol therapy (not to progressive/ relapsed disease, transplant related TEAE, or intercurrent illness) and that comparison between treatment arms would be used to assess for potential contribution from quizartinib treatment. This is in contrast to the Applicant's approach to adjudication where their physician reviewers attempted to assign the AE to either study drug and/or chemotherapy. When comparing root cause assignments, FDA considered the Applicant's root cause in agreement with FDA's use of TEAE treatment-related if they attributed the AE to either chemotherapy or study drug. FDA did not agree with the Applicants root cause of death in the 27 cases listed in Table 78 below. We note that in 25 of these cases, the Applicant attributed the root cause to an AE secondary to AML. For these cases, FDA considered these events to be related to the treatment, since most were complications from cytopenia such as infections and bleeding events and these cytopenias were greatly exacerbated by recent treatments with chemotherapy and study drugs without mention of refractory or relapsed disease. We would also note that the Applicant was inconsistent with the approach to such cases, with cases of sepsis-related deaths occurring during induction alternatively being attributed to an adverse event from chemotherapy or as

disease-related AE without clear reason for the different attribution.

Table 78: Subjects with differing root cause of death between the FDA's and the Applicant's adjudication

Arm	Study Day of Death*	Treatment Phase	FDA Root Cause of death	Root Cause of Death by Sponsor	Proximate Cause of Death	Unique Subject Identifier
Placebo	11	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Pulmonary haemorrhage	(b) (6)
Placebo	11	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Respiratory failure	
Placebo	14	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Encephalitis	
Placebo	22	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Haemorrhage intracranial	
Placebo	23	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Candida sepsis	
Placebo	29	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Cerebrovascular accident	
Placebo	36	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Sepsis	
Placebo	39	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Septic shock	
Placebo	117	Consolidation	AE treatment related	Adverse Event: Related/secondary to AML Disease	Septic shock	
Placebo	294	Continuation	AE related to transplant	Adverse Event: Related/secondary to AML Disease	Respiratory failure	
Quizartinib	2	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Febrile neutropenia	

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Quizartinib	5	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Pneumonia
Quizartinib	5	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Septic shock
Quizartinib	6	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Sepsis
Quizartinib	8	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Klebsiella sepsis
Quizartinib	15	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Klebsiella sepsis
Quizartinib	18	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Acute respiratory distress syndrome
Quizartinib	21	Induction	AE treatment related	Adverse Event: Related/secondary to AML	Mucormycosis
Quizartinib	27	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Sepsis
Quizartinib	28	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Sepsis
Quizartinib	29	Induction	AE treatment related	Adverse Event: Related/secondary to AML	Brain oedema (following ischemic stroke)
Quizartinib	35	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Septic shock
Quizartinib	68	Induction	AE treatment related	Adverse Event: Related/secondary to AML Disease	Brain oedema (cerebral hemorrhage)
Quizartinib	72	Consolidation	AE treatment related	Adverse Event: Related/secondary to AML Disease	Septic shock
Quizartinib	104	Consolidation	AE treatment related	unable to judge	Death
Quizartinib	109	Consolidation	AE treatment related	unable to judge	Pulmonary embolism

(b) (6)

Quizartinib	122	Consolidation	AE treatment related	Adverse Event: Related/secondary to AML Disease	Pulmonary sepsis

(b) (6)

Source: FDA Analysis

*Note that Study Day is measured from the first day of quizartinib, not from the first day of chemotherapy

There were also two cases that the Applicant was unable to judge the cause of death.

Subject (b) (6), was a 51-year-old male assigned to the quizartinib treatment. He presented back to hospital at the end of consolidation cycle 1 with chest pain, SOB, and cyanosis that was diagnosed as a PE and treated as such. However, the Applicant's physician reviewers noted that a definitive diagnosis of PE was not made, and the subject died several days later after their status worsened. Due to the proximity to study treatment, FDA considered this death treatment related. Although, FDA agrees that the proximal cause of death was not clear from narrative, PE could have been consistent with the described presentation.

Subject (b) (6), was a 69-year-old male assigned to the quizartinib treatment. The subject died in his sleep at end of consolidation cycle 1, 10 days after last dose of quizartinib and 24 days after last dose of HiDAC. This subject had not had issues with QTc prolongation while on study. Due to the proximity to chemotherapy and quizartinib treatment, FDA considered this treatment related.

FDA noticed an unexpected signal in the early deaths on the quizartinib arm while reviewing patient narratives. We noted that there was an overrepresentation of Russian sites in the early induction deaths in general and on the quizartinib arm in particular. While the overall induction on-treatment death rate was 6.1% for all patients on both arms of Study AC220-A-U302, Russian sites had an on-treatment induction death rate of 32% (6/19) and randomized induction death rate of 37% (7/19; one patient died after randomization but prior to receiving treatment with quizartinib). Most of these deaths were on the quizartinib arm (5/6 and 6/7, respectively). When FDA reviewed the death narratives, 5/6 induction on-treatment deaths described rapidly progressive septic shock unresponsive to initial treatment. We also noted that the choice of empiric antibiotics did not reflect the standard of care generally employed in the treatment of neutropenic patients. It is unclear if a more traditional choice of antibiotics might have changed the outcomes for these cases. The remaining case was hemorrhagic stroke that occurred in a patient after a second cycle of induction chemotherapy.

Serious Adverse Events

Data:

Table 79 – TESAEs in ≥2% of Subjects in in the Quizartinib Arm of Study AC220-A-U302 or in the 30 to 60 mg Dose Group of the All AML Pool by SOC and PT (Safety Analysis Set)

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SOC <i>PT</i>	Study AC220-A-U302		All AML Pool			
	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)	Quizartinib <30 mg N = 30 n (%)	Quizartinib 30 to 60 mg N = 669 n (%)	Quizartinib >60 mg N = 382 n (%)	Total Quizartinib N = 1081 n (%)
Any TESAE	143 (54.0)	123 (45.9)	9 (30.0)	412 (61.6)	304 (79.6)	725 (67.1)
During Induction Phase ^a	75 (28.3)	66 (24.6)	NA	NA	NA	NA
During Consolidation Phase ^a	59 (34.1)	54 (30.9)	NA	NA	NA	NA
During Continuation Phase ^a	39 (33.6)	34 (37.0)	NA	NA	NA	NA
Infections and infestations	76 (28.7)	71 (26.5)	5 (16.7)	230 (34.4)	157 (41.1)	392 (36.3)
<i>Pneumonia</i>	17 (6.4)	15 (5.6)	2 (6.7)	62 (9.3)	52 (13.6)	116 (10.7)
<i>Septic shock</i>	11 (4.2)	8 (3.0)	0	19 (2.8)	6 (1.6)	25 (2.3)
<i>Sepsis</i>	10 (3.8)	14 (5.2)	0	32 (4.8)	26 (6.8)	58 (5.4)
<i>Klebsiella sepsis</i>	7 (2.6)	1 (0.4)	0	9 (1.3)	0	9 (0.8)
Blood and lymphatic system disorders	38 (14.3)	32 (11.9)	0	137 (20.5)	155 (40.6)	292 (27.0)
<i>Febrile neutropenia</i>	29 (10.9)	22 (8.2)	0	106 (15.8)	131 (34.3)	237 (21.9)
Gastrointestinal disorders	22 (8.3)	15 (5.6)	1 (3.3)	62 (9.3)	60 (15.7)	123 (11.4)
Respiratory, thoracic and mediastinal disorders	14 (5.3)	12 (4.5)	3 (10.0)	46 (6.9)	24 (6.3)	73 (6.8)
General disorders and administration site conditions	14 (5.3)	10 (3.7)	3 (10.0)	56 (8.4)	57 (14.9)	116 (10.7)
<i>Pyrexia</i>	8 (3.0)	5 (1.9)	0	26 (3.9)	20 (5.2)	46 (4.3)
Investigations	10 (3.8)	7 (2.6)	1 (3.3)	26 (3.9)	46 (12.0)	73 (6.8)
Cardiac disorders	7 (2.6)	10 (3.7)	3 (10.0)	25 (3.7)	25 (6.5)	53 (4.9)
Renal and urinary disorders	6 (2.3)	5 (1.9)	1 (3.3)	21 (3.1)	13 (3.4)	35 (3.2)

SOC PT	Study AC220-A-U302		All AML Pool			
	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)	Quizartinib <30 mg N = 30 n (%)	Quizartinib 30 to 60 mg N = 669 n (%)	Quizartinib >60 mg N = 382 n (%)	Total Quizartinib N = 1081 n (%)
Hepatobiliary disorders	6 (2.3)	4 (1.5)	0	10 (1.5)	7 (1.8)	17 (1.6)
Immune system disorders	5 (1.9)	2 (0.7)	0	16 (2.4)	2 (0.5)	18 (1.7)
Nervous system disorders	5 (1.9)	9 (3.4)	1 (3.3)	26 (3.9)	33 (8.6)	60 (5.6)
Neoplasms benign, malignant and unspecified	4 (1.5)	4 (1.5)	0	20 (3.0)	77 (20.2)	97 (9.0)

^a Percentages calculated based on subjects entering each phase as listed in Table 21: Subject Disposition in Study AC220-A-U302 (induction N = 265 and N = 268, consolidation N = 173 and N = 175, continuation N = 116 and N = 92, for quizartinib and placebo, respectively).

Notes: Percentage is calculated using the N in the column heading as the denominator. If a subject had more than 1 event per SOC (or PT) level, the subject was counted once at each level of summation. AEs were coded using MedDRA Version 24.0. Percent cutoff was applied at SOC and PT level.

Source: ISS Table 4.1.11

No subjects in the <30 mg and the 30 to 60 mg groups of the Healthy Volunteer Pool experienced TESAEs; 1 subject in the >60 mg group had a TESA of abscess limb, which was not considered to be related to study drug by the investigator.

Table 80 – Treatment-emergent SAEs by SOC and PT in ≥5 Subjects in Any Treatment Arm in Study AC220-007 – Cumulative Data - 21 Dec 2020 Database Lock (Safety Analysis Set)

SOC PT	Quizartinib Monotherapy (N=241) n (%)	Salvage Chemotherapy ^a (N=94) n (%)
Subjects with any serious TEAEs	169 (70.1)	37 (39.4)
Infections and infestations	103 (42.7)	21 (22.3)
<i>Pneumonia</i>	25 (10.4)	3 (3.2)
<i>Sepsis</i>	17 (7.1)	4 (4.3)
<i>Neutropenic sepsis</i>	7 (2.9)	2 (2.1)
<i>Cellulitis</i>	6 (2.5)	0 (0.0)

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SOC PT	Quizartinib Monotherapy (N=241) n (%)	Salvage Chemotherapy^a (N=94) n (%)
<i>Urinary tract infection</i>	6 (2.5)	0 (0.0)
<i>Septic shock</i>	5 (2.1)	1 (1.1)
<i>Upper respiratory tract infection</i>	5 (2.1)	0 (0.0)
Blood and lymphatic system disorders	67 (27.8)	9 (9.6)
<i>Febrile neutropenia</i>	51 (21.2)	9 (9.6)
<i>Anaemia</i>	6 (2.5)	0 (0.0)
Gastrointestinal disorders	19 (7.9)	1 (1.1)
<i>Nausea</i>	5 (2.1)	0 (0.0)
<i>Vomiting</i>	5 (2.1)	0 (0.0)
Nervous system disorders	16 (6.6)	2 (2.1)
<i>Haemorrhage intracranial</i>	5 (2.1)	2 (2.1)
<i>Syncope</i>	5 (2.1)	0 (0.0)
General disorders and administration site conditions	15 (6.2)	3 (3.2)
<i>Pyrexia</i>	8 (3.3)	2 (2.1)
Renal and urinary disorders	9 (3.7)	0 (0.0)
<i>Renal failure acute</i>	6 (2.5)	0 (0.0)
Investigations	9 (3.7)	0 (0.0)
<i>ECG QT prolonged</i>	5 (2.1)	0 (0.0)

^a Subjects who received salvage chemotherapy received a median (min, max) of 1 cycle (1, 2) for all 3 treatment regimens (LoDAC, MEC, and FLAG-IDA)

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 first dose of study drug, on or after first dose of study drug and up to 30 days after last dose of study drug. AEs collected after 30 days after the last dose of study drug were not considered TEAEs unless they were treatment related.

Subjects may have more than 1 event per SOC 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.

Source: AC220-007 CSR Addendum Table 14.3.1.16-II

The Applicant's Position:

In Study AC220-A-U302, more subjects in the quizartinib arm experienced TESAEs, compared to the placebo arm (143 subjects [54.0%] and 123 subjects [45.9%], respectively). Quizartinib is associated with development of myelosuppression in treated subjects, which is a risk factor for the development of infections. In the AC220-A-U302 study, infections (pneumonia, septic shock, and sepsis) and blood disorders (febrile neutropenia) were the most commonly reported TESAЕ in the study.

Overall, the incidence of serious infections and cytopenias was generally well balanced between the 2 treatment arms, consistent with the use of induction and consolidation chemotherapy in the study. The majority of these events occurred predominantly in the Induction and Consolidation Phases of the study; however serious cytopenias and infections (pneumonia) also occurred in the Continuation Phase, reflecting the known myelosuppressive effect of quizartinib. Serious infections are a known risk for subjects with AML receiving intensive cytarabine and anthracycline chemotherapy (Baluch, 2019; Afessa, 2006).

Generally, the types of TESAEs reported in the 30 to 60 mg group of the All AML Pool were consistent with those reported in Study AC220-A-U302.

SAEs reported from the pivotal study are consistent with those observed in the quizartinib AML development program, which included subjects with R/R disease, receiving quizartinib monotherapy.

The FDA's Assessment:

FDA performed an analysis of all-grade treatment-emergent SAEs utilizing FDA grouped terms occurring in $\geq 2\%$ of subjects on Study AC220-A-U302, which is presented in Table 81 below. The results agreed with the Applicant's analysis overall but differed in the rates of grouped events. It is notable that despite higher rate of overall TESAEs in the quizartinib arm (54% quizartinib versus 46% placebo) that there was not a strong signal in any one TESAЕ to account for this difference. FDA utilized criteria of occurrence in at least 5% of subjects and an event rate 2% greater on the quizartinib arm to determine TESAEs that were likely increased by quizartinib exposure beyond the high background rate of intensive chemotherapy treatment. With these criteria, only the TESAЕ of Febrile neutropenia was more common in quizartinib arm (11% quizartinib versus 8% placebo) than the placebo arm and included in labeling. FDA considered a lower event threshold rate of at least 2% of quizartinib-treated subjects and an event rate 2% greater on the quizartinib arm to determine TESAEs but even these criteria would not have yielded additional quizartinib associated TESAEs.

Table 81: FDA analysis of TESAEs in $\geq 2\%$ Subjects on Study AC220-A-U302

	QUIZARTINIB	PLACEBO
	N = 265	N = 268
	All grades	All grades
	n (%)	n (%)
Patients with TESAEs	143 (54)	123 (46)

Infections And Infestations		
Sepsis (GT)	38 (14)	35 (13)
Pneumonia (GT)	21 (8)	21 (8)
Fungal Infection (GT)	6 (2.3)	5 (1.9)
No SOC		
Dyspnea (GT)	6 (2.3)	4 (1.5)
Diarrhea (GT)	6 (2.3)	5 (1.9)
Herpesvirus Infection (GT)	6 (2.3)	4 (1.5)
Blood And Lymphatic System Disorders		
Febrile Neutropenia*	29 (11)	22 (8)
Neutropenia (GT)	8 (3.0)	5 (1.9)
Thrombocytopenia (GT)	3 (1.1)	9 (3.4)
General Disorders And Administration Site Conditions		
Pyrexia	8 (3.0)	5 (1.9)
Source: FDA analysis using adae.xpt, adsl.xpt		
GT: group term, see Appendix 19.5		
*indicates ≥2% greater on quizartinib arm		

FDA conducted the same analysis of TESAЕ in the ISS AML population as shown in Table 82. We again saw that the most reported TESAЕs were Febrile neutropenia, sepsis, and pneumonia.

Table 82: FDA analysis of TESAЕs in ≥ 2% Subjects on ISS AML population

		Quizartinib N=1081
SOC	PT	n (%)
Blood and lymphatic system disorders	Febrile neutropenia	208 (19.2%)
	Anemia (GT)	23 (2.1%)
Infections and infestations	Sepsis (GT)	126 (11.7%)
	Pneumonia (GT)	117 (10.8%)
	Urinary tract infection (GT)	25 (2.3%)
	Cellulitis (GT)	23 (2.1%)
Gastrointestinal disorders	Gastrointestinal hemorrhage (GT)	33 (3.1%)
General disorders and administration site conditions	Pyrexia	38 (3.5%)
Source: FDA analysis using adae.xpt, adsl.xpt		

GT: group term, see Appendix 19.5

Overall, the spectrum of TESAEs with quizartinib treatment were in line with expected complications from AML and complications from treatment. Within the context of the Study AC220-A-U302, only febrile neutropenia showed a rate increase >2% over the chemotherapy/placebo arm.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 83 – Summary of Study Drug Discontinuation in Study AC220-A-U302

Treatment Discontinuation Due to	Study AC220-A-U302	
	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)
AE	58 (21.9)	23 (8.6)
Death	0	1 (0.4)
Refractory disease	41 (15.5)	70 (26.1)
Relapse	44 (16.6)	65 (24.3)
Non-protocol-specified AML therapy	12 (4.5)	6 (2.2)
Pregnancy	0	1 (0.4)
Investigator decision	10 (3.8)	7 (2.6)
Failure to meet continuation criteria	5 (1.9)	12 (4.5)
Subject decision to stop study drug	25 (9.4)	23 (8.6)
Lost to follow-up	1 (0.4)	0
Other	16 (6.0)	11 (4.1)

Notes: Due to the differences in study design and subject populations in the All AML Pool with different criteria for study drug discontinuation the inclusion of the All AML Pool in this representation is not feasible or meaningful. Percentages are based on the number of subjects randomized unless otherwise noted. Source: AC220-A-U302 CSR Table 14.1.1.1.1

Table 84 – TEAEs Associated with Study Drug Discontinuation in ≥1% of Subjects in Either Arm of Study AC220-A-U302 or in the 30 to 60 mg Dose Group of the All AML Pool by SOC and PT, Overall Study Period (Safety Analysis Set)

SOC <i>PT</i>	Study AC220-A-U302		All AML Pool
	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)	Quizartinib 30 to 60 mg (N = 669) n (%)
Any TEAE	54 (20.4)	23 (8.6)	135 (20.2)
During Induction Phase ^a	26 (9.8)	11 (4.1)	NA
During Consolidation Phase ^a	10 (5.8)	5 (2.9)	NA
During Continuation Phase ^a	18 (15.5)	7 (7.6)	NA
Infections and infestations	19 (7.2)	11 (4.1)	41 (6.1)
<i>Septic shock</i>	9 (3.4)	1 (0.4)	10 (1.5)
<i>Pneumonia</i>	2 (0.8)	3 (1.1)	9 (1.3)
Blood and lymphatic system disorders	8 (3.0)	0	20 (3.0)
<i>Thrombocytopenia</i>	3 (1.1)	0	4 (0.6)
Respiratory, thoracic and mediastinal disorders	6 (2.3)	6 (2.2)	10 (1.5)
Gastrointestinal disorders	6 (2.3)	0	11 (1.6)
Investigations	5 (1.9)	1 (0.4)	12 (1.8)
Cardiac disorders	3 (1.1)	2 (0.7)	6 (0.9)
Metabolism and nutrition disorders	3 (1.1)	0	3 (0.4)
Nervous system disorders	4 (1.5)	3 (1.1)	11 (1.6)
General disorders	3 (1.1)	1 (0.4)	16 (2.4)
<i>Disease progression</i>	0	0	8 (1.2)

^a Percentages were calculated based on subjects entering each phase as listed in Table 21: Subject Disposition in Study AC220-A-U302 (induction N=265 and N=268, consolidation N=173 and N=175, continuation N=116 and N=92, for quizartinib and placebo, respectively).

Note: Study drug refers to quizartinib or placebo. If a subject had more than 1 event per SOC (or PT) level, the subject was counted once at each level of summation. Percent cutoff was applied at SOC and PT level.

AEs were coded using MedDRA Version 24.0.

Data cutoff date: 13 Aug 2021. Sources: ISS Table 4.1.13, AC220-A-U302 CSR Tables 10.16, 14.3.2.2.1 and 14.3.1.1.

The Applicant's Position:

In Study AC220-A-U302 overall, infections (septic shock, pneumonia and sepsis) and cytopenias (thrombocytopenia, neutropenia, and febrile neutropenia) were the most frequent events associated with study drug discontinuation. The percentage of subjects with TEAEs associated with study drug discontinuation was higher with quizartinib than with placebo; this difference was observed in all phases with the highest incidence and difference

between quizartinib and placebo seen in the Continuation Phase. The higher incidence of TEAE associated with discontinuation in the Continuation Phase is likely due to the longer duration of this phase, with accrual of events. Infections associated with quizartinib discontinuation tended to occur in the early phases of the study, whereas discontinuation due to TEAEs of cytopenias was more frequent in the Continuation Phase. In the Continuation Phase, cytopenias (thrombocytopenia, neutropenia, and anemia) and gastrointestinal disorders (nausea, diarrhea, and vomiting) were the most frequent events associated with study drug discontinuation and were reported by subjects only in the quizartinib arm (AC220-A-U302 CSR Table 14.3.2.2.1).

Management of QT interval prolongation with quizartinib includes quizartinib dose modification and interruption. However, only 2 subjects (0.8%) in the quizartinib arm discontinued due to TEAEs of ECG QT prolonged.

The incidence and types of TEAEs associated with discontinuation in the 30 to 60 mg group of the All AML Pool were consistent with those reported in Study AC220-A-U302.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of study drug discontinuation events. FDA assessed TEAEs leading to study drug discontinuation in Study AC220-A-U304 with FDA group terms as shown in Table 85 below. Our analysis agreed with the Applicant's in that sepsis was the most common TEAE causing treatment discontinuation on Study AC220-A-U302. Sepsis and pneumonia were the most common TEAEs in the ISS AML Quizartinib pool causing study drug discontinuation. Per the tabulations below, sepsis as a cause of discontinuation was included in quizartinib labeling.

Table 85: FDA analysis of Study AC220-A-U302 TEAEs leading to study drug discontinuation in ≥ 2% Subjects

	QUIZARTINIB N = 265		PLACEBO N = 268	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
TEAEs leading to discontinuation	54 (20)	27 (10)	23 (9)	19 (7)
Infections And Infestations				
Sepsis (GT)*	14 (5)	2 (0.8)	3 (1.1)	2 (0.7)
Source: FDA analysis using adae.xpt, adsl.xpt GT: group term, see Appendix 19.5 *indicates ≥2% greater on quizartinib arm				

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 86 – Summary of TEAE with Study Drug Interruption or Dose Reduction in (≥2% of Subjects) in the Quizartinib Arm of Study AC220-A-U302 or in the 30 to 60 mg Dose Group of the All AML Pool by Preferred Term (Safety Analysis Set)

PT	Study AC220-A-U302		All AML Pool
	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)	Quizartinib 30 to 60 mg (N = 669) n (%)
Any TEAE associated with study drug interruption	90 (34.0)	54 (20.1)	213 (31.8)
During Induction Phase ^a	24 (9.1)	30 (11.2)	NA
During Consolidation Phase ^a	14 (8.1)	13 (7.4)	NA
During Continuation Phase ^a	65 (56.0)	22 (23.9)	NA
<i>Neutropenia</i>	19 (7.2)	2 (0.7)	29 (4.3)
<i>Neutrophil count decreased</i>	9 (3.4)	0	10 (1.5)
<i>ECG QT prolonged</i>	7 (2.6)	3 (1.1)	21 (3.1)
<i>Thrombocytopenia</i>	6 (2.3)	1 (0.4)	11 (1.6)
<i>Platelet count decreased</i>	6 (2.3)	0	8 (1.2)
<i>Pneumonia</i>	5 (1.9)	1 (0.4)	17 (2.5)
<i>Febrile neutropenia</i>	4 (1.5)	2 (0.7)	21 (3.1)
Any TEAE associated with study drug dose reduction	50 (18.9)	17 (6.3)	^{-b}
During Induction Phase ^a	7 (2.6)	3 (1.1)	NA
During Consolidation Phase ^a	4 (2.3)	0	NA
During Continuation Phase ^a	42 (36.2)	14 (15.2)	NA
<i>Neutropenia</i>	16 (6.0)	3 (1.1)	^{-b}
<i>ECG QT prolonged</i>	10 (3.8)	1 (0.4)	^{-b}
<i>Neutrophil count decreased</i>	9 (3.4)	0	^{-b}
<i>Thrombocytopenia</i>	8 (3.0)	2 (0.7)	^{-b}

^a Percentages calculated based on subjects entering each phase as listed in Table 21: Subject Disposition in Study AC220-A-U302 (induction N=265 and N=268, consolidation N=173 and N=175, continuation N=116 and N=92, for quizartinib and placebo, respectively).

^b Integration of data for All AML Pool was not performed, since dose reductions due to a TEAE were not captured across all clinical studies included in the All AML Pool in a manner consistent enough to allow for pooled analysis.

Note: If a subject had more than 1 event per PT level, the subject was counted once at each level of summation. AEs were coded using MedDRA Version 24.0.

Data cutoff date: 13 Aug 2021. Sources: ISS Table 4.1.14, AC220-A-U302 CSR Tables 14.3.2.2.2 and 14.3.2.2.3

The Applicant's Position:

In Study AC220-A-U302, dose interruption and dose reduction due to TEAEs occurred more frequently in quizartinib-treated subjects. Overall, infections (pneumonia, septic shock, and sepsis) and cytopenias (neutropenia, neutrophil count decreased, thrombocytopenia, and platelet count decreased) were the most frequent events associated with study drug dose reduction and dose interruption. Infections associated with quizartinib dose reduction and interruption tended to occur in the early phases of the study, whereas discontinuation, dose reduction, or dose interruption due to TEAEs of cytopenias was more frequent in the Continuation Phase.

Management of QT interval prolongation with quizartinib includes quizartinib dose modification and interruption. Therefore, TEAEs of ECG QT interval prolonged associated with quizartinib interruption or dose reduction were reported commonly in the study (7 subjects [2.6%] and 10 subjects [3.8%], respectively).

The incidence and types of TEAEs associated with dose interruption in the 30 to 60 mg group of the All AML Pool were consistent with those reported in Study AC220-A-U302. Integration of data for the All AML Pool was not performed for dose reduction, as these data were not captured consistently across all clinical studies included in the All AML Pool.

The FDA's Assessment:

FDA conducted an analysis of TEAEs leading to dose interruptions using FDA group terms from Study AC220-A-U302 as shown in Table 87 below. This shows the results for TEAEs with a frequency of 2% or greater. Per FDA group terms, the most frequent TEAE leading to dose interruption was neutropenia in 11% of quizartinib treated patients. For labeling, we assess quizartinib related interruptions of clinical significance as those occurring in $\geq 2\%$ of subjects and $\geq 2\%$ greater on the quizartinib arm than the placebo. Of those listed in the table only neutropenia, myelosuppression, and thrombocytopenia were included in labeling.

Table 87: FDA analysis of Study AC220-A-U304 TEAEs leading to study drug interruptions in $\geq 2\%$ Subjects

TEAEs leading to Interruptions	QUIZARTINIB N = 265		PLACEBO N = 268	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3- 4 n (%)
Patients with TEAEs	90 (34)	71 (27)	54 (20)	44 (16)
Infections And Infestations				
Sepsis (GT)	8 (3.0)	8 (3.0)	9 (3.4)	9 (3.4)
Pneumonia (GT)	5 (1.9)	5 (1.9)	2 (0.7)	2 (0.7)
No SOC				

Diarrhea (GT)	8 (3.0)	3 (1.1)	8 (3.0)	6 (2.2)
Hypertransaminasemia (GT)	8 (3.0)	3 (1.1)	4 (1.5)	4 (1.5)
Myelosuppression (GT)*	8 (3.0)	6 (2.3)	0 (0.0)	0 (0.0)
Investigations				
Electrocardiogram Qt Prolonged	7 (2.6)	1 (0.4)	3 (1.1)	2 (0.7)
Skin And Subcutaneous Tissue Disorders				
Rash (GT)	5 (1.9)	4 (1.5)	3 (1.1)	2 (0.7)
Blood And Lymphatic System Disorders				
Neutropenia (GT)*	28 (11)	26 (10)	2 (0.7)	2 (0.7)
Thrombocytopenia (GT)*	12 (4.5)	5 (1.9)	1 (0.4)	0 (0.0)
Source: FDA analysis using adae.xpt, adsl.xpt GT: group term, see Appendix 19.5 *indicates ≥2% greater on quizartinib arm				

FDA also investigated TEAEs that led to dose reductions using FDA group terms. Table 88 shows that most dose reductions were due to neutropenia, thrombocytopenia, or QTc prolonged. These TEAEs were included in labeling as leading to dose reductions.

Table 88: FDA analysis of Study AC220-A-U304 TEAEs leading to study drug dose reductions in ≥ 2% Subjects

TEAEs leading to dose reductions	QUIZARTINIB N = 265		PLACEBO N = 268	
	Grades 1-4 n (%)	Grades 3-4 n (%)	Grades 1-4 n (%)	Grades 3-4 n (%)
Patients with TEAEs	50 (19)	33 (12)	17 (6)	10 (3.7)
Blood And Lymphatic System Disorders				
Neutropenia (GT)*	24 (9)	19 (7)	3 (1.1)	3 (1.1)
Thrombocytopenia (GT)*	12 (4.5)	7 (2.6)	2 (0.7)	2 (0.7)
Investigations				
Electrocardiogram Qt Prolonged*	10 (3.8)	0 (0.0)	1 (0.4)	0 (0.0)
Source: FDA analysis using adae.xpt, adsl.xpt GT: group term, see Appendix 19.5 *indicates ≥2% greater on quizartinib arm				

Significant Adverse Events

Data:

The proportions of subjects with Grade 3/4 events were similar between the treatment arms. The most frequently reported Grade 3/4 TEAEs in the quizartinib arm included cytopenias (febrile neutropenia, neutropenia, neutrophil count decreased, and thrombocytopenia), hypokalemia, and infections (pneumonia), of which the events of neutropenia and neutrophil count decreased occurred at a ≥ 5 percentage points higher incidence in the quizartinib arm than in the placebo arm (eCTD 2.7.4 Table 2.1.2.3).

Generally, the pattern and incidence of Grade 3/4 TEAEs in the 30 to 60 mg group of the All AML Pool were consistent with those in the quizartinib arm of Study AC220-A-U302. Blood cytopenias were the most frequently reported Grade 3/4 events in the All AML Pool, with no observed dose response trend. Infections (pneumonia and sepsis) were the second most frequently reported types of severe TEAE; no dose-dependent trend was noted for these TEAEs (eCTD 2.7.4 Table 2.1.2.3).

The Applicant's Position:

Blood cytopenias (neutropenia, thrombocytopenia, and anemia) and infections were the most common severe (Grade 3/4) TEAEs. Severe cytopenias are expected to occur in subjects receiving induction and consolidation chemotherapy, and management of these is part of routine clinical care for subjects with newly diagnosed AML. Overall, the majority of TEAEs of blood cytopenias were managed with study drug interruptions or dose reductions and few subjects discontinued quizartinib due to these events. AEs reported are described in other sections of this document.

The FDA's Assessment:

FDA agrees with the Applicants assessment that blood cytopenias and infections were the most common severe TEAEs. FDA conducted analysis of grade 1-4 and grade 3-4 TEAEs with FDA group terms in Table 94 below. However, we note that although severe cytopenias are expected from intensive chemotherapy, the rates of cytopenias reported as severe TEAEs were higher on the quizartinib arm of this blinded study. This indicates that quizartinib worsened cytopenias beyond those induced by intensive chemotherapy alone.

Treatment-emergent Adverse Events and Adverse Reactions

Data:

Table 89 – Overview of Treatment-emergent Adverse Events in the Study AC220-A-U302 or in the 30 to 60 mg Dose Group of the All AML Pool (Safety Analysis Set)

Category	Study AC220-A-U302		All AML Pool
	Quizartinib N=265 n (%)	Placebo N=268 n (%)	Quizartinib 30 to 60 mg N=669 n (%)
All Grade TEAE	264 (99.6)	265 (98.9)	664 (99.3)
Grade 3 to 5	244 (92.1)	240 (89.6)	598 (89.4)
Grade 3-4	214 (80.8)	214 (79.9)	495 (74.0)
Grade 3	126 (47.5)	127 (47.4)	247 (36.9)
Grade 4	88 (33.2)	87 (32.5)	248 (37.1)
Grade 5 (deaths due to an AE)	30 (11.3)	26 (9.7)	104 (15.5)
Discontinuation due to an AE	54 (20.4)	23 (8.6)	135 (20.2)
Dose interruption due to an AE	90 (34.0)	54 (20.1)	213 (31.8)
Dose reduction due to an AE	50 (18.9)	17 (6.3)	- ^a

^a Integration of data for All AML Pool was not performed, since dose reductions due to a TEAE were not captured across all clinical studies included in the All AML Pool in a manner consistent enough to allow for pooled analysis.

Notes: Percentage is calculated using number of subjects in the column heading as denominator. AEs were coded using MedDRA Version 24.0.

Sources: ISS Table 4.1.1, AC220-A-U302 CSR Table 14.3.2.2.3

Table 90 – All Adverse Drug Reactions in Study AC220-A-U302

SOC <i>PT or Grouped Term</i>	Quizartinib + Standard Chemotherapy (N = 265)		Placebo + Standard Chemotherapy (N = 268)	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Gastrointestinal disorders				
<i>Diarrhoea^a</i>	98 (37.0)	10 (3.8)	94 (35.1)	10 (3.7)
<i>Nausea</i>	90 (34.0)	4 (1.5)	84 (31.3)	5 (1.9)
<i>Abdominal pain^b</i>	78 (29.4)	6 (2.3)	59 (22.0)	3 (1.1)
<i>Vomiting</i>	65 (24.5)	0	53 (19.8)	4 (1.5)
<i>Dyspepsia</i>	30 (11.3)	1 (0.4)	23 (8.6)	2 (0.7)
Nervous system disorders				
<i>Headache^c</i>	73 (27.5)	0	53 (19.8)	2 (0.7)

SOC <i>PT or Grouped Term</i>	Quizartinib + Standard Chemotherapy (N = 265)		Placebo + Standard Chemotherapy (N = 268)	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
General disorders and administration site conditions				
<i>Oedema^d</i>	50 (18.9)	1 (0.4)	51 (19.0)	4 (1.5)
Infections and infestations				
<i>Upper respiratory tract infections^e</i>	48 (18.1)	5 (1.9)	27 (10.1)	6 (2.2)
<i>Fungal infections^f</i>	40 (15.1)	15 (5.7)	26 (9.7)	8 (3.0)
<i>Herpes infections^g</i>	37 (14.0)	8 (3.0)	22 (8.2)	4 (1.5)
<i>Bacteraemia^h</i>	30 (11.3)	19 (7.2)	11 (4.1)	10 (3.7)
Metabolism and nutrition disorders				
<i>Decreased appetite</i>	46 (17.4)	13 (4.9)	36 (13.4)	5 (1.9)
Respiratory, thoracic and mediastinal disorders				
<i>Epistaxis</i>	40 (15.1)	3 (1.1)	29 (10.8)	1 (0.4)
Investigations				
<i>ECG QT prolongedⁱ</i>	37 (14.0)	8 (3.0)	11 (4.1)	3 (1.1)
Blood and lymphatic system disorders				
<i>Pancytopenia</i>	7 (2.6)	6 (2.3)	1 (0.4)	1 (0.4)
Cardiac disorders				
<i>Cardiac arrest^j</i>	2 (0.8)	0	1 (0.4)	0
<i>Ventricular fibrillation^j</i>	1 (0.4)	0	1 (0.4)	0

^a Diarrhoea includes diarrhoea and diarrhoea haemorrhagic.

^b Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, and gastrointestinal pain.

^c Headache includes headache, tension headache, and migraine.

^d Oedema includes oedema, oedema peripheral, fluid retention, fluid overload, peripheral swelling, generalised oedema, face oedema, swelling face, and localised oedema.

^e Upper respiratory tract infections include upper respiratory tract infection, nasopharyngitis, rhinitis, laryngopharyngitis, pharyngitis bacterial, viral pharyngitis, pharyngotonsillitis, sinusitis, acute sinusitis, and tonsillitis.

^f Fungal infections include bronchopulmonary aspergillosis, Aspergillus infection, aspergillosis oral, fungaemia, oral candidiasis, vulvovaginal candidiasis, Candida infection, oropharyngeal candidiasis, hepatosplenic candidiasis, gastrointestinal candidiasis, systemic candida, fungal infection, lower respiratory tract infection fungal, oral fungal infection, fungal skin infection, mucormycosis, systemic mycosis, onychomycosis, and hepatic infection fungal.

^g Herpes infections include oral herpes, herpes virus infection, herpes simplex, human herpesvirus 6 infection, genital herpes, herpes dermatitis, and herpes zoster.

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^h Bacteraemia includes bacteraemia, Klebsiella bacteraemia, Staphylococcal bacteraemia, Enterococcal bacteraemia, Streptococcal bacteraemia, Device-related bacteraemia, Escherichia bacteraemia, Corynebacterium bacteraemia, and Pseudomonas bacteraemia.

ⁱ ECG QT prolonged includes ECG QT prolonged, and ECG QT interval abnormal.

^j One subject experienced 2 events (ventricular fibrillation and cardiac arrest).

Note: Percentages are based on TEAE incidence. Fatal TEAEs included fungal infections (2 subjects [0.8%]) and cardiac arrest (1 subject [0.4%]).

Sources: eCTD M5.3.5.3 ADR Justification Summary Table 6.1

Table 91 – All New or Worsening Laboratory Abnormalities (Adverse Drug Reactions) in Subjects Receiving Quizartinib in Study AC220-A-U302 (Safety Analysis Set)

Laboratory Abnormality ^a	Quizartinib + Standard Chemotherapy ^b (N = 265)		Placebo + Standard Chemotherapy ^b (N = 268)	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
ALT increased	58.9	12.1	60.1	10.4
Platelet count decreased	40.0	40.0	44.0	44.0
Hemoglobin decreased	37.4	35.5	45.5	42.5
Neutrophil count decreased	21.9	21.5	21.6	20.1

^a Terms based on laboratory data

^b Standard chemotherapy: cytarabine (cytosine arabinoside) and anthracycline (daunorubicin or idarubicin)

Source: ADR Justification Summary Table 6.2, eCTD 5.3.5.3.

Safety Profile During Continuation Monotherapy

Table 92 – Treatment-emergent Adverse Events by Preferred Term Occurring in ≥10% Total Subjects and ≥2% More Frequent on Quizartinib Compared with Placebo in the Continuation Phase of Study AC220-A-U302 (Safety Analysis Set)

PT	Quizartinib N=116 n (%)	Placebo N=92 n (%)
Neutropenia	42 (36.2)	6 (6.5)
Nausea	27 (23.3)	8 (8.7)
Diarrhoea	24 (20.7)	10 (10.9)
Upper respiratory tract infection	20 (17.2)	9 (9.8)

<i>PT</i>	Quizartinib N=116 n (%)	Placebo N=92 n (%)
<i>Thrombocytopenia</i>	20 (17.2)	8 (8.7)
<i>Cough</i>	19 (16.4)	11 (12.0)
<i>Anaemia</i>	19 (16.4)	4 (4.3)
<i>Vomiting</i>	17 (14.7)	7 (7.6)
<i>Neutrophil count decreased</i>	17 (14.7)	4 (4.3)
<i>ALT increased</i>	15 (12.9)	7 (7.6)
<i>Headache</i>	14 (12.1)	8 (8.7)
<i>Oedema peripheral</i>	14 (12.1)	8 (8.7)

Source: eCTD M5.3.5.1 AC220-A-U302 CSR Supplemental Table 14.3.1.3.1.1

TEAEs identified as adverse drug reactions (ADRs) for the Continuation Phase of Study AC220-A-U302 are described below.

The most common adverse reactions in the quizartinib arm during continuation monotherapy were neutrophil count decreased (88%), platelet count decreased (72%), hemoglobin decreased (55%), ALT increased (49%), upper respiratory tract infections (28%), nausea (23%) and diarrhea (21%). No fatal adverse reactions occurred during continuation. The most common Grade 3 or 4 adverse reactions reported in subjects with quizartinib were neutrophil count decreased (72%), platelet count decreased (24%), and hemoglobin decreased (18%).

Serious adverse reactions in the quizartinib arm during Continuation monotherapy were herpes infections (3.4%), neutropenia (2.6%), upper respiratory tract infections (1.7%), and vomiting (1.7%).

The most common adverse reactions associated with dose interruption of quizartinib during Continuation monotherapy were neutropenia (24%), thrombocytopenia (10%), and ECG QT prolonged (4.3%). The most common adverse reactions associated with dose reduction of quizartinib were neutropenia (21%), thrombocytopenia (10%), and ECG QT prolonged (5%). The most common adverse reactions associated with permanent discontinuation of quizartinib during Continuation monotherapy were thrombocytopenia (2.6%), nausea, neutropenia and decreased appetite (1.7% each).

Quizartinib monotherapy for R/R AML-Adverse Drug Reactions

**Table 93 – Adverse Drug Reactions Observed in Study AC220-007 – Cutoff Date of 22 Feb 2018
(Safety Analysis Set)**

ADR	Quizartinib N = 241 n (%)		Salvage Chemotherapy ^a N = 94 n (%)	
	All Grades	Grades ≥3	All Grades	Grades ≥3
Infections and infestations				
<u>Very common</u>				
Infection ^{b, c}	167 (69.3)	108 (44.8)	61 (64.9)	32 (34.0)
Blood and lymphatic system disorders				
<u>Very common</u>				
Febrile neutropenia	81 (33.6)	74 (30.7)	26 (27.7)	20 (21.3)
<u>Common</u>				
Pancytopenia	9 (3.7)	9 (3.7)	3 (3.2)	1 (1.1)
Metabolism and nutrition disorders				
<u>Very common</u>				
Decreased appetite	49 (20.3)	6 (2.5)	10 (10.6)	1 (1.1)
Nervous system disorders				
<u>Common</u>				
Dysgeusia ^d	23 (9.5)	0	1 (1.1)	0
Vascular disorders				
<u>Very common</u>				
Bleeding ^{b, e}	119 (49.4)	24 (10.0)	36 (38.3)	8 (8.5)
Gastrointestinal disorders				
<u>Very common</u>				
Vomiting	80 (33.2)	8 (3.3)	20 (21.3)	1 (1.1)
Nausea	116 (48.1)	6 (2.5)	39 (41.5)	1 (1.1)
Abdominal pain ^f	54 (22.4)	5 (2.1)	17 (18.1)	1 (1.1)
Stomatitis ^g	41 (17.0)	5 (2.1)	19 (20.2)	4 (4.3)
Diarrhoea	70 (29.0)	4 (1.7)	34 (36.2)	3 (3.2)
<u>Common</u>				
Dyspepsia	20 (8.3)	0	6 (6.4)	0
Skin and subcutaneous tissue disorder				
<u>Very common</u>				

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ADR	Quizartinib N = 241 n (%)		Salvage Chemotherapy ^a N = 94 n (%)	
	All Grades	Grades ≥3	All Grades	Grades ≥3
Rash ^h	55 (22.8)	6 (2.5)	17 (18.1)	0
<u>Common</u>				
Acute febrile neutrophilic dermatosis	8 (3.3)	4 (1.7)	1 (1.1)	1 (1.1)
General disorders and administration site conditions				
<u>Very common</u>				
Asthenic conditions ⁱ	95 (39.4)	19 (7.9)	27 (28.7)	1 (1.1)
Pyrexia	92 (38.2)	6 (2.5)	42 (44.7)	4 (4.3)
Oedema peripheral ^j	52 (21.6)	3 (1.2)	22 (23.4)	0
Investigations				
<u>Very common</u>				
WBC count decreased ^k	218 (90.5)	200 (83.0)	75 (79.8)	70 (74.5)
Lymphocyte count decreased ^k	193 (80.1)	145 (60.2)	56 (59.6)	46 (48.9)
Neutrophil count decreased ^k	149 (61.8)	141 (58.5)	45 (47.9)	43 (45.7)
Platelet count decreased ^k	148 (61.4)	136 (56.4)	47 (50.0)	47 (50.0)
Hemoglobin decreased ^k	163 (67.6)	128 (53.1)	52 (55.3)	32 (34.0)
Potassium decreased ^k	83 (34.4)	26 (10.8)	26 (27.7)	11 (11.7)
Blood bilirubin increased ^k	66 (27.4)	10 (4.1)	19 (20.2)	2 (2.1)
ECG QT prolonged	64 (26.6)	10 (4.1)	2 (2.1)	0
ALT increased ^k	99 (41.1)	9 (3.7)	20 (21.3)	1 (1.1)
AST increased ^k	84 (34.9)	4 (1.7)	12 (12.8)	1 (1.1)
ALP increased ^k	108 (44.8)	3 (1.2)	13 (13.8)	1 (1.1)
Magnesium decreased ^k	33 (13.7)	2 (0.8)	3 (3.2)	0
Weight decreased	27 (11.2)	1 (0.4)	5 (5.3)	0

^a Salvage chemotherapy: LoDAC, MEC, or FLAG-IDA.

^b Including fatal outcomes.

^c Infections include the following reported PTs: sepsis/septic shock, pneumonia, urinary tract infection, upper respiratory tract infection, cellulitis, and other infections.

^d Dysgeusia includes the following reported PTs: dysgeusia and ageusia.

^e Bleeding includes the following reported PTs: epistaxis, petechiae, intracranial haemorrhage, and other bleeding.

^f Abdominal pain includes the following reported PTs: abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.

^g Stomatitis includes the following reported PTs: stomatitis and aphthous stomatitis.

^h Rash includes the following reported PTs: rash, rash maculo-papular, rash generalized, rash erythematous, rash papular, rash pruritic, rash macular, and toxic skin eruption.

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ⁱ Asthenic conditions include the following reported PTs: fatigue, asthenia, and malaise.

^j Oedema peripheral includes the following reported PTs: oedema peripheral and gravitational oedema.

^k Frequency based on laboratory values.

Note: The following terminologies have been used in order to classify the occurrence of ADRs: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10000$ to $< 1/1000$); and very rare ($< 1/10000$).

Note: AEs were coded by using MedDRA Version 16.1.

The Applicant's Position:

The most common ADRs were ALT increased, cytopenias, and gastrointestinal disorders. Adverse reactions with a fatal outcome were fungal infections and cardiac arrest. Serious adverse reactions in $\geq 2\%$ of subjects were neutropenia, fungal infections and herpes infections. Severe (Grade 3/ 4) ADRs were cytopenias (neutrophil count decreased, platelet count decreased, and hemoglobin decreased). Overall, ADRs for quizartinib were manageable by dose modification and routine clinical practice.

The profile of quizartinib ADR for the proposed indications are consistent with the overall safety profile of quizartinib determined in the development program for R/R AML.

The FDA's Assessment:

FDA tabulations of TEAEs agreed with the Applicant's in terms of rate of any TEAE, grade 3 or 4 TEAEs, grade 5 TEAEs, and TEAEs leading to either dose discontinuations, dose reductions, or dose interruptions. Table 94 shows FDA tabulation of the most common grade 1-4 and grade 3-4 TEAEs that occurred in at least 10% of subjects on Study AC220-A-U302.

Table 94: FDA analysis of Study AC220-A-U302 common ($\geq 10\%$) TEAEs

	QUIZARTINIB N = 265		PLACEBO N = 268	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	n (%)	n (%)	n (%)	n (%)
Patients with TEAEs	263 (99)	243 (92)	265 (99)	240 (90)
Gastrointestinal Disorders				
Diarrhea (GT)*	112 (42)	22 (8)	105 (39)	22 (8)
Mucositis (GT)*	101 (38)	14 (5)	88 (33)	11 (4.1)
Nausea*	90 (34)	4 (1.5)	84 (31)	5 (1.9)
Abdominal Pain (GT)*	80 (30)	6 (2.3)	60 (22)	3 (1.1)
Vomiting*	65 (25)	0 (0.0)	53 (20)	4 (1.5)
Constipation	56 (21)	1 (0.4)	69 (26)	0 (0.0)
Dyspepsia*	30 (11)	1 (0.4)	23 (9)	2 (0.7)
Infections And Infestations				

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Sepsis (GT)*	75 (28)	49 (18.5)	69 (26)	54 (20)
Upper Respiratory Tract Infection (GT)*	56 (21)	7 (2.6)	32 (12)	8 (3.0)
Pneumonia (GT)	51 (19)	40 (15)	50 (19)	43 (16)
Fungal Infection (GT)*	42 (16)	17 (6)	27 (10)	8 (3)
Herpesvirus Infection (GT)*	36 (14)	8 (3)	22 (8)	5 (1.9)
Skin And Subcutaneous Tissue Disorders				
Rash (GT)	98 (37)	13 (4.9)	99 (37)	14 (5)
Pruritus	35 (13)	2 (0.8)	40 (15)	0 (0.0)
General Disorders And Administration Site Conditions				
Pyrexia	112 (42)	12 (4.5)	109 (41)	13 (4.9)
Edema (GT)	57 (22)	1 (0.4)	55 (21)	4 (1.5)
Fatigue (GT)	41 (15)	3 (1.1)	43 (16)	2 (0.7)
Hepatobiliary disorders				
Hypertransaminasemia (GT)*	51 (19)	18 (7)	37 (14)	17 (6)
Musculoskeletal And Connective Tissue Disorders				
Musculoskeletal Pain (GT)	71 (27)	5 (1.9)	85 (32)	5 (1.9)
Arthralgia	29 (11)	1 (0.4)	35 (13)	2 (0.7)
Blood And Lymphatic System Disorders				
Febrile Neutropenia*	117 (44)	115 (43)	113 (42)	110 (41)
Neutropenia (GT)*	77 (29)	69 (26)	38 (14)	32 (12)
Thrombocytopenia (GT)*	47 (18)	34 (13)	36 (13)	31 (12)
Anemia (GT)*	29 (11)	15 (6)	19 (7)	14 (5)
Metabolism And Nutrition Disorders				
Hypokalaemia	93 (35)	50 (19)	96 (36)	44 (16)
Decreased Appetite*	46 (17)	13 (4.9)	36 (13)	5 (1.9)
Hypomagnesaemia	30 (11)	1 (0.4)	30 (11)	1 (0.4)
Hypophosphataemia	27 (10)	18 (7)	24 (9)	16 (6)
Hypocalcaemia	26 (10)	2 (0.8)	29 (11)	8 (3.0)
Immune System Disorders				
Hypersensitivity (GT)	29 (11)	3 (1.1)	27 (10)	4 (1.5)
Investigations				
Electrocardiogram Qt Prolonged*	36 (14)	8 (3.0)	11 (4.1)	3 (1.1)
Respiratory, Thoracic And Mediastinal Disorders				
Cough (GT)	52 (20)	1 (0.4)	50 (19)	0 (0.0)
Epistaxis*	40 (15)	3 (1.1)	29 (11)	1 (0.4)
Dyspnea (GT)	22 (8)	6 (2.3)	28 (10)	7 (2.6)
Nervous System Disorders				

Headache*	73 (28)	0 (0.0)	53 (20)	2 (0.7)
Vascular Disorders				
Hypertension	29 (11)	13 (4.9)	33 (12)	18 (7)
Injury, Poisoning And Procedural Complications				
Transfusion Reaction (GT)	17 (6)	1 (0.4)	34 (13)	2 (0.7)
Psychiatric Disorders				
Insomnia*	37 (14)	0 (0.0)	30 (11)	0 (0.0)
Eye Disorders				
Eye Irritation (GT)*	28 (11)	0 (0.0)	19 (7)	0 (0.0)
Cardiac Disorders				
Arrhythmia (GT)	28 (11)	6 (2.3)	34 (13)	10 (3.7)
Source: FDA analysis using adae.xpt, adsl.xpt				
GT: group term, see Appendix 19.5				
*indicates ≥2% greater on quizartinib arm				

Due to the high rate of TEAEs induced by the intensive chemotherapy backbone, FDA identified those TEAEs that occurred in at least 10% of subjects and ≥2% of patients on the quizartinib arm than placebo as quizartinib-related adverse events. These are marked in Table 94 above with (*) following the preferred term and were included in labeling. As the Applicant's analysis similarly showed, the most common TEAEs were GI toxicity, infectious complications, and cytopenias. It is notable that although quizartinib increased the occurrence rate of some of the above TEAEs, many of the TEAEs either occurred at the same as or more frequently on the placebo arm. Moreover, other than QTc prolonged and neutropenia, quizartinib did not induce a significant shift to higher toxicity (higher rates of grade 3 or 4) for the common TEAEs listed above.

FDA looked at the rate of TEAEs that occurred in the monotherapy maintenance phase of protocol treatment to understand both the potential risk of treatment during this longest phase of treatment and the toxicity incurred from quizartinib in patients without the high background rate of AEs caused by active disease or intensive chemotherapy. Table 95 shows that the most common TEAE in quizartinib-treated patients during continuation therapy was neutropenia (48% grade 1-4 and 43% with grade 3-4). Other common TEAEs that were at least 2% more common with quizartinib during this phase included GI toxicity (diarrhea, nausea, abdominal pain, vomiting, decreased appetite), thrombocytopenia, upper respiratory infections, herpesvirus infections (shingles and HSV), mucositis, hypertransaminasemia, QTc prolonged, musculoskeletal pain, cough, and headache. It is interesting to note that despite the high rate of neutropenia, subjects were not at high risk of neutropenic fever or sepsis. Instead, there was an increase in milder infections such as reactivation of latent herpes viruses and a higher rate of reported upper respiratory infections.

During the maintenance phase, analysis of TEAE by history of transplant showed that rate of individual TEAEs in quizartinib arm were an average of 8% higher if the subject had received a transplant compared to those that did not. For example, the rate of neutropenia during the maintenance phase was 51% for quizartinib-treated patients that underwent transplant but only 43% for those that had not been transplanted (Table 96). All of the listed TEAEs followed this trend except for QT prolongation, whose TEAE rate was not increased by history of transplant (10% quizartinib-HSCT vs 13% quizartinib-nonHSCT). The majority of reported TEAEs during this phase occurred during the first year of maintenance treatment.

Table 95: FDA analysis of Study AC220-A-U302 common (≥10%) TEAEs during the continuation phase

	QUIZARTINIB N = 116		PLACEBO N = 92	
	Grades 1-4 n (%)	Grades 3-4 n (%)	Grades 1-4 n (%)	Grades 3-4 n (%)
Patients with TEAEs	109 (94)	91 (78)	84 (91)	52 (57)
Infections And Infestations				
Upper Respiratory Tract Infection (GT)*	35 (30)	1 (0.9)	14 (15)	0 (0.0)
No SOC				
Diarrhea (GT) *	26 (22)	4 (3.4)	12 (13)	2 (2.2)
Hypertransaminasemia (GT) *	23 (20)	7 (6)	9 (10)	3 (3.3)
Mucositis (GT) *	20 (17)	1 (0.9)	7 (8)	0 (0.0)
Edema (GT) *	19 (16)	1 (0.9)	11 (12)	2 (2.2)
Anemia (GT) *	19 (16)	6 (5)	4 (4.3)	2 (2.2)
Herpesvirus Infection (GT) *	16 (14)	4 (3.4)	8 (9)	2 (2.2)
Dyspnea (GT)	7 (6)	0 (0.0)	10 (11)	2 (2.2)
Gastrointestinal Disorders				
Nausea*	27 (23)	2 (1.7)	8 (9)	1 (1.1)
Abdominal Pain (GT) *	17 (15)	1 (0.9)	6 (7)	0 (0.0)
Vomiting*	17 (15)	0 (0.0)	7 (8)	0 (0.0)
Blood And Lymphatic System Disorders				
Neutropenia (GT) *	56 (48)	49 (42)	10 (11)	4 (4.3)
Thrombocytopenia (GT) *	30 (26)	15 (13)	11 (12)	5 (5)
Investigations				
Electrocardiogram Qt Prolonged*	13 (11)	0 (0.0)	2 (2.2)	0 (0.0)
Skin And Subcutaneous Tissue Disorders				

Rash (GT)	21 (18)	2 (1.7)	16 (17)	0 (0.0)
Metabolism And Nutrition Disorders				
Decreased Appetite*	13 (11)	4 (3.4)	5 (5)	0 (0.0)
General Disorders And Administration Site Conditions				
Pyrexia	16 (14)	0 (0.0)	16 (17)	2 (2.2)
Fatigue (GT)	15 (13)	2 (1.7)	12 (13)	0 (0.0)
Musculoskeletal And Connective Tissue Disorders				
Musculoskeletal Pain (GT) *	23 (20)	1 (0.9)	17 (18)	1 (1.1)
Arthralgia	13 (11)	0 (0.0)	16 (17)	0 (0.0)
Respiratory, Thoracic And Mediastinal Disorders				
Cough (GT) *	20 (17)	1 (0.9)	12 (13)	0 (0.0)
Nervous System Disorders				
Headache*	14 (12)	0 (0.0)	8 (9)	1 (1.1)
Source: FDA analysis using adae.xpt, adsl.xpt GT: group term, see Appendix 19.5 *indicates ≥2% greater on quizartinib arm				

Overall, quizartinib added a modest amount of toxicity to the combination chemotherapy phase of treatment as indicated by the analysis of common all-grade and severe grade TEAEs above.

Table 96: FDA analysis of Study AC220-A-U302 selected common TEAEs during the continuation phase by transplant status

Transplant status	HSCT+				HSCT-			
	QUIZARTINIB		PLACEBO		QUIZARTINIB		PLACEBO	
	N = 70		N = 49		N = 46		N = 43	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Patients with TEAEs	69 (99)	57 (81)	46 (94)	27 (55)	40 (87)	31 (67)	38 (88)	19 (44)
Blood And Lymphatic System Disorders								
Neutropenia (GT)	36 (51)	32 (46)	6 (12)	2 (4.1)	20 (43)	17 (37)	4 (9)	2 (4.7)
Thrombocytopenia (GT)	21 (30)	10 (14)	3 (6)	2 (4.1)	9 (20)	5 (11)	8 (19)	3 (7)

Anemia (GT)	17 (24)	6 (9)	4 (8)	2 (4.1)	2 (4.3)	0 (0)	0 (0)	0 (0)
Infections And Infestations								
Upper Respiratory Tract Infection (GT)	23 (33)	0 (0.0)	8 (16)	0 (0.0)	12 (26)	1 (2.2)	6 (14)	0 (0.0)
Herpesvirus Infection (GT)	13 (19)	3 (4.3)	4 (8)	1 (2.0)	3 (7)	1 (2.2)	4 (9)	1 (2.3)
Source: FDA analysis using adae.xpt, adsl.xpt GT: group term, see Appendix 19.5								

Laboratory Findings

Data:

Table 97 – New or Worsening Laboratory Abnormalities (≥10% of Subjects [All Grades]) in Study AC220-A-U302 (Safety Analysis Set)

Laboratory Abnormality ^a	Quizartinib (N = 265)		Placebo (N = 268)	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Creatinine increased	86.8	4.2	88.8	5.2
ALT increased	58.9	12.1	60.1	10.4
Lymphocyte count decreased	58.5	54.3	54.5	51.1
Hypokalemia	57.4	21.5	55.6	18.3
Hyperglycemia	53.2	4.9	54.1	7.1
GGT increased	52.1	14.3	52.2	15.3
Hypoalbuminemia	51.7	1.9	43.7	4.1
AST increased	51.3	5.7	48.5	3.7
Hypophosphatemia	50.2	20.8	47.0	18.7
ALP increased	49.4	1.5	46.6	1.9
Hypomagnesemia	42.3	1.9	41.4	1.1
Platelet count decreased	40.0	40.0	44.0	44.0

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Anemia	37.4	35.5	45.5	42.5
Blood bilirubin increased	32.8	6.8	35.4	4.5
Hypocalcemia	30.9	2.3	26.1	1.5
Hyponatremia	28.7	3.8	32.8	5.6
Lipase increased	22.6	7.5	25.0	7.8
Hyperuricemia	22.6	1.9	25.7	1.5
Neutrophil count decreased	21.9	21.5	21.6	20.1
CPK increased	21.9	1.9	6.3	0.4
WBC decreased	18.1	18.1	17.9	17.9
Hyperkalemia	15.1	1.1	11.2	0.7
INR increased	14.7	0	20.5	0
Hypermagnesemia	13.2	2.6	8.2	1.1
Hypertriglyceridemia	12.5	1.1	15.7	0.7
Hypernatremia	12.5	0	10.1	0.4

^aTerms based on laboratory data.

Source: eCTD M5.3.5.1 AC220-A-U302 CSR Supplemental Table 14.3.5.1.5

Table 98 – Prolonged Thrombocytopenia (platelets <50,000 cells/mm³) or Neutropenia (ANC <500 cells/mm³) Past Induction Cycle 1 Day 42 in Absence of Active Leukemia in Study AC220-A-U302 (Safety Analysis Set)

Category	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)
Subjects with prolonged thrombocytopenia (platelets <50,000 cells/mm ³) in absence of active leukemia	14 (5.3)	5 (1.9)
Subjects with prolonged neutropenia (ANC <500 cells/mm ³) in absence of active leukemia	14 (5.3)	7 (2.6)
Subjects with prolonged thrombocytopenia (platelets <50,000 cells/mm ³) or prolonged neutropenia (ANC <500 cells/mm ³) in absence of active leukemia	22 (8.3)	11 (4.1)

Note: In absence of active leukemia: subjects achieved CR, CRi, or MLFS per IRC assessment by Induction Cycle 1 Day 42. Source: eCTD M5.3.5.1 AC220-A-U302 CSR Supplemental Table 14.3.4.4.1

Table 99 – Prolonged Thrombocytopenia (Platelets <50,000 cells/mm³) or Neutropenia (ANC <500 cells/mm³) past Consolidation Cycle 1 Day 42 in Absence of Active Leukemia in Study AC220-A-U302 (Safety Analysis Set)

Category	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)
Subjects with prolonged thrombocytopenia (platelets <50,000 cells/mm ³) in absence of active leukemia	0	0
Subjects with prolonged neutropenia (ANC <500 cells/mm ³) in absence of active leukemia	0	0
Subjects with prolonged thrombocytopenia (platelets <50,000 cells/mm ³) or prolonged neutropenia (ANC <500 cells/mm ³) in absence of active leukemia	0	0

Note: In absence of active leukemia: subjects achieved CR, CRi, or MLFS per IRC assessment by Consolidation Cycle 1 Day 42. Source: eCTD M5.3.5.1 AC220-A-U302 CSR Supplemental Table 14.3.4.4.2

The hematology parameters assessed were platelets, hemoglobin, WBCs, neutrophils, and lymphocytes. The blood chemistry parameters assessed were sodium, magnesium, potassium, calcium, serum creatinine, ALT, AST, total bilirubin (TBL), and ALP. Hepatic function abnormalities are presented in Table 107 and the rest of the laboratory data are summarized below.

In Study AC220-A-U302, as expected in a population of subjects with AML, many hematology parameter values were outside the normal range at baseline and during the study. For most subjects, Grade 3 or 4 values were observed for neutrophils, WBC, hemoglobin, platelets, and lymphocytes with treatment.

Approximately 15% of subjects in each treatment arm had severe hypokalemia during the study (shifts from normal potassium levels or Grade 1 hypokalemia at baseline to Grade 3 or 4 hypokalemia).

Shifts in renal function parameters (glomerular filtration rate [GFR] and creatinine clearance) were observed infrequently among subjects in both treatment arms. Approximately 4% of subjects in both treatment arms had shifts to GFR <30 mL/min/1.73 m², and 2% of subjects had shifts to creatinine clearance of <30 mL/min.

Similar decreases in hematology parameters, non-hepatic chemistry evaluations, and renal laboratory parameters to those observed in Study AC220-A-U302 were observed in the 30 to 60 mg group of the All AML Pool.

The Applicant's Position:

Quizartinib has a myelosuppressive effect and shifts in hematological parameters (anemia, neutropenia, thrombocytopenia, lymphopenia) were observed in the pivotal study.

No clinically meaningful changes over time were found in clinical chemistry parameters in either treatment arm. Overall, shifts in these chemistry parameters were observed infrequently after treatment. Although hypokalemia is a risk factor for QT prolongation and associated arrhythmia events with quizartinib, no difference in severe hypokalemia (Grade 3 /4) was observed with quizartinib treatment relative to placebo treatment in Study AC220-A-U302

The FDA's Assessment:

FDA agrees with the Applicant's assessment of laboratory shifts. FDA analysis was generally in agreement with the Applicant's results. However, it is important to note that the unique situation of acute leukemia and induction of remission means that most patients present with baseline abnormalities in many labs and then develop further worsening with induction chemotherapy. High baseline labs obscure on-treatment worsening that might occur after resolution with remission attainment and hides prolonged abnormalities. Moreover, induction/consolidation chemotherapy essentially make all patients severely cytopenic. Therefore, FDA used a combination of laboratory shift analysis and laboratory values reported as TEAEs to capture laboratory adverse events induced by treatment. To ascertain which labs were worsening with quizartinib treatment above the background of intensive chemotherapy, we again used a threshold of $\geq 2\%$ worse on the quizartinib arm compared to placebo as indicated with (*) in Table 100 below. One notable lab that did show a marked difference with quizartinib treatment was elevations of creatine kinase (25% with quizartinib versus 7% with placebo). It is interesting that creatinine kinase showed this elevation with quizartinib-treatment while musculoskeletal pain was less common on the quizartinib arm overall (27% vs 32%) and only slightly more common on the quizartinib arm during maintenance (20% quizartinib versus 18% placebo) . While analysis of delayed count recovery reflected some of the myelosuppression induced by quizartinib treatment, perhaps the best assessment of this effect is shown in Table 95 reflecting use of continuous quizartinib treatment given to patients in remission.

Table 100: FDA analysis of Study AC220-A-U302 new or worsening laboratory abnormalities

	QUIZARTINIB		PLACEBO	
	N = 265		N = 268	
	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
CREATININE (UMOL/L) - Increased	221/259 (85)	11/259 (4.2)	228/267 (85)	13/267 (4.9)

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ALANINE AMINOTRANSFERASE (U/L) - Increased	152/256 (59)	31/256 (12)	160/267 (60)	27/267 (10)
POTASSIUM (MMOL/L) - Decreased*	151/260 (58)	57/260 (22)	146/266 (55)	48/266 (18)
POTASSIUM (MMOL/L) - Increased*	36/260 (14)	2/260 (0.8)	28/266 (11)	2/266 (0.8)
GLUCOSE (MMOL/L) - Increased	139/254 (55)	12/254 (4.7)	143/266 (54)	19/266 (7)
LYMPHOCYTES (10 ⁹ /L) - Decreased*	142/238 (60)	135/238 (57)	139/255 (55)	131/255 (51)
ASPARTATE AMINOTRANSFERASE (U/L) - Increased* ¹	132/255 (52)	15/255 (6)	126/264 (48)	10/264 (3.8)
ALBUMIN (G/L) - Decreased*	131/246 (53)	4/246 (1.6)	112/254 (44)	11/254 (4.3)
ALKALINE PHOSPHATASE (IU/L) - Increased*	129/254 (51)	4/254 (1.6)	123/264 (47)	5/264 (1.9)
PHOSPHATE (MMOL/L) - Decreased*	129/247 (52)	54/247 (22)	121/252 (48)	48/252 (19)
GAMMA GLUTAMYL TRANSFERASE (U/L) - Increased	128/250 (51)	35/250 (14)	138/258 (53)	39/258 (15)
MAGNESIUM (MMOL/L) - Decreased*	107/250 (43)	5/250 (2.0)	105/257 (41)	3/257 (1.2)
MAGNESIUM (MMOL/L) - Increased*	33/250 (13)	6/250 (2.4)	20/257 (8)	3/257 (1.2)
PLATELETS (10 ⁹ /L) - Decreased	106/258 (41)	106/258 (41)	118/267 (44)	118/267 (44)
HEMOGLOBIN (G/L) - Decreased	97/258 (38)	92/258 (36)	121/267 (45)	113/267 (42)
BILIRUBIN (UMOL/L) - Increased	82/258 (32)	18/258 (7)	91/265 (34)	12/265 (4.5)
CORRECTED CALCIUM (MMOL/L) - Decreased*	79/245 (32)	5/245 (2.0)	67/246 (27)	4/246 (1.6)
SODIUM (MMOL/L) - Decreased	73/260 (28)	9/260 (3.5)	86/267 (32)	14/267 (5)
SODIUM (MMOL/L) - Increased*	33/260 (13)	0/260 (0.0)	27/267 (10)	1/267 (0.4)
URATE (UMOL/L) - Increased	56/251 (22)	4/251 (1.6)	65/256 (25)	4/256 (1.6)
LIPASE (U/L) - Increased	51/200 (26)	14/200 (7)	63/209 (30)	21/209 (10)
CREATINE KINASE (IU/L) - Increased*	50/199 (25)	5/199 (2.5)	13/187 (7)	1/187 (0.5)
NEUTROPHILS (10 ⁹ /L) - Decreased	50/242 (21)	50/242 (21)	52/257 (20)	49/257 (19)
LEUKOCYTES (10 ⁹ /L) - Decreased	48/258 (19)	48/258 (19)	48/267 (18)	48/267 (18)
PROTHROMBIN INTL. NORMALIZED RATIO (RATIO) - Increased	38/212 (18)	0/212 (0.0)	53/223 (24)	0/223 (0.0)
TRIGLYCERIDES (MMOL/L) - Increased	25/81 (31)	3/81 (3.7)	32/85 (38)	2/85 (2.4)
CHOLESTEROL (MMOL/L) - Increased* ²	21/83 (25)	1/83 (1.2)	21/92 (23)	0/92 (0.0)

Source: FDA analysis using adlb.xpt, adsl.xpt

*indicates $\geq 2\%$ greater on quizartinib arm

¹AST increased was not included in USPI. Instead hypertransaminasemia was included in the common TEAE table at it was thought to better reflect the toxicity from treatment.

²cholesterol increased was not included in USPI since it was only assessed twice during the study (beginning and end of study visit) and comparative values were only available for 30% of patients.

Note that certain laboratory values listed in the USPI were within 1% higher than FDA's calculations, and therefore, FDA accepted the Applicant's values.

Vital Signs

Data:

Weight and vital sign measurements (systolic and diastolic blood pressure, and pulse rate) were assessed at time points indicated in the study protocols.

Table 101 – Summary of Vital Signs and Change From Baseline Per Study Phase in Study AC220-A-U302 (Safety Analysis Set)

Category	Quizartinib (N=265)			Placebo (N=268)		
	Baseline	Max Postbaseline		Baseline	Max Postbaseline	
		Result	Change From Baseline		Result	Change From Baseline
Induction Phase						
Heart rate (bpm)						
Median	80	89	7	78	90	12
Min, max	55, 125	64, 132	-29, 60	52, 125	56, 163	-24, 85
Systolic blood pressure (mmHg)						
Median	120	130	10	120	130	10
Min, max	85, 190	83, 186	-74, 78	81, 173	95, 185	-48, 70
Diastolic blood pressure (mmHg)						
Median	70	80	6	70	80	10
Min, max	41, 97	50, 116	-34, 45	39, 99	55, 100	-30, 41
Consolidation Phase						

Category	Quizartinib (N=265)			Placebo (N=268)		
	Baseline	Max Postbaseline		Baseline	Max Postbaseline	
		Result	Change From Baseline		Result	Change From Baseline
Heart rate (bpm)						
Median	76	89	12	78	89.5	12
Min, max	50, 130	60, 125	-38, 49	50, 111	60, 133	-24, 48
Systolic blood pressure (mmHg)						
Median	120	130	10	120	130	10
Min, max	90, 163	90, 225	-32, 88	90, 178	94, 180	-52, 64
Diastolic blood pressure (mmHg)						
Median	70	80	10	70	80	10
Min, max	43, 99	50, 105	-18, 42	48, 96	46, 102	-18, 40
Continuation Phase						
Heart rate (bpm)						
Median	80	90	9	80.5	90	10
Min, max	55, 120	55, 141	-30, 79	57, 127	62, 146	-19, 58
Systolic blood pressure (mmHg)						
Median	125	135	10	120	135	10
Min, max	89, 171	102, 177	-29, 43	83, 178	100, 175	-39, 77
Diastolic blood pressure (mmHg)						
Median	79	84	6	75.5	86	10
Min, max	51, 100	60, 118	-21, 32	50, 95	55, 108	-25, 40

Notes: Baseline for Induction/Consolidation/Continuation Phases is defined as the last non-missing value on or prior to the first dose date of study drug (quizartinib/placebo) within the Induction/Consolidation/Continuation Phase. Source: AC220-A-U302 CSR Table 14.3.5.2.1

The Applicant's Position:

No clinically meaningful changes from baseline in blood pressure, pulse rate, or weight were observed in either treatment arm of Study AC220-A-U302 or in the All AML Pool.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Electrocardiograms

Data:

Quizartinib prolongs QT interval in a dose-dependent and exposure-dependent manner. Regular ECG monitoring was required per study protocol in the AC220-A-U302 study. The schedule of assessments in the protocol specified the time points at which laboratory evaluations were conducted.

ECG data were obtained in triplicate and were analyzed in a central laboratory, with the central ECG reading utilized for the safety analyses. ECG matched with quizartinib PK measurements were used for the concentration-QTc E-R analysis.

More frequent assessments were performed during the Induction and Consolidation Phases of the study, with the frequency of testing reduced in the Continuation Phase. More frequent ECG recordings were required during quizartinib initiation and dose escalation.

The Applicant's Position:

The results of the ECG data analysis are discussed under the respective topic of QT prolongation and associated clinical events in Section 8.2.5.1.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. QT prolongation is further discussed below.

QT

Data:

Quizartinib prolongs QT interval in a dose-dependent and exposure-dependent manner.

The Applicant's Position:

The results of the QT interval data analysis are discussed under the respective topic of QT prolongation and associated clinical events in Section 8.2.5.1.

The FDA's Assessment:

FDA agrees with the Applicant's position that quizartinib prolongs the QT interval in a dose-dependent and exposure-dependent manner.

Immunogenicity

The Applicant's Position:

Not applicable. Immunogenic potential is low for small molecules and immunogenicity was not assessed.

The FDA's Assessment:

FDA agrees with Applicant's position. The immunogenicity for small molecules is low, and there was no indication in the TEAE analysis of an issue with immunologic problems.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 QT Prolongation and Potentially Associated Clinical Events

Data:

Table 102 – Overview of QT Prolongation and Potentially Associated Clinical Events Based on Predefined MedDRA Search Criteria^a in Study AC220-AU302 and the 30 to 60 mg Dose Group of the All AML Pool (Safety Analysis Set)

AE Category	Study AC220-A-U302		All AML Pool
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib 30 to 60 mg N = 669 n (%)
Cardiac events potentially associated with QT prolongation, any TEAE	49 (18.5)	30 (11.2)	173 (25.9)
Grade ≥3	18 (6.8)	8 (3.0)	44 (6.6)
TESAE	4 (1.5)	2 (0.7)	20 (3.0)

^a Based on definition of search criteria summarized in Table 69.

Notes:

Percentage is calculated using number of subjects in the column heading as denominator.

TEAE Grade ≥3 represent the maximum TEAE grade.

Source: ISS Table 4.1.27

Table 103 – Events Identified by the Torsade de Pointes/QT Prolongation SMQ Search in the Study AC220-A-U302 and the 30 to 60 mg Dose Group of the All AML Pool (Safety Analysis Set)

PT	Study AC220-A-U302		All AML Pool
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib 30 to 60 mg N = 669 n (%)
Subjects with any identified events	49 (18.5)	30 (11.2)	173 (25.9)
<i>ECG QT prolonged</i>	36 (13.6)	11 (4.1)	133 (19.9)
<i>Fall</i>	5 (1.9)	7 (2.6)	25 (3.7)

PT	Study AC220-A-U302		All AML Pool
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib 30 to 60 mg N = 669 n (%)
<i>Syncope</i>	7 (2.6)	5 (1.9)	20 (3.0)
<i>Presyncope</i>	4 (1.5)	7 (2.6)	10 (1.5)
<i>Cardiac arrest</i>	2 (0.8)	0	3 (0.4)
<i>Ventricular tachycardia</i>	1 (0.4)	1 (0.4)	3 (0.4)
<i>Loss of consciousness</i>	1 (0.4)	1 (0.4)	2 (0.3)
<i>Arrhythmia</i>	0	0	0
<i>Death</i>	1 (0.4)	0	1 (0.1)
<i>Cardio-respiratory arrest</i>	0	0	0
<i>ECG QT interval abnormal</i>	1 (0.4)	0	1 (0.1)
<i>Torsade de pointes</i>	0	0	0
<i>Ventricular fibrillation</i>	1 (0.4)	0	1 (0.1)
<i>Ventricular arrhythmia</i>	0	1 (0.4)	0

Note: The percentage is calculated using the number of subjects in the column heading as denominator.

AEs were coded using MedDRA Version 24.0.

One event of TdP occurred in a subject receiving 90 mg of quizartinib (not shown on the table)

Source: ISS Table 4.1.28

Table 104 – Events Identified by the Torsade de Pointes/QT Prolongation SMQ Search in Study AC220-007 – Cumulative Data - 21 Dec 2020 Database Lock (Safety Analysis Set)

PT	Quizartinib N = 241, n (%)	Salvage Chemotherapy ^a N = 94, n (%)
Subjects with any identified events	74 (30.7)	7 (7.4)
<i>ECG QT prolonged</i>	64 (26.6)	2 (2.1)
<i>Syncope</i>	12 (5.0)	2 (2.1)
<i>Ventricular tachycardia</i>	1 (0.4)	2 (2.1)
<i>Cardiac arrest</i>	0	1 (1.1)

Notes: Subjects who received salvage chemotherapy received a median (minimum, maximum) of 1 cycle (1, 2) for all 3 treatment regimens (LoDAC, MEC, and FLAG-IDA)

A TEAE is defined as an AE that occurs, having been absent before the first dose of study drug or worsened in severity after first dose of study drug, on or after first dose of study drug and up to 30 days after last dose of study

drug. AEs collected after 30 days after the last dose of study drug were not considered TEAEs unless they were treatment related.

Subjects may have more than one event per SOC and PT. At each level of subject summarization, a subject was counted once if he/she reported one or more AEs.

AEs were coded using MedDRA Version 16.1.

Source: AC220-007 CSR Addendum Table 14.3.1.24-II

Table 105 – Summary of Notable ECG in the Study AC220-A-U302 and the 30 to 60 mg Dose Group of the All AML Pool (Safety Analysis Set)

QTcF Interval, ms	Study AC220-A-U302		All AML Pool
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib 30 to 60 mg N = 669 n (%)
New >450	91 (34.3)	48 (17.9)	284 (42.5)
New >480	20 (7.5)	6 (2.2)	75 (11.2)
New >500	6 (2.3)	2 (0.7)	17 (2.5)
New >450 and ≤480	73 (27.5)	43 (16.0)	221 (33.0)
New >480 and ≤500	15 (5.7)	4 (1.5)	59 (8.8)
Increase >30 ms from baseline	146 (55.1)	87 (32.5)	388 (58.0)
Increase >60 ms from baseline	27 (10.2)	13 (4.9)	73 (10.9)

Note: Based on central assessment of ECG. New implies a newly occurring ECG abnormality, which is defined as an abnormal postbaseline ECG finding that is not present at baseline.

Source: ISS Table 7.1.1

A concentration-QTcF (C-QTcF) E-R analysis was also conducted to assess the subject characteristics that may have impacted QTc prolongation.

In Study AC220-A-U302, a direct-response maximum effect (Emax) model best described the C-QTcF relationship between quizartinib concentrations and QTcF. The median model-predicted ΔQTcF at Cmax,ss in subjects with newly diagnosed AML in Study AC220-A-U302 during the Continuation Phase at 30 mg and 60 mg, assuming no dose interruption or discontinuation, were 18.4 ms (90% CI: 16.3, 20.5) and 24.1 ms (90% CI: 21.4, 26.6), respectively.

The covariates that were tested in the C-QTcF model included hypokalemia, serum calcium and magnesium concentrations, age, body weight, sex, race, and use of QT-prolonging drugs, beta-blocker drugs, and anthracycline. Age and hypokalemia had an effect on the baseline QTcF. The covariate analysis on the drug effect model identified age, concurrent daunorubicin use, hypokalemia, and calcium levels as statistically significant covariates on Emax. However, interindividual variability on Emax was increased after including the covariate effects, and these effects were not seen in the graphical analysis. In addition, age, daunorubicin use, and hypokalemia effects were estimated with high uncertainty with RSE >34%. As a result, these covariate effects were not retained in the model. The remaining covariates had no effect on the baseline QTcF.

Concomitant administration of QT-prolonging medications had no impact on the observed QTcF increases associated with quizartinib concentrations. More than 80% of subjects in the quizartinib arm of Study AC220-A-U302 used at least one concomitant medication with a 'known' risk of QT prolongation according to the Arizona Center for Education and Research on Therapeutics (AZCERT) classification, which overlapped for at least 1 day with quizartinib administration. Most common drugs in this category were antifungals (fluconazole), antiemetics (ondansetron) and antibiotics (ciprofloxacin, levofloxacin; Table 106).

Table 106 – Most Common (≥5% Subjects) Concomitant Medications – QT-prolonging Drugs Overlapped with Quizartinib/Placebo by AZCERT Classification (Known Risk) and Preferred Term in the Study AC220-A-U302 (Safety Analysis Set)

AZCERT Classification Preferred Term	Quizartinib N=265 n (%)	Placebo N=268 n (%)
Subjects with any concomitant QT-prolonging medications in known risk that overlapped for at least 1 day with quizartinib/placebo	223 (84.2)	213 (79.5)
Fluconazole	106 (40.0)	105 (39.2)
Ondansetron	83 (31.3)	82 (30.6)
Levofloxacin	76 (28.7)	69 (25.7)
Ciprofloxacin	75 (28.3)	72 (26.9)

Source: eCTD M5.3.5.1 AC220-A-U302 CSR Supplemental Table 14.1.4.2.5.1

The Applicant's Position:

Quizartinib is associated with QTc prolongation in a dose-dependent manner. QTc prolongation may increase the risk of ventricular arrhythmias or TdP. While the incidence of TEAEs of ECG QT prolonged in the study was higher in the quizartinib arm than in the placebo arm, the majority of events were asymptomatic and Grade 1 or 2, and the incidence of Grade 3 QTcF prolongation was low, demonstrating that QTcF prolongation with quizartinib is manageable with dose modification or interruption and correction of additional risk factors (eg, monitoring for and correction of electrolyte abnormalities, quizartinib dose modification for QTcF prolongation, and for concomitant strong CYP3A inhibitor use). Ventricular arrhythmia events were infrequent in the study: 2 subjects (0.8%) in the quizartinib arm experienced cardiac arrest with recorded ventricular fibrillation (both during the Induction Phase), 1 with fatal outcome, in the presence of severe hypokalemia, and 1 subject died in his sleep with no cause of death identified and who had no significant QTc prolongation on ECG while on study drug. In the overall AML development program, the incidence of ventricular arrhythmia events was low at the recommended quizartinib doses.

QT prolongation is a notable risk to be mitigated. Quizartinib is a CYP3A substrate, and concomitant administration of strong CYP3A inhibitors increases quizartinib exposure. Therefore, quizartinib dose should be reduced when used concomitantly with strong CYP3A inhibitors and the study protocol allowed for the use of concomitant strong CYP3A inhibitors with appropriate quizartinib dose reduction. In addition, concomitant administration of QT-prolonging medications, which were allowed in the study as warranted in the care of AML subjects, may potentially lead to increased incidence of QT prolongation with quizartinib. However, in Study AC220-A-U302 a large proportion of subjects received QT-prolonging medications concomitantly, the QTcF analysis while receiving QT-prolonging medications was not notably different from when these same subjects were not on concomitant QT-prolonging medications.

The FDA's Assessment:

FDA notes that preclinical characterization of quizartinib and its major metabolite AC886 suggested that it could affect the cardiac action potential. Specifically, patch clamp experiments showed that quizartinib and AC886 inhibited hERG current (I_{Kr}) and I_{Ks} currents. These experiments showed greater partial inhibition of I_{Ks} with 67% or 27% inhibition at 3 μ M for Quizartinib or AC886, respectively. This is compared to only 16% or 12% for I_{Kr} inhibition at 3 μ M of Quizartinib or AC886, respectively. To place this in perspective, the Cmax concentration in people administered 60 mg quizartinib is approximately 1 μ M for quizartinib and 0.3 μ M for the AC886 metabolite. Therefore, although inhibition of both rectifying currents was observed, it is thought that the predominant effect on cardiac repolarization would be due to the greater inhibition of the I_{Ks} current.

Most drugs that prolong the QTc interval inhibit hERG channel and the I_{Kr} current. Therefore, clinical experience to date in terms of QTc monitoring, level of risk relative to QTc interval prolongation, and the combined effect of the polypharmacy of QTc prolonging medications on the QTc interval are based on inhibition of I_{Kr} . It remains unclear how much of that experience can be extrapolated to I_{Ks} inhibitors. At least two other approved drugs have shown inhibition of the I_{Ks} current, arsenic trioxide and indapamide. Arsenic trioxide blocks both the I_{Kr} and the I_{Ks} currents and is well-known for its cardiac side effects including QT prolongation, Torsade de Pointes, and sudden death. Given the dual blockade noted for arsenic trioxide, it is hard to extrapolate the contribution toward the overall risk from I_{Ks} inhibition. Indapamide is a blood pressure medication first approved in 1983 with dual thiazide type diuretic effects and direct with vasodilatory effects. While preclinical studies have shown the I_{Ks} current inhibition and case reports have described episodes of Torsade de Pointes in patients taking indapamide, it seems to have been generally well tolerated, and the current USPI does not note a risk of QT prolongation or TdP.

Insight concerning blockade of the I_{Ks} current is informed by patients with Long QT syndrome 1 (LQT1), a genetic condition where mutations in the channel responsible for I_{Ks} impair its

function. These patients have diminished shortening of the QT interval when the heart rate increases and are at increased risk of TdP during times of elevated heart rate and when recovering from elevated heart rate. Expert consensus recommendations for these patients include avoidance of QT prolonging medications, identification and correction of electrolyte abnormalities, and the use of beta blockers. While the first two recommendations were incorporated into the quizartinib development program, the use of beta-blocker therapy to treat acquired forms of Long QT syndrome is not standard. Based on the risk of greater QT interval prolongation with heart rate increases, we recommend a post-marketing requirement for an exercise test study in healthy volunteers and patients to evaluate the impact of heart rate on the cardiac safety of quizartinib. The patient study should include patients on beta-blockers to observe for mitigating effects on the incidence of quizartinib-related adverse reactions.

This preclinical evidence portended the increased rate of QTc prolonged AEs reported in the above safety analysis in both the newly diagnosed patients and in the overall ISS population. Indeed, dedicated response analysis of changes in QTcF during the continuation phase showed dose dependent increase in the change in QTcF during this phase of treatment. Two caveats to this analysis are that patients must have tolerated quizartinib through two prior phases of treatment to reach the continuation phase, selecting out those patients that could not tolerate quizartinib or had extreme QTcF responses to quizartinib. Secondly, dosing during this phase of treatment was dependent on the change of QTcF. Therefore, these results do not reflect the response that would be expected from a population randomly assigned to either dose level but rather what might be expected if dose escalation was dependent on change in QTcF and after disregarding patients that could not tolerate quizartinib treatment. The trend suggests diminishing elevation of QTcF for the marginal increase in dose, when this trend reflects the selection of patients to the higher dose that had less increase in QTcF change with the lower dose.

We agree with the Applicant that most subjects Study AC220-A-U302 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 lumped 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.

Risk of Torsade de Pointes and Cardiac Arrest

As noted above, there were no reported cases of Torsade by PT analysis in Study AC220-A-U302 study. However, there were two cases of cardiac arrest on the quizartinib arm, one grade 4 and

one grade 5. There were no reported cases of cardiac arrest or Torsade de Pointes on the placebo arm.

The Grade 4 event occurred in 63 year old female patient (Subject ID (b) (6)) who developed ventricular fibrillation and cardiac arrest on day 5 of quizartinib treatment. The patient had personal history of Long QT syndrome diagnosed years prior to developing AML and had a pretreatment QTcF of 463. She was started at a reduced dose of quizartinib of 20 mg daily due to being on a strong CYP3A inhibitor Posaconazole (which is also a QT prolonging medication). During these days, the patient was also placed on standing furosemide, which induced severe hypokalemia to 2.4 by the time of the cardiac arrest. She was cardioverted and had resumption of spontaneous circulation. QTcF after the event was reported as 587 ms. Tracing of the VF were not available for FDA review. She was permanently discontinued from study treatment.

FDA comment: This patient should have been excluded from the study due to her personal history of Long QT syndrome and pretreatment QTcF being above the 450ms cutoff. However, even with these risk factors, we see how concomitant QTc prolonging medications and severe iatrogenic hypokalemia increased the chances of this event.

The Grade 5 event occurred in a 54 year old female patient (Subject (b) (6)) who developed cardiac arrest on day 79 of treatment. The subject was not in remission after a first cycle of induction and underwent a second induction cycle followed by quizartinib. It was noted during this second quizartinib cycle that treatment was interrupted on day 72 for prolonged QTc of 493 but resumed the next day (day 73) at a reduced dose of 30 mg (40->30mg). On study day 78 the patient was noted to have severe hypokalemia with a potassium of 2.6. Quizartinib dosing was not held and was continued with potassium supplementation (including IV potassium). The next day (day 79), the patient was reported in good clinical condition at 12:30 but had sudden cardiac arrest at 14:00. FDA review of the tracing from the event was consistent with Torsade de Pointes. The medical team was unable to restore normal rhythm, and the patient passed away. Other QTc prolonging medications the patient was taking at the time of the event included ciprofloxacin, linezolid, and piperacillin/tazobactam.

FDA comment: Per the narrative, the patient had resolution of her initial QTc prolongation to a QTc 407 the day prior (day 78) to her cardiac arrest. This is despite reports that her serum potassium that day was severely low at 2.6.

The common features of these two cases include middle aged women, recovering from induction chemotherapy, exposure to several QTc prolonging medications, and severe hypokalemia. Avoiding QTc prolonging medications and severe hypokalemia appear to be two

factors that can be addressed to mitigate the clinical risk of ventricular arrhythmia and cardiac arrest.

While the Applicant contends that the rate of QTc prolongation was manageable and asymptomatic, they do not satisfactorily address that 2/265 (0.8%) of quizartinib-treated patients had a cardiac arrest during the first phase of treatment. FDA and the Applicant both agree that additional factors including history of long QT syndrome, hypokalemia, and concomitant QTc prolonging medications contributed to these two events. However, FDA views this as disconcerting since it suggests that Study Investigators, despite protocol warnings and contraindications about the risk of quizartinib treatment, still enrolled and treated a patient with a history of Long QT syndrome, continued to prescribe concomitant QTc prolonging medications with quizartinib and prolonged QTc, and continued quizartinib treatment despite patients having severe hypokalemia (potassium levels $<3 \mu\text{M}$). Moreover, these events are potentially fatal arrhythmias that should be prevented from occurring. Once a patient develops TdP, treatment is challenging even in the inpatient hospital setting. Also, as noted earlier, although *FLT3*-ITD mutant AML is serious life-threatening disease, the availability of an alternative FDA approved *FLT3* inhibitor for this indication and line of therapy necessitates that appropriate precaution be taken with the choice of patient and with respect to quizartinib-specific patient management. Lastly, these events occurred in younger patients during their initial treatment with intention to cure. This means that possibly preventable deaths that occur might be in patients that would otherwise be long-term survivors. Therefore, we conclude that active measures to ensure provider education of these factors, including absolute contraindications, temporary contraindications, unique mechanism of action, and patient monitoring guidelines are necessary for the safe and effective use of quizartinib outside the intensive monitoring of a clinical trial.

Lastly, in order to track the incidence of severe and fatal cardiac arrhythmias in patients treated with quizartinib, with its unique mechanism of QT interval prolongation, we recommend a post-marketing requirement for a prospective, observational study to further assess the risk.

8.2.5.2 Hepatic Function Abnormalities

Data:

Table 107 – Liver Chemistry Abnormalities in the Study AC220-A-U302 and the 30 to 60 mg Dose Group of the All AML Pool (Safety Analysis Set)

Category	Study AC220-A-U302		All AML Pool
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib 30 to 60 mg N = 669 n (%)
ALT or AST			
≥3 × ULN	79 (29.8)	61 (22.8)	147 (22.0)
≥5 × ULN	34 (12.8)	29 (10.8)	53 (7.9)
≥10 × ULN	10 (3.8)	9 (3.4)	13 (1.9)
≥20 × ULN	2 (0.8)	2 (0.7)	3 (0.4)
TBL			
≥2 × ULN	26 (9.8)	23 (8.6)	60 (9.0)
ALP			
≥2 × ULN	33 (12.5)	39 (14.6)	110 (16.4)
Concurrent TBL elevation with ALT or AST elevation^a			
TBL ≥2 × ULN with ALT or AST ≥3 × ULN	10 (3.8)	11 (4.1)	22 (3.3)
TBL ≥2 × ULN with ALT or AST ≥3 × ULN and ALP <2 × ULN	9 (3.4)	7 (2.6)	17 (2.5)

^a Concurrent TBL elevation with AST/ALT elevation is defined as TBL elevation (TBL ≥2 × ULN) occurring on or within (ie, after) 32 days of the AST/ALT elevation (AST/ALT ≥3 × ULN).

Note: Only includes laboratory data collected after the first dose of study drug and no more than 30 days after the last dose of study drug.

Source: ISS Table 5.1.2

Table 108 – Treatment-emergent Adverse Events in the Category of Hepatotoxicity in >2% of Subjects in Study AC220-A-U302 and the 30 to 60 mg Dose Group of the All AML Pool based on Predefined MedDRA Search Criteria^a (Safety Analysis Set)

AE Category <i>PT</i>	Study AC220-A-U302		All AML Pool
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib 30 to 60 mg N = 669 n (%)
Hepatotoxicity, any grade	91 (34.3)	73 (27.2)	208 (31.1)
Grade ≥3	44 (16.6)	37 (13.8)	85 (12.7)
TESAE	7 (2.6)	6 (2.2)	15 (2.2)

<i>PT</i>			
<i>ALT increased</i>	42 (15.8)	27 (10.1)	92 (13.8)
<i>AST increased</i>	28 (10.6)	19 (7.1)	67 (10.0)
<i>Blood bilirubin increased</i>	16 (6.0)	14 (5.2)	47 (7.0)
<i>GGT increased</i>	24 (9.1)	25 (9.3)	36 (5.4)
<i>Hyperbilirubinaemia</i>	8 (3.0)	8 (3.0)	12 (1.8)
<i>Hepatic function abnormal</i>	7 (2.6)	4 (1.5)	10 (1.5)

^a See Table 69 for the definition of search criteria.

Note: Percentage is calculated using the number of subjects in the column heading as denominator. TEAE Grade ≥ 3 represent the maximum TEAE grade.

Sources: ISS Tables 4.1.27 and 4.1.28

The Applicant's Position:

In Study AC220-A-U302, 91 subjects (34.3%) in the quizartinib arm and 73 subjects (27.2%) in the placebo arm experienced hepatic TEAEs in the reviewed SMQs. Most of the events identified were non-serious and none resulted in a fatal outcome see (Table 108).

Treatment-emergent AEs and serious AEs in the quizartinib arm were mainly liver function test (LFT) abnormalities and had alternative/contributing factors (such as sepsis, baseline LFT abnormalities, concomitant hepatotoxic medication, and autoimmune hemolytic anemia), improved on continued study drug administration, or had no recurrence on rechallenge. No serious cases of hepatic failure or toxic hepatitis were observed in Study AC220-A-U302 (ISS Table 4.1.30).

The incidence of TESAEs of hepatic failure or drug-induced liver injury was low in the All AML Pool. The reported cases of drug-induced liver injury, hepatic failure, or acute hepatic failure had alternative etiologies and risk factors, including sepsis, cardiac failure, AML progression with liver involvement, and GVHD.

In Study AC220-A-U302, elevations of AT were mostly limited to ≥ 3 to $<10 \times$ ULN and occurred in numerically higher percentages of subjects in the quizartinib arm than in the placebo arm. Elevations of TBL $\geq 2 \times$ ULN occurred in similar percentages of subjects in both treatment arms. Similar percentages of subjects in the quizartinib and placebo arms had concurrent AT $\geq 3 \times$ ULN with TBL $\geq 2 \times$ ULN (see Table 107).

The LFT abnormalities in the 30 to 60 mg group of the All AML Pool were consistent with those observed in Study AC220-A-U302 (see Table 107). Overall, subjects with concurrent AT $\geq 3 \times$ ULN and TBL $\geq 2 \times$ ULN had additional contributing factors identified, most frequently co-suspect concomitant medications, severe infection or sepsis, AML disease progression or GVHD, or had combination liver enzyme elevations that were mild and transient, resolved on continued study drug administration, or did not reoccur upon rechallenge. There were no

notable differences in findings across the dose groups. An evaluation of these subjects does not reveal a pattern of liver injury associated with quizartinib therapy.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. FDA independently screened (both broadly and narrowly) for Hy's law cases in the laboratory data from Study AC220-A-U302. We found that subjects that met criteria for screening had transient elevations of LFTs that resolved either without change in study drug dosing or with study drug interruption. No patients on the quizartinib arm of the study had to discontinue study drug due to elevated LFTs alone whereas one patient on the placebo arm discontinued study drug for hyperbilirubinemia.

8.2.5.3 Congestive Heart Failure and Ischemic Heart Disease

Data:

Table 109 – Overview of Cardiac Failure and Ischemic Heart Disease based on Predefined MedDRA Search Criteria^a in the Study AC220-A-U302 and the 30 to 60 mg Dose Group of the All AML Pool (Safety Analysis Set)

AE Category	Study AC220-A-U302		All AML Pool
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib 30 to 60 mg N = 669 n (%)
Cardiac failure, any TEAE	7 (2.6)	6 (2.2)	21 (3.1)
Grade ≥3	5 (1.9)	2 (0.7)	11 (1.6)
TESAE	5 (1.9)	2 (0.7)	8 (1.2)
IHD, any TEAE	1 (0.4)	6 (2.2)	10 (1.5)
Grade ≥3	1 (0.4)	4 (1.5)	3 (0.4)
TESAE	0	3 (1.1)	3 (0.4)

^a See Table 69 for definition of search criteria.

Percentage is calculated using number of subjects in the column heading as denominator.

TEAE Grade ≥3 represent the maximum TEAE grade.

Source: ISS Table 4.1.27

The Applicant's Position:

In Study AC220-A-U302, the numbers of subjects with TEAEs within the CHF category were low and similar between the quizartinib and placebo arms. No events resulted in a fatal outcome.

Review of the events of cardiac failures and associated conditions was generally confounded by other significant concurrent medical conditions (infections, such as sepsis and septic shock, and aortic stenosis) or concurrent cardiotoxic chemotherapy.

Review of the reported events of ischemic heart disease (IHD) did not reveal a specific trend in the nature, characteristics, or time of onset of event, or any evidence of association with quizartinib therapy.

Results in the 30 to 60 mg group of the All AML Pool were similar to those in Study AC220-A-U302.

The FDA's Assessment:

FDA agrees that the rates of cardiac failure and ischemic cardiac disease were rare and generally balanced between study arms. However, FDA notes that one on-treatment death was due to ventricular dysfunction (Subject ^{(b) (6)}). This patient died on study day 138 during the consolidation phase of treatment. The patient had worsening of cardiac function for several weeks after cessation of study drug. The case was complicated by previous anthracycline use, limited exposure to quizartinib, and continued worsening of cardiac function after cessation of quizartinib.

8.2.5.4 Differentiation Syndrome and Acute Febrile Neutrophilic Dermatositis

Of the 1081 subjects treated with quizartinib in the All AML Pool, 2 subjects (0.2%; both in the >60 mg group) had investigator-reported TEAEs of differentiation syndrome (DS) in the setting of R/R AML (Table 110).

Data from Study AC220-007 in subjects with R/R AML using the FDA criteria ([Norsworthy, 2020](#)) for DS identified 67 (27.8%) quizartinib-treated subjects and 34 of the 94 subjects (36.2%) treated with salvage chemotherapy. On Applicant medical review, no events were assessed as definite or probable DS in Study AC220-007. A total of 12 quizartinib-treated subjects (5%) were identified as having possible DS based on the clinical presentation, though a clear alternative etiology may have been present. None had a fatal outcome due to possible DS. No medical review of salvage chemotherapy cases was done.

No events of DS were reported in subjects with newly diagnosed AML from Study AC220-A-U302 (Table 110).

Using the same FDA's algorithmic approach for identification of potential cases of DS, 76 of the 265 subjects (28.7%) were identified from the AC220-A-U302 study dataset. Based on the Applicant review, all the events identified from the search were assessed as 'not a DS'. Of note, 79 of the 268 subjects (29.5%) in the placebo arm of Study AC220-A-U302 were also identified as having potential DS using the FDA's algorithm. Cases in placebo-treated subjects were not further evaluated.

Table 110 – Investigator-reported TEAE of Differentiation Syndrome and Acute Febrile Neutrophilic Dermatositis in the Study AC220-A-U302 and the All AML Pool (Safety Analysis Set)

PT	Study AC220-A-U302		All AML Pool			
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib <30 mg N = 30 n (%)	Quizartinib 30 to 60 mg N = 669 n (%)	Quizartinib >60 mg N = 382 n (%)	Total Quizartinib N = 1081 n (%)
Subjects with any TEAEs						
DS	0	0	0	0	2 (0.5)	2 (0.2)
Acute febrile neutrophilic dermatosis	0	0	0	10 (1.5)	10 (2.6)	20 (1.9)

Source: ISS Table 4.1.24

The Applicant's Position:

Quizartinib can cause terminal differentiation of AML blast cells ([Sexauer, 2012](#)), which can potentially lead to the development of DS in subjects with R/R AML receiving quizartinib monotherapy.

DS is dependent on differentiation of blasts cells and as such is considered unlikely to occur in subjects with newly diagnosed AML receiving induction and consolidation chemotherapy, where rapid disappearance of myeloid blasts occurs. Data from the AC220-A-U302 study has not identified any occurrence of differentiation in quizartinib-treated subjects.

The FDA's Assessment:

FDA reviewed the possible cases of DS identified from Study AC220-A-U302 and agreed that they had alternative etiologies that were explained by the clinical context (culture positive infections, neutropenic fever responding to empiric antibiotics, etc.) and responded quickly to alternative treatments or were confirmed to be from alternative causes. FDA notes that in the R/R setting, there were cases of DS identified by investigators and by screening of Study AC220-007 for possible DS cases (12 possible cases noted above). Moreover, there were 20 cases of acute febrile neutrophilic dermatosis identified in the ISS population but not within Study AC220-A-U302.

Of note, FDA disagrees with the Applicant that there were no fatal cases of DS on Study AC220-007. FDA adjudicated 3 cases of possible DS that contributed to the patients' death and these cases are detailed below.

- USUBJID (b) (6) was a 62-year-old male who met Montesinos criteria on D1 (on 30 mg quizartinib) when he presented with G1 febrile neutropenia and then G1

hypotension on D4, with no stop date. Initially treated with antibiotics, he subsequently presented with neutropenic sepsis on D9 which was also treated with antibiotics; a blood culture was positive for *e. faecium* on D8 supporting an infectious etiology for these symptoms, but the neutropenic sepsis worsened on D23, when he developed multiple skin lesions which were erythematous and painful. Of note a CT on D20 showed “diffuse swelling of the subcutaneous tissues and platysma muscle on the left side of the jaw but no discrete collection or mass lesion, which could mean inflammatory or infectious process.” On D24 a CXR showed fluid overload and the patient developed hypoxemia, treated with diuretics. On D25 his PICC line was removed as it was thought to be the source of the skin lesions. Quizartinib was interrupted on D28 due to sepsis, but it was restarted on D37 at a reduced dose (20 mg). On D46 the patient was noted to be hemodynamically stable with improving inflammatory markers, and quizartinib was reescalated to 30 mg; the patient subsequently deteriorated (unknown date) with sepsis, arm pain, swelling, and an MRI showing myositis of the right abductor muscles, as well as fast AFib with refractory blood pressure, noted in the narrative to be due to electrolyte abnormality. The quizartinib was discontinued on D55, and on D64 the patient died of neutropenic sepsis. The patient’s WBC count decreased from >293000 at screening to 500 at the end of treatment, the blast count decreased from >287000 at screening to undetectable at the end of treatment, and the ANC peaked at 320 on D45, without much change throughout the treatment course. Also, on D30 the BM showed no blasts, but a note showed that “there are a number of nucleated cells in the trails which are mainly neutrophils.” The patient was treated with antibiotics and supportive care, but no steroids.

Reviewer comment: Although it is possible that all of the symptoms above were due to infection, the combination of fever, fluid overload, myositis and hypotension in the setting of disappearance of blasts and a BM with predominantly neutrophils, that improved with quizartinib interruption and dose reduction, and rapidly deteriorated with dose re-escalation, and was not treated with steroids, must be considered at least possibly a case on the DS/AFND spectrum due to the quizartinib. The restarting and dose-escalation of quizartinib and lack of steroid administration in this case highlight the fact that an event on this spectrum was not in the differential diagnosis for practitioners treating patients with quizartinib.

- USUBJID (b) (6) was a 31-year-old female who presented with respiratory distress/dyspnea and fever on D42 of quizartinib (30 mg), with bilateral pleural effusions and peripheral edema. Associated WBC was 21930, no report of whether or not there were blasts, although per the narrative quizartinib was discontinued on this day due to PD (no data from ADLB dataset post D29). She was treated with antibiotics and supportive care, no steroids were administered. She died on D44 due to G5 respiratory distress. Notably, she had been hospitalized from D19 onward with febrile neutropenia and staph bacteremia treated with antibiotics and supportive care; these resolved and she developed G3 lung infection, suspected to be fungal on D23, which improved on D37, and her dyspnea

associated with this resolved on D39 as well. Of note, quizartinib had been decreased to 20 mg on D19 due to QT prolongation, and was increased back to 30 mg on D41, 1 day prior to development of the ultimately fatal respiratory distress and 3 days prior to death.

Reviewer comment: The proximity of the increased quizartinib dose to her symptoms, the resolution of the previous bacterial infection, the rapidity of progression of symptoms in the context of pleural effusions and peripheral edema and the lack of administration of steroids, all without evidence of a rapid increase in blast count, raise the concern for DS as a COD in this patient.

- USUBJID (b) (6) was a 47-year-old female who presented on D22 of quizartinib therapy (90mg) with a rash and subsequent pyrexia, general aches and right eye swelling; the rash was diagnosed as AFND (no biopsy mentioned). The patient had associated dyspnea, and a CT showed “chest infection”; a bronchoscopy was positive for rhino- and enterovirus on PCR. WBC was 1100 and ANC was 800, and remained between 700-800 throughout the course. Treatment included antibiotics and steroids. Quizartinib was interrupted on D29; pyrexia and AFND resolved on D37 and 42, respectively, and quizartinib was restarted at 60 mg daily on D43 and interrupted again on D71 due to an “arm wound.” She presented again on D78 with AFND and pyrexia with associated edema, feeling “unwell” and diarrhea; per the narrative she was “noted to have...sepsis” and dyspnea. WBC was 1700 with an ANC of 600, no blasts. CXR showed “widespread consolidation” and per the narrative she was diagnosed with a fungal infection and parainfluenza. Quizartinib was permanently discontinued due to these events. Treatment included antibiotics and steroids. All events were ongoing at the time of death on D89, which was assessed as due to progressive AML. It is noted that no labs were included in the ADLB dataset beyond D69, BMA had 0% blasts at C2D1(D29), and no peripheral blasts were recorded in that dataset beyond D8 (0.24).

Reviewer comment: The associated dyspnea, pyrexia and AFND in the setting of decreasing blasts raise the possibility that this is a fatal event on the DS/AFND spectrum.

FDA agrees with Applicant’s supposition that DS is unlikely to occur within the treatment regimen under consideration for newly diagnosed patients. This is likely due to debulking effect of induction chemotherapy and the relative resistance of AML cells remaining after induction chemotherapy to undergo differentiation from a 14-day course of quizartinib. FDA included DS and AFND in labeling since these were serious events that might occur if quizartinib is used outside of the indicated population. Labeling noted that these occurred within development program but in a different clinical setting.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

321

Version date: July 2021 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Refer to Section 8.1.2 for PRO results.

The Applicant's Position:

Notwithstanding the caveats with respect to interpretation of the data discussed previously, the subscales relevant for safety and tolerability included are fatigue and nausea/vomiting, where improvement was noticeable in the Continuation Phase for both subscales. The results for fatigue and nausea/vomiting suggest no detrimental impact from addition of quizartinib to standard-of-care chemotherapy for newly diagnosed *FLT3*-ITD (+) AML.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that both nausea/vomiting and fatigue as components of PRO results were improved from baseline. However, we note that the results suggested greater PRO scale improvement with placebo than with quizartinib. Interestingly, this difference is reflected in the higher rate of nausea (23% quizartinib vs. 9% placebo) and vomiting (15% quizartinib vs. 8%) reported as TEAEs in quizartinib-treated patients during the continuation phase than in the placebo treated patients (Table 95). However, fatigue reported as a TEAE during this phase showed no difference (13% quizartinib vs. 13% placebo). This suggests that PRO data might better capture patient fatigue than fatigue reported as a TEAE.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Subgroup analyses of TEAEs by intrinsic factors (eg, age, sex, race, and ethnicity) and extrinsic factors (eg, geographic region and concomitant medications) were performed for Study AC220-A-U302 and the All AML Pool.

The analyses according to race, ethnicity, and geographic region were hampered by the limited number of subjects in some of the subgroups (Black/African American, Hispanic/Latino), but in general, the type and incidence of the TEAEs most frequently reported across the overall Safety Analysis Set (gastrointestinal disorders, infections, pyrexia, cytopenias, skin disorders, hypokalemia, ALT increased, and ECG QT prolonged) were similar in the different subgroups (ISS Table 4.1.15).

There were some notable findings in subgroup analyses observed for QT interval prolongation, with the TEAE of QT prolongation reported more frequently in females compared with males, higher percentages of females than males who had QTcF >450 ms and QTcF >480 ms, and increases in QTcF >30 ms or >60 ms in the quizartinib arm of Study AC220-A-U302. However, no differences in QTcF >500 ms were observed between males and females in either treatment arm (Table 10.27, CSR AC220-A-U302, eCTD 5.3.5.1).

Similarly, concomitant use of strong CYP3A inhibitor was shown to be associated with a higher incidence of QTcF prolongation on ECG in Study AC220-A-U302 and the 30 to 60 mg group of the All AML Pool.

In contrast, age appeared not to be a factor impacting the incidence of QT interval prolongation based on reported TEAE or ECG data, with no clear trend for increased incidence with increased age in Study AC220-A-U302 and the 30 to 60 mg dose group of the All AML Pool (ISS Table 7.1.2).

A subgroup analysis by use of QT-prolonging medication and by duration of treatment showed that concomitant administration of QT-prolonging medications had no significant impact on the incidence of QTcF prolongation (Module 2.7.4, Section 4.2). The incidence of QTcF prolongation (>450 ms and change from baseline >60 ms) appeared to increase with longer treatment duration, although this is likely a feature of event accrual during the longer follow-up time in subjects with longer treatment duration.

As summarized in Section 19.4.3.4, the C-QTcF E-R analysis showed that age, daunorubicin, hypokalemia, and calcium levels but not sex, body weight, or concomitant QT-prolonging medications were as identified as significant covariates.

The Applicant's Position:

Overall, the safety data with quizartinib were generally similar across different age, sex, and concomitant use of strong CYP3A inhibitor subgroups in Study AC220-A-U302 and the 30 to 60 mg dose group of the All AML Pool. With the limitations outlined above, the type and incidence of the TEAEs most frequently reported were generally similar in the different subgroups of race, ethnicity, and geographic region.

Although some numerical differences in the incidence of some categories of TEAEs (eg, TESAEs, TEAEs associated with death as outcome, and TEAEs associated with study drug discontinuation or interruption) were observed these were assessed as not indicative of clinically meaningful differences in the safety profile of quizartinib.

The FDA's Assessment:

FDA agrees with the Applicant's position. The FDA notes that multiple studies have indicated that females are more susceptible to acquired long QT syndrome.

8.2.8. Specific Safety Studies/Clinical Trials

Data:

No specific safety studies are included in the NDA.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

No human carcinogenicity studies have been conducted.

The Applicant's Position:

In Study AC220-A-U302, 7 subjects (2.6%) in the quizartinib arm and 8 subjects (3.0%) in the placebo arm experienced a TEAE in the MedDRA SOC Neoplasms benign, malignant and unspecified. No individual PT was reported by >1 subject in the quizartinib arm.

No specific trend could be identified in the nature of the neoplastic events reported from the study, and based on the available information, no evidence of causal association with quizartinib could be identified (ISS Table 4.1.3).

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Events were balanced between arms and without clear trend to occurrence.

Human Reproduction and Pregnancy

Data:

Women of childbearing potential were required to have a negative serum pregnancy test upon entry into Study AC220-A-U302 and required to use highly effective birth control as defined in the clinical study protocol upon enrollment, during the Treatment Period and for 6 months following the last dose of study drug. Men were required to be surgically sterile or willing to use highly effective birth control as defined in the clinical study protocol upon enrollment, during the Treatment Period, and for 6 months following the last dose of study drug. There was 1 case of pregnancy in the placebo arm of Study AC220-A-U302 and no lactation-related events were reported in the quizartinib development program (see Table 21: Subject Disposition in Study AC220-A-U302).

The Applicant's Position:

In an embryo-fetal development study in rats, fetotoxicity (lower fetal weights and effects on skeletal ossification) and teratogenicity (high incidence of fetal malformations) were observed. However, no clinical studies have been conducted that assess the use of quizartinib during

pregnancy or breastfeeding. While one case of pregnancy was reported in Study AC220-A-U302, this case occurred on the placebo arm; no pregnancies have been reported in quizartinib-treated subjects in the clinical development program.

There are no human data on the effect of quizartinib on fertility. Based on findings in animals, female and male fertility may be impaired with treatment with quizartinib.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that embryo-fetal toxicity was observed in animal studies and is a potential risk to humans. Therefore, embryo-fetal toxicity has been included in warnings and precautions section of the USPI. Lastly, impaired fertility was observed in animal studies and this information was also included in the USPI.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Quizartinib is currently being investigated in the Phase 1/2 pediatric study, AC220-A-U202, in R/R *FLT3*-ITD (+)AML.

Study AC220-A-U202 (NCT03793478) is ongoing to evaluate the safety, PK, PD, and efficacy of quizartinib in combination with fludarabine and cytarabine (FLA) chemotherapy for re-induction chemotherapy, and as a single agent continuation therapy in pediatric R/R *FLT3*-ITD (+) AML subjects aged ≥ 1 month old to 18 years old (and young adults up to 21 years old). As of September 2022, 9 subjects (aged between 3 and 17 years old) have been treated in the Phase 1 dose-escalation cohort with quizartinib 40 mg/m² if body surface area (BSA) <1.5 m², or 60 mg if BSA ≥ 1.5 m². There were no deaths during treatment; 4 subjects died during the long-term follow-up (3 due to disease progression and 1 due to GVHD after bone marrow transplant). A DLT occurred in 1 subject: delayed ANC and platelet recovery. TESAEs were reported by 7 subjects; none of the reported TESAe were fatal. Apart from SAEs of sepsis and febrile neutropenia, which were both reported by 2 subjects each, the remaining events were reported by single subjects and included: empyema, streptococcal sepsis, bilirubin conjugated increased, sinus tachycardia, seizure, dyspnea, hypoxia, pulmonary edema, distributive shock, herpes zoster reactivation, and anal fissure. Two subjects discontinued study treatment because of an AE (ECG QT prolonged and thrombocytopenia). The most common Grade ≥ 3 TEAEs were blood cytopenias. No subjects experienced QTcF >500 ms, and 1 subject had QTcF >480 ms.

No new safety signals have been detected and the safety profile is consistent with the known safety profile from quizartinib experience in adult subjects.

Safety and PK continue to be evaluated to determine the recommended Phase 2 for the expansion cohort (≥ 1 to ≤ 21 years) and the dose-escalation cohort for the younger age cohort (≥ 1 month to <1 year old).

The effects of quizartinib on growth have not been assessed and currently remains unknown.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Study AC220-A-U302 is ongoing. The effects of quizartinib on growth have not been assessed. Safety results in the 9 subjects treated to date are comparable to the those observed in adult studies.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

Cumulatively, there have been 3 reports of accidental overdose in the All AML Pool, which were reported as SAEs (ISS Table 4.1.11). Symptoms associated with overdose included vomiting, but there were no effects on QTcF interval duration.

The Applicant's Position:

No studies have been conducted that assess drug overdose, and there is limited clinical experience with quizartinib overdose. Repeated doses up to 450 mg have been clinically evaluated in subjects, and the DLT was prolongation of the QT interval. There are no specific antidotes to quizartinib. For substantial overdose, supportive measures should be provided as necessary, with the evaluation of hematology and ECG monitoring as well as attention to serum electrolytes and concomitant medications that may predispose to QT interval prolongation and/or TdP. Patients should be managed with symptomatic and supportive care.

No studies have been conducted that assess drug abuse. However, given the nature of quizartinib, drug abuse is not anticipated. No studies have been conducted that assess withdrawal or rebound effects of quizartinib. However, given the target patient population and the nature of quizartinib, no such effects are anticipated.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. While higher exposure to the drug would be expected to induce higher rates of adverse events, the fact that the development program tested doses 10-fold greater than the proposed dose in the induction and consolidation setting provides a measure of assurance that accidental overdose within this range of exposure would at least be tolerated temporarily. We agree that supportive care and attention to electrolyte and ECG monitoring would be appropriate based on recommended labeling in general. Lastly, we concur that given the mechanism of action, adverse event profile, and the lack of euphoric effects from use that quizartinib abuse is not anticipated.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

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Version date: July 2021 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Data:

Quizartinib was approved by the MHLW in Japan in June 2019 for the treatment of patients with R/R *FLT3*-ITD (+) AML, as detected by an MHLW-approved assay based on the improved response rates and OS in R/R *FLT3*-ITD (+) AML subjects in a randomized Phase 3 study, referred to as Study AC220-007 (QuANTUM-R; [Cortes, 2019](#)).

Cumulatively as of 28 Oct 2021, an estimated 228 patients have received quizartinib in the postmarketing setting, all of whom were in Japan. The safety profile of quizartinib in the postmarketing setting is consistent with the safety profile as established in the development program, and no new safety concerns have been identified. Reported SAEs were mostly events related to AML disease progression and cytopenias (neutrophil count decreased, and febrile neutropenia). Events related to AML disease progression were also the most common events associated with fatal outcome. Reported AEs of ECG QT prolonged were mostly non-serious and not associated with any ventricular arrhythmia events (eCTD 2.7.4, Section 8).

The Applicant's Position:

Review of post marketing safety data did not reveal any new safety concerns and the reported events were generally consistent with the safety profile established in the quizartinib development program as summarized above.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the post marketing safety data from to date.

Expectations on Safety in the Postmarket Setting

Data:

The safety and tolerability profile of quizartinib has been adequately characterized for use in the intended population in Study AC220-A-U302. The safety profile seen is also consistent with that observed throughout the quizartinib clinical development program as evidenced by data for the 30 to 60 mg dose level in the All AML Pool. QT interval prolongation and the associated potential risk of ventricular arrhythmias and blood cytopenias and infections are the main safety risks for quizartinib in patients with newly diagnosed *FLT3*-ITD (+) AML. The risk of QT prolongation/ventricular arrhythmia has been adequately managed with the risk mitigation procedures implemented in Study AC220-A-U302, which comprise ECG monitoring for QT prolongation, QTcF-based quizartinib dose interruption and reduction, and correction of additional risk factors (eg, monitoring for and correction of electrolyte abnormalities, quizartinib dose modification for concomitant strong CYP3A inhibitor use) and more frequent monitoring of ECG during concomitant therapy with known QT prolongation.

The Applicant's Position:

Management of myelosuppression and associated risk of infections and bleeding is part of the routine clinical practice for the treatment of patients with newly diagnosed AML. In the study, events associated with myelosuppression could be appropriately managed by transfusion and growth factor support, as well as through protocol-specified study drug dose modifications. Overall, the majority of TEAEs of blood cytopenias were managed with study drug interruptions or dose reductions, and few subjects discontinued quizartinib due to these events.

These measures are expected to adequately mitigate the risks conveyed in the proposed label and are readily implemented within standard medical practice for the treatment of newly diagnosed AML. The risk minimization measures for the risk of QT prolongation/ventricular arrhythmias in the quizartinib label will be supplemented by additional communication to prescribers and patients/caregivers.

Safety risks beyond those included in the proposed draft label are not anticipated. The risks of DDIs with strong CYP3A inhibitors, strong and moderate CYP3A inducers, embryo-fetal toxicity, and female and male fertility are also adequately conveyed in the proposed labeling.

The FDA's Assessment:

FDA does not fully agree with the Applicant's assessment. While the FDA does anticipate that the most common AEs related to GI toxicity, cytopenia, and infections are standard in the clinical setting of acute leukemia, the FDA has concluded that additional measures must be implemented to further minimize the risk of ventricular arrhythmias in quizartinib-treated patients. The Applicant has proposed a communication plan REMS to assist with provider and patient education concerning this risk. However, the FDA clinical team concluded that additional active and required education measures should be implemented to ensure the safe use of quizartinib in clinical practice (i.e., REMS with Elements to Assure Safe Use [ETASU]).

8.2.11. Integrated Assessment of Safety

Data:

See data in Sections 8.2.4 and 8.2.5.

In the pivotal study, in both treatment arms, more than half of the deaths during the study were attributed to AML disease progression or to AEs that were considered secondary to AML. More early deaths (ie, deaths within 60 days of the initiation of study drug) occurred with quizartinib compared with placebo. In total, 20 subjects (7.5%) and 13 subjects (4.9%), respectively died within 60 days of the study drug initiation, of which 15 subjects (5.7%) and 9 subjects (3.4%), respectively, died within 30 days of study drug initiation. In both treatment arms, the majority of early deaths were due to AEs (Table 72).

Treatment-emergent AEs associated with death as outcome occurred in 30 subjects (11.3%) in the quizartinib arm and 26 subjects (9.7%) in the placebo arm during the overall study period. In both treatment arms, the most frequently reported TEAEs with an outcome of death

(including early deaths) were due to infections, which occurred mainly in the Induction and Consolidation Phases and were more common in the quizartinib arm (Table 74). Infections are a known risk for subjects with AML receiving induction and consolidation chemotherapy.

More subjects in the quizartinib arm of Study AC220-A-U302 experienced TEAEs associated with study drug discontinuation compared with placebo (54 subjects [20.4%] and 23 subjects [8.6%], respectively). The most frequently reported TEAEs associated with discontinuation of quizartinib were infections (septic shock, sepsis, and pneumonia) and cytopenias (thrombocytopenia, neutropenia, and febrile neutropenia). In the placebo arm, the most common TEAE associated with discontinuation were also infections (pneumonia).

The most frequently reported TEAEs in both treatment arms of Study AC220-A-U302 were gastrointestinal disorders (diarrhea, nausea, and vomiting), infections and infestations (pneumonia and sepsis), general disorders and administration site conditions (pyrexia, oedema peripheral, and fatigue), and blood and lymphatic system disorders (febrile neutropenia, neutropenia, thrombocytopenia, and anemia).

Among the most commonly reported TEAEs ($\geq 20\%$), the events of nausea, vomiting, febrile neutropenia, neutropenia, and headache, occurred more frequently (in $\geq 2\%$ more subjects) in the quizartinib arm than in the placebo arm.

The Applicant's Position:

Safety data from Study AC220-A-U302 were consistent with the safety profile of quizartinib as established over the prior development program and no new safety concerns were identified. The most common types of TEAEs are those commonly seen in subjects with newly diagnosed AML receiving standard intensive chemotherapy and generally occurred at comparable rates in the quizartinib and placebo arms. Blood cytopenias (neutropenia, thrombocytopenia, and anemia) and infections were the most common severe and serious TEAEs and the most common categories of events associated with quizartinib discontinuation, interruption, and dose reduction.

The incidence of TEAEs associated with fatal outcome was low, and the most common fatal TEAEs (including those occurring within 30 and 60 days of the start of quizartinib) were infections, which are a known risk for subjects with AML receiving induction and consolidation chemotherapy.

There was no clinically relevant variability of the safety profile across subpopulations and no evidence of increasing toxicity with long-term treatment with quizartinib for up to 36 cycles (3 years). No new event types were observed among subjects receiving quizartinib >12 cycles (12 months), and the most frequently reported TEAEs occurred at similar incidence rates regardless of length of treatment duration, with the exception of blood disorders, which increased with longer treatment duration. Quizartinib was not associated with clinically apparent drug-induced liver injury.

Quizartinib causes QT interval prolongation in a dose-dependent and exposure-dependent manner, and QT interval prolongation on ECG was commonly observed in Study AC220-A-U302. However, most of the QT prolongation events were of mild or moderate severity and were manageable by quizartinib dose modification and correction of additional risk factors (eg, monitoring for and correction of electrolyte abnormalities, quizartinib dose modification for QTcF prolongation, and for concomitant strong CYP3A inhibitor use) and more frequent monitoring of ECG during concomitant therapy with known QT prolongation. QT prolongation is a risk factor for the occurrence of ventricular arrhythmias, including TdP, which were observed at very low incidence at the recommended doses of quizartinib and generally occurred in subjects with other significant risk factors for cardiac arrhythmia. This further demonstrates that the clinical impact of QT prolongation can be appropriately managed with QTc-based dose modifications, correction of electrolyte abnormalities, and dose adjustments for concomitant use with strong CYP3A inhibitors.

As a substrate of CYP3A, quizartinib should not be administered concomitantly with strong or moderate CYP3A inducers.

Although no data in humans are available that assess the use of quizartinib during pregnancy or breastfeeding or its effect on fertility, nonclinical safety data indicate that quizartinib can be associated with fetotoxicity and teratogenicity if administered during pregnancy and that impaired fertility could occur in treated patients.

Overall, QT interval prolongation and the associated potential risk of ventricular arrhythmias and blood cytopenias and infections are the main safety risks for quizartinib in subjects with newly diagnosed *FLT3*-ITD (+) AML. Results from Study AC220-A-U302 have demonstrated an acceptable safety and tolerability profile of quizartinib in the target population when given in combination with standard induction and consolidation chemotherapy and then continued as monotherapy for up to 36 cycles with the proposed dosing regimen.

The safety data across the quizartinib development program in subjects with AML are consistent with the findings from the pivotal study AC220-A-U302. Apart from DS, which is considered a potential risk for quizartinib monotherapy for the treatment of patients with R/R AML, but is not anticipated to occur in patients with newly diagnosed AML receiving quizartinib in combination with chemotherapy, the safety profile of quizartinib is consistent across different AML indications and patient populations. Similarly, available post marketing safety data for quizartinib in patients with R/R AML have not revealed any additional safety concerns.

The safety results and efficacy observed in Study AC220-A-U302 establish that quizartinib is an effective and well-tolerated treatment option when combined with standard chemotherapy then as continuation monotherapy, for adults with newly diagnosed *FLT3*-ITD (+) AML. Therefore, the Applicant concludes that the data from Study AC220-A-U302 support a positive overall benefit-risk profile for quizartinib for the proposed indication.

The FDA's Assessment:

FDA analysis of safety event rates differed with the Applicant's because of the use of FDA derived group terms as detailed in the Table 94 above. FDA also disagreed with Applicant's root cause of 27 deaths that occurred within 30 days of treatment as noted above. The overall safety profile for quizartinib based on FDA analysis of clinical trials is summarized in Table 111 below.

Table 111: Safety summary of the pivotal study AC220-A-U302 and quizartinib-treated AML patients from the ISS

	AC220-A-U302		ISS AML
	Quizartinib (N=265)	Placebo (N=268)	Quizartinib N = 1081
Total Deaths	130 (49%)	156 (58%)	816 (75%)
30-day Mortality	15 (5.7%)	9 (3.4%)	52 (4.8%)
60-day Mortality	20 (7.5%)	13 (4.9%)	124 (11.5%)
On-treatment deaths*	32 (12%)	25 (9%)	311 (29%)
Grade 5 TEAEs	30 (11%)	26 (10%)	255 (24%)
All-Grade TEAEs	264 (100%)	265 (99%)	1073 (99%)
Grade 3-5 TEAEs	244 (92%)	240 (90%)	965 (89%)
Serious TEAEs (SAEs)	143 (54%)	123 (46%)	725 (67%)
All-Cause discontinuation	212 (80%)	219 (82%)	1005 (93%)
TEAE with discontinuation	58 (22%)	23 (9%)	192 (18%)
* Indicates death that occurred within 30 days of treatment			
Source: FDA analysis using adae.xpt, adsl.xpt			

Total deaths were higher on the placebo arm than the quizartinib arm, which is reflective of the OS analysis. On-treatment deaths and grade 5 TEAEs were similar between arms but slightly

higher on the quizartinib arm, suggesting increased toxicity with quizartinib treatment. Increased toxicity is also reflected in the higher rate of TEAEs with discontinuation and serious TEAEs seen on the quizartinib arm. However, the rate of all-grade TEAEs and Grade 3-5 TEAEs (90% vs 92%) was essentially the same between arms. The increase in toxicity over the placebo arm is not unexpected for an add-on trial design where the backbone therapy is known to carry significant toxicity.

In the ISS AML population, total deaths, on-treatment deaths, Grade 5 TEAEs, and serious TEAEs were higher, likely reflecting the higher acuity of the R/R AML patients; although, higher quizartinib exposure could have contributed. The rate of TEAEs with discontinuation, however, was similar.

The safety profile of the most common TEAEs in Study AC220-A-U302 were generally consistent with those that occur in AML patients undergoing intensive induction and consolidation chemotherapy treatment. It is notable that only a subset of the most frequently occurring TEAEs were increased on the quizartinib arm with others being the same between both arms or higher on the placebo arm. The general category for these common TEAEs increased over placebo were GI toxicity, cytopenias, and infections. It is important to note, as seen by the results of the placebo arm, that these events are common in the clinical context and clinicians that treat AML are experienced with their general management.

Analysis of the safety profile of quizartinib during the maintenance phase of treatment allowed a comparison between quizartinib and placebo without the high background rate of TEAEs that occurred with induction and consolidation chemotherapy. As with the first two phases of treatment, the most common TEAEs that were increased with quizartinib treatment over placebo were cytopenias, infections, and GI toxicity. Interestingly, when these common TEAEs were further assessed in patient based on their transplant status, we saw that patients that had undergone HSCT during consolidation had higher rates of cytopenias and infection TEAEs during the maintenance phase than patients that had only undergone chemotherapy consolidation. This showed that maintenance therapy was less well tolerated post-HSCT consolidation than in patients that had only undergone chemotherapy consolidation.

The toxicity that occurs with quizartinib treatment that is not common in AML or from standard treatment is QT prolongation and risk of ventricular arrhythmias. Indeed, 2/265 (0.8%) of quizartinib treated patients had a cardiac arrest during the first phase of treatment on Study AC220-A-U302. While the Applicant notes that rate of QT prolongation seems manageable compared to other QT prolonging medications, the risk of cardiac arrest is not accurately reflected from this rate. FDA has concluded that the novel mechanism of QT prolongation increases the risk of cardiac arrest beyond the risk that would be otherwise suggested by more traditional QT prolonging medications (I_{Kr} inhibitors). This might be due to concomitant QT prolonging medications synergizing with quizartinib or to baseline QTc changes incompletely capturing the risk of ventricular arrhythmia for I_{Ks} inhibitors. Therefore, FDA concludes that

additional risk mitigations measures that ensure clinician education of these unique aspects of quizartinib mechanism of QT prolongation and mitigation measures are required for safe use in clinical practice.

Therefore, to mitigate the risks of serious and fatal cardiac toxicities, we recommend a REMS with ETASU to 1) ensure prescribers are able to identify the unique QT prolonging mechanism of quizartinib, 2) sure prescribers are able to identify the risk factors that are associated with Torsades de Pointes and cardiac arrest with quizartinib, and 3) ensure prescribers are able to identify the importance of providing risk mitigation measures including QTc interval monitoring, electrolyte monitoring and repletion, avoidance of concomitant QTc prolonging medications, and dose modifications/dose interruptions when indicated. With these additional safety measures, FDA agrees with the Applicant that based on the totality of efficacy and safety data, the benefit/risk profile of quizartinib in the treatment of patients with newly diagnosed *FLT3*-ITD AML is favorable.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

QuANTUM-First demonstrated a statistically significant effect on OS, with HR 0.78 (95% CI: 0.62, 0.98). No improvement was demonstrated for the key secondary endpoint of EFS. Of note, the EFS results are sensitive to choice of window for induction failure (defined per protocol as failure to achieve CR within 42 days of the start of the last cycle of induction chemotherapy). Exploratory analyses suggest that long duration of CR is observed with quizartinib (median duration of CR 38.6 months).

Based on our current analyses of data from QuANTUM-First, we note that patients may not benefit from quizartinib continuation/maintenance therapy post-HSCT. In an exploratory subgroup analysis of the 89/208 (43%) of patients who received maintenance therapy with VANFLYTA or placebo following consolidation chemotherapy, the OS HR was 0.40 (95% CI: 0.19, 0.84). Of 119/208 (57%) of patients who received maintenance therapy with VANFLYTA or placebo following HSCT, the OS HR was 1.62 (95% CI: 0.62, 4.22). For RFS, the corresponding hazard ratios were 0.93 (95% CI: 2.00) and 0.71 (95% CI: 0.35, 1.43). As the unadjusted analyses do not account for the unbalance in post-randomization variables and/or baseline characteristics between treatment arms among patients who entered Continuation, additional analyses attempted to account for such features. Results from these adjusted analyses were similar. Thus, these analyses suggest inconclusive evidence regarding use of quizartinib as continuation/maintenance therapy after HSCT.

While QuANTUM-First demonstrated a statistically significant effect on OS, questions remain about which patients in the intended population have a positive benefit-risk. Early OS (<6 months) was lower in the quizartinib arm due in part to increased infections. No single subgroup appears to be driving this effect. Likewise, it is unclear whether quizartinib continuation provides any benefit to patients who receive HSCT. Though this conclusion is based on exploratory post-hoc analyses, a more formal analysis is not possible since QuANTUM-First was inadequately designed to isolate the effect of continuation therapy. To date, no FLT3 TKI has definitively demonstrated improved efficacy for continued treatment following HSCT (Levis, 2019).

8.4. Conclusions and Recommendations

The FDA's Assessment:

The review team was able to verify or clarify the efficacy and safety endpoints as provided by the Applicant. Substantial evidence of effectiveness was established based on improvement in overall survival demonstrated on the quizartinib treatment arm of the adequate and well controlled clinical Study AC220-A-U302 and on the supporting evidence provided by Study AC220-007 demonstrating achievement of CR+CRh with quizartinib monotherapy in the R/R setting. The review team noted that while maintenance appeared to benefit patients who had not undergone HSCT, those that had undergone HSCT did not benefit from quizartinib maintenance. Ultimately, there was inadequate demonstration of favorable benefit-risk for quizartinib maintenance post-HSCT. See Sections 1 and 8 for more information. This led to the limitations of use statement that quizartinib is not indicated as maintenance monotherapy following allogenic hematopoietic stem cell transplant as improvement in OS with quizartinib in this setting has not been demonstrated. Lastly, the review team did not find the original management plan proposed by the Applicant sufficient to mitigate quizartinib-induced QTc prolongation and the risk of fatal cardiac arrhythmia. The review team asked the Applicant to develop an adequate REMS program to mitigate these risks, which the Applicant assented to at the end of the review cycle. Review of the REMS program follows below in section 12.

X

X

Primary Statistical Reviewer

Statistical Team Leader

X

X

Primary Clinical Reviewer

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

Meetings with two separate Special Government Employees (SGEs) were conducted on February 27, 2023 and March 6, 2023. Noting the lack of statistical significance of the secondary efficacy endpoints of EFS and CR rate on QuANTUM-First, the lack of an OS benefit in patients treated with quizartinib maintenance post-HSCT, and the unique risk of QTc prolongation, FDA requested a discussion of benefit-risk for the proposed indication, as well as the need for additional education and risk mitigation measures to prevent serious and potentially fatal arrhythmias. The Agency requested that the SGE comment on the following:

1. Whether quizartinib has a favorable benefit-risk profile for its proposed indication "...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."
2. If the SGE concludes that the benefit-risk profile is favorable, the Agency requests commentary on the following items:
 - a. Whether the benefit-risk profile is favorable for quizartinib continuation monotherapy following consolidation chemotherapy and/or HSCT.
 - b. Whether additional education and risk mitigation measures are needed (e.g., communication plan, certification of healthcare providers and pharmacists, etc.), in addition to a boxed warning, to convey information and management guidelines on quizartinib's unique, serious, and potentially fatal risk of arrhythmias.

The two SGEs concluded that quizartinib has a favorable benefit-risk for use in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy. Both SGEs, however, noted concerns with the benefit of post-HSCT maintenance therapy with quizartinib. SGE #1 expressed concerns regarding isolation of the impact of maintenance without having randomization just prior to initiation of maintenance. They conveyed that there is no evidence to support the efficacy of post-HSCT maintenance and only weak evidence of benefit post-consolidation chemotherapy in the absence of HSCT. They thought, however, that physicians would likely use the product for maintenance in patients tolerating the drug in the absence of HSCT. SGE #2 noted an unlikely benefit of maintenance therapy in the post-HSCT setting, but that without HSCT, patients appeared to benefit from post-consolidation therapy. They noted reservations with over-interpretation of the subgroup

data, which may lead physicians to prescribe quizartinib the way it was administered on the study. They encouraged conveying the additional data on the impact of maintenance to physicians so that they could justify variations from how the study was conducted.

Regarding the unique, serious and potentially fatal risk of arrhythmias, the two SGEs concluded that the risk demonstrated in the trial and the unique mechanism of QT prolongation necessitated measures beyond labeling to effectively educate the relevant providers. SGE#1 noted that with number of drugs now reported to prolong the QT interval, that physicians have become blasé about QT prolongation and would not appreciate the additional risk incurred by blockade of the slow potassium channel. SGE#2 also noted that required education that clearly conveys the unique and serious risks of blockage of this alternative potassium channel would be critical to the safe use of quizartinib. They both noted that a required REMs program that provided a brief overview of the novel mechanism of action would be essential to mitigate this potentially fatal risk. The REMS program should also educate the providers on the important factors common to TdP cases (females, severe hypokalemia, concomitant QT prolonging medications) in addition to appropriate management of quizartinib when these risks occur. They both noted that required REMS training for various products have become a requirement of attending on inpatient leukemia services and that these trainings have not been overly burdensome.

10 Pediatrics

The Applicant's Position:

The Applicant and FDA reached agreement on an agreed initial Pediatric Study Plan (Ref. ID 4895995). Per this agreement, the Applicant is including in this application a waiver request for the conduct of studies in pediatric subjects <1 month with *FLT3*-ITD (+) AML on the grounds that such studies would be highly impractical due to the rarity of *FLT3*-ITD mutation in this age group. Per the same agreement, the Applicant is including in this application a request for deferral of submission of results from agreed upon pediatric studies (ie, the study reports) of quizartinib for all ages ≥1 month because the drug product is anticipated to be ready for approval for use in adult subjects with *FLT3*-ITD (+) newly diagnosed AML before the clinical pediatric studies agreed upon are complete as provided for under 21 U.S.C. 355c(4)(A)(i)(I). Pursuant to the agreed upon initial Pediatric Study Plan, the Applicant is conducting Study AC220-A-U202 ([NCT03793478](#)) in addition to a modeling and extrapolation study to generate efficacy data from the adult newly diagnosed *FLT3*-ITD (+) AML Study AC220-A-U302 that is supporting this application.

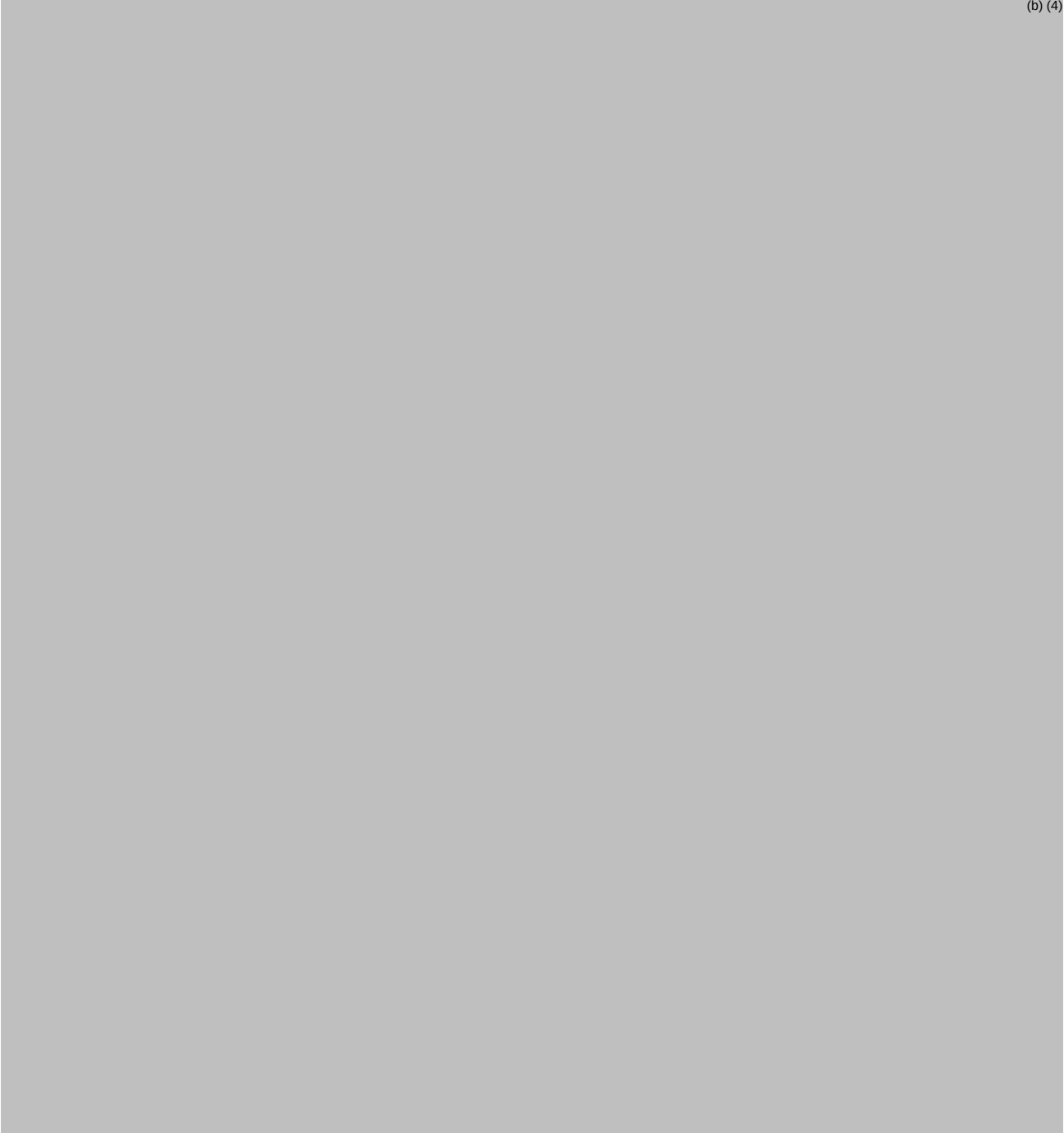
The FDA's Assessment:

FDA agrees with the Applicant's assessment of their pediatric studies. Study AC220-A-U202 has been open for several years and has been slowly accruing patients. Despite being ongoing, the study has not yet achieved its objective to complete assessment of quizartinib in pediatric patients. Therefore, the Applicant's request for deferral is permissible. Moreover, FDA agrees that partial waiver for study of pediatric patients less than one year of age is also permissible. Lastly, completion and submission of a final CSR for Study AC220-A-U202 will be included as a PMR for quizartinib approval as detailed in section 13.

11 Labeling Recommendations

Data: The table below provides a high-level summary of the changes made by the FDA to the US Prescribing Information (USPI) for VANFLYTA (quizartinib) NDA 216993; see the USPI and Medication Guide attached to the approval letter for final labeling.

(b) (4)



The Applicant's Position:

Based on the results from Study AC220-A-U302, the Applicant proposes the label components summarized in the table above.

The FDA's Assessment:

FDA revised the USPI and MG as described in the table above.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The Division of Risk Management (DRM) in the Office of Surveillance and Epidemiology (OSE) reviewed this Application and concurs with the review team that additional risk evaluation and mitigation strategies (REMS) are required to ensure the risks of quizartinib can be adequately managed in the post-marketing setting.

The specific goal of the REMS with elements to assure safe use (ETASU) is to mitigate the risk of

severe and fatal cardiac arrhythmias by ensuring that prescribers are able to identify the unique QT prolonging mechanism of quizartinib, risk factors associated with Torsades de Pointes and cardiac arrest with quizartinib, and the importance of providing risk mitigation measures including QTc interval monitoring, electrolyte monitoring and repletion, avoidance of concomitant QTc prolonging medications, and dose modification/dose interruptions when indicated.

Components of the REMS for quizartinib will include ETASU A (certification of prescribers) and ETASU B (certification of pharmacies that dispense quizartinib). Under ETASU A, prescribers must obtain certification by enrolling and completing training including a knowledge assessment regarding the risks of cardiac arrhythmias and agree to counsel patients on the risks and provide them with a patient wallet card. Under ETASU B, pharmacies must be certified and verify that prescribers are certified before dispensing quizartinib.

As part of the REMS, the Sponsor must submit REMS Assessments annually from the date of the initial approval. Depending on the findings from formal assessment of the REMS, FDA may modify the REMS or consider other regulatory actions. In the future, if the REMS assessments and/or data from other sources indicates that prescribers have gained familiarity with the risks of cardiac arrhythmias with quizartinib and are taking appropriate actions to reduce and manage the risks, FDA may re-evaluate the REMS to determine if continuation of REMS is necessary.

Refer to REMS review from DRM for additional details.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following PMRs/PMCs will be issued to the Applicant:

1. PMR #1: Conduct a clinical study to confirm the appropriate dose of quizartinib, and to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of quizartinib in combination with fludarabine and cytarabine, in pediatric patients ages ≥ 1 month to < 18 years with relapsed/refractory FLT3-ITD positive AML. Patients should be followed for at least 12 months (52 weeks). Include at least 16 patients ≥ 1 month to < 18 years old, including a minimum of 4 patients < 12 years old.
2. PMR #2: Conduct an exercise test study in healthy subjects to further evaluate the serious risk of QTc prolongation with quizartinib. Evaluate the impact of rapid acceleration in heart rate on the cardiac safety of quizartinib using a standardized test protocol such as Bruce protocol, modified Bruce protocol, or graded-intensity bicycle exercise test. Identify QT/QTc and RR intervals at rest, peak exercise, and recovery, and capture the incidence of arrhythmias and other adverse reactions.
3. PMR #3: Conduct a sub-maximal exercise test study in patients with AML to further evaluate the serious risk of QTc prolongation with quizartinib. Evaluate the impact of rapid acceleration in heart rate on the cardiac safety of quizartinib using a 24-Hour Holter study with sub-maximal exercise (e.g., postural provocation – i.e., supine to standing). Identify QT/QTc and RR intervals at rest and sub-maximal exercise and capture the incidence of arrhythmias and other adverse reactions. Include patients on beta-blockers in order to observe for mitigating effects on the incidence of quizartinib-related adverse reactions.
4. PMR #4: Conduct a randomized trial of quizartinib maintenance therapy that compares the recommended dosage of 53 mg daily to a lower dosage (e.g., 26.5 mg daily) to further characterize serious adverse reactions including but not limited to the rates of Grade ≥ 3 adverse reactions, Grade ≥ 3 neutropenia, QTc interval prolongation, and dose reductions, interruptions, and discontinuations due to adverse reactions and provide an analysis of dose- and exposure-response relationships for safety. Incorporate systematically assessed patient-reported outcome assessments to further characterize safety and tolerability, including patient-reported symptoms, function, and overall side effect impact. Eligible patients will include newly diagnosed, FLT3-ITD positive AML patients in complete remission following consolidation and exclude patients who underwent allogeneic hematopoietic stem cell transplantation. The study should also provide an analysis of dose- and exposure-response relationships for efficacy, including overall survival and relapse-free survival.

5. PMR #5: 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.
6. PMR #6: Conduct a clinical pharmacokinetic trial to assess the magnitude of change in exposure of quizartinib and its metabolite AC886 and to determine appropriate dosing recommendations of quizartinib in patients with severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.
7. PMC #1: Conduct exploratory analyses aimed at identifying potential mechanisms of primary and acquired resistance to quizartinib using longitudinal samples for cytogenetic and mutational analyses collected at baseline and at the end of treatment or time of relapse from patients treated with quizartinib in QuANTUM-First. Include a discussion of the results in the context of the available published literature.
8. PMC #2: Conduct a clinical pharmacokinetic trial to assess the magnitude of decreased exposure of quizartinib and its metabolite AC886, and to determine appropriate dosing recommendations for quizartinib, with coadministration of a weak CYP3A inducer. Design and conduct the trial in accordance with the FDA Guidance for Industry: Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.

14 Division Director (DHOT) (NME ONLY)

Haleh Saber, PhD

15 Division Director (OCP)

Brian Booth, PhD

16 Division Director (OB)

Yuan-Li Shen, PhD

17 Division Director (Clinical)

R. Angelo de Claro, MD

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Marc Theoret, MD

19 Appendices

19.1. References

The Applicant's References:

Afessa B, Peters SG. Major complications following hematopoietic stem cell transplantation. *Semin Respir Crit Care Med*. 2006; 27(3):297-309.

Altman JK, Foran JM, Pratz KW, et al. Phase 1 study of quizartinib in combination with induction and consolidation chemotherapy in patients with newly diagnosed acute myeloid leukemia. *Am J Hematol*. 2018; 93(2):213-21.

Aikawa T, Togashi N, Iwanaga K, et al. Quizartinib, a selective FLT3 inhibitor, maintains antileukemic activity in preclinical models of RAS-mediated midostaurin-resistant acute myeloid leukemia cells. *Oncotarget*. 2020 Mar 17;11(11):943-55.

Baluch A, Shewayish S. Neutropenic Fever. *Infections in Neutropenic Cancer Patients*. 2019;105-17.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics*. 1982; 38(1):29-41.

Burnett AK, Bowen D, Russell N. AC220 (quizartinib) can be safely combined with conventional chemotherapy in older patients with newly diagnosed acute myeloid leukaemia: experience from the AML18 pilot trial. *Blood*. 2013; 122(21):622.

Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol*. 2003;21(24):4642-9. Erratum in: *J Clin Oncol*. 2004;22(3):576.

Cortes JE, Khaled S, Martinelli G, et al. Quizartinib versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial [published correction appears in *Lancet Oncol*. 2019 Jul;20(7):e346]. *Lancet Oncol*. 2019; 20(7):984-97.

De Kouchkovsky I, Abdul-Hay M. Acute myeloid leukemia: a comprehensive review and 2016 update. *Blood Cancer J*. 2016; 6(7):1-10.

Deschler B, Binek K, Ihorst G, et al. Prognostic factor and quality of life analysis in 160 patients aged > or =60 years with hematologic neoplasias treated with allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2010 Jul;16(7):967-75.

Dimopoulos MA, Delforge M, Hajek R, et al. Lenalidomide, melphalan, and prednisone, followed by lenalidomide maintenance, improves health-related quality of life in newly diagnosed

multiple myeloma patients aged 65 years or older: results of a randomized phase III trial. *Haematologica*. 2013 May;98(5):784-8.

Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017; 129(4):424–47.

Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015; 373(12):1136-52.

FDA, Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Draft guidance for industry: acute myeloid leukemia: developing drugs and biological products for treatment; Aug 2020 [cited 13 May 2022]. Available from: <https://www.fda.gov/media/140821/download>

Grimwade D, Walker H, Harrison G, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11. *Blood* 2001; 98:1312-20.

Heuser M, Ofran Y, Boissel N, et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncol*. 2020; 31(6):697-712.

Ishizuka H, Konno K, Shiina T, et al. Species differences in the transport activity for organic anions across the bile canalicular membrane. *J Pharmacol Exp Ther*. 1999; 290(3):1324-30.

Kennedy VE, Smith CC. FLT3 mutations in acute myeloid leukemia: key concepts and emerging controversies. *Front Oncol*. 2020; 10:612880.

Kottaridis P, Gale R, Frew M, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. *Blood*. 2001; 98(6):1752-9.

Levis M, Pham R, Smith BD, et al. In vitro studies of a FLT3 inhibitor combined with chemotherapy: sequence of administration is important to achieve synergistic cytotoxic effects. *Blood*. 2004; 104(4):1145-50.

Lyman SD, Jacobsen SE. c-KIT ligand and Flt3 ligand: stem/progenitor cell factors with overlapping yet distinct activities. *Blood*. 1998; 91:1101-34

McClure NS, Sayah FA, Xie F, et al. Instrument-defined estimates of the minimally important difference for EQ-5D-5L index scores. *Value Health*. 2017 Apr;20(4):644-50.

Mead AJ, Linch DC, Hills RK, et al. FLT3 tyrosine kinase domain mutations are biologically distinct from and have a significantly more favorable prognosis than FLT3 internal tandem duplications in patients with acute myeloid leukemia. *Blood*. 2007; 110(4):1262-1270.

- Nepomuceno R, Rooks A, Gardner M, et al. Differential inhibition of FLT3-ITD, FLT3 WT and KIT by quizartinib as assessed by modified PIA Assay. *Blood*. 2014; 124(21):951.
- Ninomiya M, Ito K, Horie T. Functional analysis of dog multidrug resistance-associated protein 2 (MRP2) in comparison with rat MRP2. *Drug Metab Dispos*. 2005; 33(2):225-32.
- Norsworthy KJ, Mulkey F, Scott EC, et al. Differentiation syndrome with ivosidenib and enasidenib treatment in patients with relapsed or refractory IDH-mutated AML: A U.S. Food and Drug Administration systematic analysis. *Clin Cancer Res*. 2020;26(16):4280-8.
- Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016; 374(23):2209-21.
- Patel JP, Gonen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med*. 2012; 366(12):1079-89.
- Pollyea DA, Bixby D, Perl A, et al. NCCN Guidelines Insights: Acute Myeloid Leukemia, Version 2.2021. *J Natl Compr Canc Netw*. 2021; 19(1):16-27.
- Roussel M, Hebraud B, Hulin C, et al. Health-related quality of life results from the IFM 2009 trial: treatment with lenalidomide, bortezomib, and dexamethasone in transplant-eligible patients with newly diagnosed multiple myeloma. *Leuk Lymphoma*. 2020 Jun;61(6):1323-33.
- Sasaki J, Kadia T, Began K, et al. Prediction of early (4-week) mortality in acute myeloid leukemia with intensive chemotherapy. *Am J Hematol*. 2022; 97(1):68-78.
- Sato T, Yang X, Knapper S, et al. FLT3 ligand impedes the efficacy of FLT3 inhibitors in vitro and in vivo. *Blood*. 2011; 117(12):3286-3293.
- SEER Cancer statistics factsheets. Acute Myeloid Leukemia. Bethesda MD, Cancer Institute [accessed 2021 May 27]. Available from: <https://seer.cancer.gov/Statfacts/html/amyl.html/>. Accessed on 27 May 2021.
- Schlenk RF, Weber D, Fiedler W, et al. Midostaurin added to chemotherapy and continued single-agent maintenance therapy in acute myeloid leukemia with FLT3-ITD. *Blood*. 2019; 133(8):840-51.
- Sexauer A, Perl A, Yang X, et al. Terminal myeloid differentiation in vivo is induced by FLT3 inhibition in FLT3/ITD AML. *Blood*. 2012 Nov 15;120(20):4205-14.
- Siegel RL, Miller KD, Fuchs H, et al. Cancer statistics, 2022. *CA Cancer J Clin*. 2022; 72(1):7-33.
- Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017; 377(5):454-64.
- Styczyński J, Tridello G, Koster L, et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. *Bone Marrow Transplant*. 2020; 55(1):126-36.

Thein MS, Ershler WB, Jemal A, et al. Outcome of older patients with acute myeloid leukemia: an analysis of SEER data over 3 decades. *Cancer*. 2013; 119(15): 2720-2727.

Thiede C, Steudel C, Mohr B, et al. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. *Blood*. 2002; 99(12):4326-35.

Yang X, Sexauer A, Levis M. Bone marrow stroma-mediated resistance to FLT3 inhibitors in FLT3-ITD AML is mediated by persistent activation of extracellular regulated kinase. *Br J Haematol*. 2014; 164(1):61-72.

The FDA's References:

Astellas and BMT CTN Announce Topline Results from Phase 3 MORPHO Trial of Gilteritinib. 2023. <https://www.astellas.com/en/news/27421>

Döhner H., Wei A., Appelbaum F., et al.; Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood* 2022; 140 (12): 1345–1377. doi: <https://doi.org/10.1182/blood.2022016867>

RYDAPT (midostaurin) Capsules, Cross Discipline Team Leader Review, 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207997Orig1Orig2s000CrossR.pdf

FDA Briefing Document: Oncologic Drugs Advisory Committee Meeting, NDA 212166, Vanflyta (Quizartinib). 2019. <https://www.fda.gov/media/124896/download>

Guidance for Industry: Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment. 2022. <https://www.fda.gov/media/162362/download>

Jen EY, Chia-Wen K, Jee EL, et al. FDA Approval: Gemtuzumab ozogamicin for the treatment of adults with newly-diagnosed CD33-positive acute myeloid leukemia. *Clin Cancer Res* February 23 2018 DOI: 10.1158/1078-0432.CCR-17-3179

Jen EY, Wang X, Li M, Li H, Lee S-L, Ni N, Przepiorka D, Vallejo J, Leong R, Ma L, Gehrke BJ, McLamore S, Theoret MR, de Claro RA. FDA Approval Summary: Oral Azacitidine for Continued Treatment of Adults with Acute Myeloid Leukemia Unable to Complete Intensive Curative Therapy. *Clin Cancer Res*. 2022 Jul 15;28(14):2989-2993.

Levis MJ, Erba HP, Montesinos P, Vrhovac R, Patkowska E, Kim H, Zak P, et al. Quantum-First Trial: FLT3-ITD-Specific MRD Clearance Is Associated with Improved Overall Survival. *Blood* 140, no. Supplement 1 (2022): 546-548.

Levis MJ, Chen Y-B, Hamadani M, Horowitz MM, Jones RJ, et al. FLT3 Inhibitor Maintenance After Allogeneic Transplantation: Is a Placebo-Controlled, Randomized Trial Ethical? J Clin Oncol 2019 37:19, 1604-1607.

Walter RB, Kantarjian HM, Huang X, Pierce SA, Sun Z, Gundacker HM, Ravandi F, Faderl SH, Tallman MS, Appelbaum FR, Estey EH. Effect of complete remission and responses less than complete remission on survival in acute myeloid leukemia: a combined Eastern Cooperative Oncology Group, Southwest Oncology Group, and M. D. Anderson Cancer Center Study. J Clin Oncol. 2010 Apr 1;28(10):1766-71. doi: 10.1200/JCO.2009.25.1066. Epub 2010 Feb 16. PMID: 20159819; PMCID: PMC2849766.

Yee KWH, O'Farrell AM, Smolich BD, et al. SU5416 and SU5614 inhibit kinase activity of wild-type and mutant FLT3 receptor tyrosine kinase. Blood. 2002; 100(8): 2941-2949. DOI 10.1182/blood-2002-02-0531

19.2. Financial Disclosure

The Applicant's Position:

The Applicant provided financial disclosure information for clinical investigators involved in the covered clinical Study AC220-A-U302. There were 0 clinical investigators with disclosable financial interests or agreements under the significant payments of other sorts financial disclosure category. No concerns were raised regarding the overall integrity of the study data.

Despite the Applicant's due diligence attempting to obtain the information, the Applicant was unable to obtain financial disclosure information for 26 investigators for Study AC220-A-U302. The Applicant has not made any significant payments of other sorts to these investigators.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Covered Clinical Study (Name and/or Number):* AC220-A-U302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2095		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>n/a</u> Significant payments of other sorts: <u>n/a</u> Proprietary interest in the product tested held by investigator: <u>n/a</u> Significant equity interest held by investigator in study: <u>n/a</u> Sponsor of covered study: <u>n/a</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>26</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

All data are included in Section 5.

The FDA's Assessment:

FDA agrees that relevant information and data are under Section 5.

19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1. Bioanalytical Methods Section

In the AC220-A-U302 trial, a validated HPLC/MS/MS methods was used to quantitate quizartinib and its major, active, metabolite AC886. The method is summarized below.

Bioanalytical method validation report name, amendments, and hyperlinks	Quantification of quizartinib (AC220) and AC886 in K ₂ EDTA human plasma by LC-MS/MS (Module 5.3.1.4 Report 1000-141851-1) Long-term stability experiment of quizartinib (AC220) and its metabolite AC886 in human plasma (Module 5.3.1.4 Report 1000-141851-1 Addendum 1) Additional long-term stability, additional matrix factor experiment, Selectivity towards Lipemic Plasma, Selectivity towards Co-administered Drugs, Stability Program with Co-administered Drug and Additional AC886-d ₄ Stock Stability (Module 5.3.1.4 Report 1000-141851-1 Addendum 2)
Method description	Quizartinib (AC220) and AC886 were quantitatively measured from human K ₂ EDTA plasma using an LC-MS/MS method. Plasma samples containing analytes were mixed with deuterated internal standards (IS) and deproteinized by organic solvents and filtered, followed by evaporation to dryness of the eluate and then reconstitution of the residue. Extracted samples were analyzed by reverse-phase chromatography with detection using a triple quadrupole mass spectrometer with an electrospray ion source operated in positive ionization mode.
Materials used for calibration curve & concentration	Matrix: Human K ₂ EDTA plasma Analytes: Quizartinib, AC886 Internal Standards: quizartinib-d ₄ , AC886-d ₄ Calibration Curve concentrations: 0.500 (LLOQ), 1.00, 5.00, 25.0, 150, 300, 450, and 500 ng/mL (ULOQ)
Validated assay range	0.500 ng/mL to 500 ng/mL
Material used for QCs & concentration	Matrix: Human K ₂ EDTA plasma Analytes: Quizartinib, AC886 Internal Standards: quizartinib-d ₄ , AC886-d ₄ QC Samples: 1.50 ng/mL, 50.0 ng/mL, 250 ng/mL, 400 ng/mL

NDA Multi-disciplinary Review and Evaluation {NDA 216993}
{VANFLYTA; quizartinib}

Minimum required dilutions	Minimum required dilution (MRD) is not applicable for small molecule LC-MS/MS.		
Source & lot of reagents (LBA)	Supplier	Quizartinib/Quizartinib-d4 (IS)	AC886/AC886-d4 (IS)
Source & lot of reagents (LBA)	Supplier	Quizartinib/Quizartinib-d4 (IS)	AC886/AC886-d4 (IS)
		Ambit Biosciences	Ambit Biosciences
	Lot No.	HQ00005/11-00181-01	006/11-00182-01
Regression model & weighting	Linear regression ($y = ax+b$) with $1/x^2$ weighting factor		
Validation parameters	Method validation summary		
Calibration curve performance during accuracy & precision	Number of calibration standards from LLOQ to ULOQ for both analytes		8
QC Performance during accuracy & precision	Cumulative precision (%CV) from LLOQ to ULOQ		
	Quizartinib:		≤5.3%
	AC886:		≤6.0%
	5 QCs (LLOQ QC, LQC, LMQC, MQC, HQC)		
	Cumulative intra-run accuracy (Bias%):		
	Quizartinib:		-9.4 to 7.2%
	AC886:		-4.6 to 7.2%
	Cumulative intra-run precision (%CV):		
	Quizartinib:		≤6.8%
	AC886:		≤5.7%
	Cumulative inter-run accuracy (%Bias):		
	Quizartinib:		-3.3 to 4.4%
	AC886:		-2.0 to 5.8%
	Cumulative inter-run precision (%CV):		
	Quizartinib:		≤8.2%
	AC886:		≤6.3%
	Total error		Not analyzed
Selectivity & matrix effect	Selectivity was tested using 6 lots of blank matrix. No interference observed in the matrix at the retention window of either analytes or internal standards. Matrix effect was tested using 6 lots of blank matrix extraction spiked with analytes at LQC and HQC against neat spikes. Internal standard normalized matrix factors are: Quizartinib: 0.99 to 1.02 with CV% ranged from 1.3 to 1.5%. AC886: 0.965 to 0.991 with CV% ranged from 1.4 to 3.4 %. No matrix effect observed.		

NDA Multi-disciplinary Review and Evaluation {NDA 216993}
{VANFLYTA; quizartinib}

Interference & specificity	Interference & specificity were evaluated in blank matrix, LQC and HQC spiked with the interfering drugs (and some of their metabolites) and common OTCs. The blank matrix samples were measured to be below LLOQ. For spiked QC responses: Quizartinib: Bias% ranged from -8.3 to 2.7% with CV%≤2.9%. AC886: Bias% ranged from -4.0 to -2.0% with CV%≤4.3. No impact from co-administered drugs or common OTCs to the quantitation of either analyte (furosemide, lansoprazole, propranolol, spironolactone and rifaximin).					
Hemolysis effect ^a	Hemolytic effect was tested at LQC and HQC using plasma with 2% (v/v) of lysed blood. Quizartinib: Bias% ranged from -4.0 to -3.3% with CV%≤8.3% AC886: Bias% ranged from -2.3 to 0.7% with CV%≤3.4%. No hemolysis effect observed.					
Lipemic effect ^a	Lipemic effect was tested with 6 lots of blank hyperlipidemic (2% lipid) matrix and spiked with LLOQ level. The responses from blank hyperlipidemic matrix relative to LLOQ were measured to be below 5% for quizartinib and below 4% for AC886. For 6 different lipidemic blank matrix samples spiked at LLOQ level: Quizartinib: Mean response Bias% is 0.8% with CV% ≤3.9%. AC886: Mean response Bias% is 5.8% with CV%≤5.7%. No lipemic effect observed.					
Dilution linearity & hook effect	Dilution linearity was established at 1500 and 5000 ng/mL (n = 6) using a factor of 20. Back-calculated mean values of 6 replicates against nominal for: Quizartinib: Bias% ranged from -3.3% to 2.6% with %CV ≤3.5% AC886: Bias% ranged from -6.0% to 1.0 % with %CV ≤2.6% The hook effect evaluate is not applicable for LC/MS/MS assay.					
Bench-top/process stability	Bench-top stability (short term) was established by using LQC and HQC for 24 hours at RT. Quizartinib: %Bias from -3.3% to -2.8% with %CV ≤5.3% AC886 %Bias from -2.0% to 5.3% with %CV ≤4.7% Process stability was established by using LQC and HQC for 84 hours at 2 to 8°C Quizartinib: %Bias from -2.7% to 0.0% with %CV ≤3.0% AC886 %Bias from -1.3% to 7.3% with %CV≤8.0%					
Freeze-Thaw stability	5 freeze-thaw cycles at -20°C and -80°C were established for both analytes at LQC (1.50 ng/mL) and HQC (400 ng/mL).					
	5 freeze-thaw cycles		@-20°C		@-80°C	
			%Bias	%CV	%Bias	%CV
	Quizartinib	LQC	0.7	≤4.5	-11.3	≤6.6
		HQC	-0.8		-9.8	
	AC886	LQC	-4.0	≤3.8	-2.7	≤3.2
HQC		-4.5	-6.5			

Long-term stability^b	Quizartinib was established by using LQC and HQC for: 409 days at -20°C: %Bias from -8.0% to 1.3% with CV% ≤5.5% 728 days at -80°C: %Bias from 6.5% to 12.9% with CV% ≤8.8% AC886 was established by using LQC and HQC for: 959 days at -20°C: %Bias from -7.3% to 12.7% with CV% ≤6.9% 727 days at -80°C: %Bias from 7.8% to 14.7% with CV% ≤3.9%
Parallelism	Not applicable
Carry over	A blank plasma sample (without IS) was injected immediately after ULOQ sample. Small percentage of carryover was observed with no impact data quality.
Clinical Studies	AC220-016, AC220-018, AC220-019, AC220-A-J101, AC220-A-J102, AC220-A-J201, AC220-A-U104, AC220-A-U105, AC220-A-U106, AC220-A-U107, AC220-A-U302

^a Lipemic and additional long-term stability data are summarized in [Report 1000-141851-1 Addendum 2](#).

^b Long-term stability data are summarized in [Report 1000-141851-1 Addendum 1](#).

Sources: Module 5.3.1.4 [Report 1000-141851-1](#), [Report 1000-141851 Addendum 1](#), and [Report 1000-141851 Addendum 2](#).

19.4.2. Population PK Analysis

19.4.1.1 Executive Summary

The FDA's Assessment:

The proposed induction and consolidation dosage and dose adjustments for concomitant strong CYP3A4 inhibitor administration are supported by the population PK (PPK) analysis.

Exposure is expected to be significantly higher following the proposed dosage during maintenance compared to the proposed dosage during induction and consolidation. The acceptability of exposure during maintenance treatment warranted further assessment detailed in Section 19.4.3.2. and additional data is required to determine an appropriate maintenance dose as described by the PMR in Section 6.2.2.3.

PPK analysis did not identify any clinically relevant differences in quizartinib or AC886 exposure according to age, weight, sex, race, weak or moderate CYP3A4 inhibitors, mild or moderate renal impairment, and mild or moderate hepatic impairment. The effect of severe renal impairment and severe hepatic impairment on quizartinib and AC886 PK has not been studied.

19.4.1.2 PPK Assessment Summary

The Applicant's Position:

General Information		
Objectives of PPK Analysis		- Characterize quizartinib and its active metabolite AC886 PK profiles - Identify the source of PK variability to support individualized dosing - Predict individual exposure for E-R assessment in Study AC220-A-U302
Study Included		AC220-014, AC220-015, AC220-016, AC220-018, AC220-A-U105, 2689-CL-0005, AC220-A-J102, 2689-CL-2004, 2689-CL-0011, AC220-A-J101, AC220-A-J201, AC220-007 and AC220-A-U302
Dose(s) Included		20 mg, 30 mg, 40 mg, 60 mg, 90 mg
Population Included		Healthy, Refractory/Relapsed AML, Newly Diagnosed AML
Population Characteristics (Tables 10 and 13)	General	Age median (range) 50.0 years (18.0, 91.0) Weight median (range) 72.0 kg (36.8, 153) Sex: Male 495 (53.1%) Race: 6 (0.6%) American Indian 169 (18.1%) Asian 79 (8.5%) Black 1 (0.1%) Native Hawaiian 603 (64.7%) White 45 (4.8%) Other 29 (3.1%) Missing
	Organ Impairment	Hepatic (NCI): 763 (81.9%) normal; 139 (14.9%) mild; 16 (1.7%) moderate; 14 (1.5%) missing Renal (CrCL): 691 (74.1%) normal; 187 (20.1%) mild; 40 (4.3%) moderate; 4 (0.4%) severe; 10 (1.1%) missing
	Pediatrics (if any)	Not applicable
No. of Subjects, PK Samples, and BLQ		273 healthy subjects and 659 AML subjects. Included in analysis: quizartinib = 14160, AC886 = 13399. BLQ: quizartinib = 1574 (9.9%), AC886 = 2374 (14.9%).
Sampling Schedule	Rich Sampling	Typically as follows but could vary slightly by studies: predose, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 288, 360, 432, and 504 h postdose
	In ITT Population	Typically as follows but could vary slightly by studies: predose, 1, 2, 4, 6, 24 h after the first dose; then predose and 2 h on other designated sampling days during the studies
Covariates Evaluated	Static	Sex, race, Japanese, Chinese or Taiwanese or Hongkongese, Korean, formulation, type of AML, NCI-ODWG grade, renal function, age, body weight, albumin, CrCL, ALT, AST, ALP, TBL
	Time-varying	CYP3A inhibitors, CYP3A inducers, antacids, H2 antagonists, PPI

Final Model	Summary	Acceptability [FDA’s comments]																																																																																																																																																																														
Software and Version	NONMEM version 7.4.4	The structure and model fit of the quizartinib PPK model and the AC886 PPK model are adequate for characterizing the PK profiles of quizartinib and AC886. The Applicant’s Table 20 and Table 25 in the PPK Assessment Summary contain an error in CV and RSE calculation; see final parameter estimates with corrected variance and RSE values in Table 112 and Table 113 . The final quizartinib and AC886 PPK models are adequate for the purpose of providing individual predicted exposure for E-R analyses.																																																																																																																																																																														
Model Structure	<i>Quizartinib: a three-compartment model with sequential zero- and first-order absorption and a first-order elimination from the central compartment. Quizartinib PK varied during the different treatment phases in newly diagnosed AML subjects which was captured by including a phase effect on the relative bioavailability (Frel) in the final model.</i> <i>AC886: a two-compartment model with first-order elimination from the central compartment and first-order formation. The final model included a phase effect on the fraction metabolized from quizartinib (fMET) to correct for the phase effect of quizartinib (Frel).</i>																																																																																																																																																																															
Model Parameter Estimates	Table 20: Parameter estimates of the final model for quizartinib <table><tr><th colspan="5">Final model for quizartinib</th></tr><tr><td>Run</td><td></td><td colspan="3">376</td></tr><tr><td>OFV</td><td></td><td colspan="3">-16373.5</td></tr><tr><td>Condition number</td><td></td><td colspan="3">985.5</td></tr></table> <table><tr><th colspan="5">Final model for quizartinib</th></tr><tr><th></th><th>Unit</th><th>Value</th><th>RSE (%)</th><th>SHR (%)</th></tr><tr><td>CL_{quiz}</td><td>L/h</td><td>6.65</td><td>1.61</td><td></td></tr><tr><td>V_{c,quiz}</td><td>L</td><td>371</td><td>3.13</td><td></td></tr><tr><td>Q_{1,quiz}</td><td>L/h</td><td>40.7</td><td>4.68</td><td></td></tr><tr><td>V_{p1,quiz}</td><td>L</td><td>312</td><td>1.95</td><td></td></tr><tr><td>Q_{2,quiz}</td><td>L/h</td><td>0.757</td><td>3.89</td><td></td></tr><tr><td>V_{p2,quiz}</td><td>L</td><td>91.9</td><td>2.24</td><td></td></tr><tr><td>T_{lag}</td><td>h</td><td>0.196</td><td>4.24</td><td></td></tr><tr><td>k_a</td><td>h⁻¹</td><td>1.10</td><td>6.28</td><td></td></tr><tr><td>D1</td><td>h</td><td>0.710</td><td>6.37</td><td></td></tr><tr><td>Fractional change in CL_{quiz} with strong CYP3A inhibitors</td><td></td><td>-0.301</td><td>7.38</td><td></td></tr><tr><td>Fractional change in F_{rel} with strong CYP3A inhibitors</td><td></td><td>0.273</td><td>10.7</td><td></td></tr><tr><td>F_{rel} for non-AML subjects</td><td></td><td>1.73</td><td>2.96</td><td></td></tr><tr><td>Fractional change in F_{rel} with moderate CYP3A inhibitors</td><td></td><td>0.116</td><td>13.8</td><td></td></tr><tr><td>Fractional change in k_a for non-AML subjects</td><td></td><td>-0.188</td><td>28.9</td><td></td></tr><tr><td>Age effect on V_{p1,quiz}</td><td>1/year</td><td>0.0152</td><td>5.97</td><td></td></tr><tr><td>Fractional change in CL_{quiz} black race</td><td></td><td>-0.261</td><td>38.0</td><td></td></tr><tr><td>Fractional change in V_{c,quiz} for female</td><td></td><td>-0.169</td><td>16.0</td><td></td></tr><tr><td>Fractional change in F_{rel} during Induction</td><td></td><td>-0.419</td><td>4.92</td><td></td></tr><tr><td>Fractional change in F_{rel} during Consolidation</td><td></td><td>-0.192</td><td>15.6</td><td></td></tr><tr><td>Fractional change in F_{rel} during Continuation</td><td></td><td>0.418</td><td>12.5</td><td></td></tr><tr><td>Shape box-cox parameter for IIV on F_{rel} for AML subjects</td><td></td><td>-1.28</td><td>14.4</td><td></td></tr></table> <table><tr><td>IIV Q_{1,quiz}</td><td>(CV)</td><td>(b) (4)</td><td>43.9</td></tr><tr><td>IIV CL_{quiz}</td><td>(CV)</td><td>(b) (4)</td><td>11.8</td></tr><tr><td>IIV V_{c,quiz}</td><td>(CV)</td><td>(b) (4)</td><td>60.2</td></tr><tr><td>IIV T_{lag}</td><td>(CV)</td><td>(b) (4)</td><td>44.5</td></tr><tr><td>IIV k_a</td><td>(CV)</td><td>(b) (4)</td><td>46.6</td></tr><tr><td>IIV D1</td><td>(CV)</td><td>(b) (4)</td><td>38.1</td></tr><tr><td>IIV F_{rel} non-AML subjects</td><td>(CV)</td><td>(b) (4)</td><td>6.58</td></tr><tr><td>IIV F_{rel} AML subjects</td><td>(CV)</td><td>(b) (4)</td><td>17.5</td></tr></table> <table><tr><td>Add. 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CL: clearance; CL_{quiz}: apparent CL of quizartinib; V_{c,quiz}: apparent V_c of quizartinib; Q_{1,quiz}: apparent inter-compartmental clearance 1 of quizartinib; V_{p1,quiz}: apparent V_p 1 of quizartinib; Q_{2,quiz}: apparent inter-compartmental clearance 2 of quizartinib; V_{p2,quiz}: apparent V_p 2 of quizartinib; T_{lag}: lag time; k_a: first-order absorption rate constant; D1: duration of zero-order input to depot compartment; F_{rel}: relative bioavailability; CYP3A: isoenzyme 3A of cytochrome P450; AML: acute myeloid leukemia; CV: coefficient of variation; IIV: interindividual variability; OFV: objective function value; R/R: relapsed/refractory; RSE: relative standard error; RUV: residual unexplained variability; SD: standard deviation; SHR: shrinkage		Final model for quizartinib					Run		376			OFV		-16373.5			Condition number		985.5			Final model for quizartinib						Unit	Value	RSE (%)	SHR (%)	CL _{quiz}	L/h	6.65	1.61		V _{c,quiz}	L	371	3.13		Q _{1,quiz}	L/h	40.7	4.68		V _{p1,quiz}	L	312	1.95		Q _{2,quiz}	L/h	0.757	3.89		V _{p2,quiz}	L	91.9	2.24		T _{lag}	h	0.196	4.24		k _a	h ⁻¹	1.10	6.28		D1	h	0.710	6.37		Fractional change in CL _{quiz} with strong CYP3A inhibitors		-0.301	7.38		Fractional change in F _{rel} with strong CYP3A inhibitors		0.273	10.7		F _{rel} for non-AML subjects		1.73	2.96		Fractional change in F _{rel} with moderate CYP3A inhibitors		0.116	13.8		Fractional change in k _a for non-AML subjects		-0.188	28.9		Age effect on V _{p1,quiz}	1/year	0.0152	5.97		Fractional change in CL _{quiz} black race		-0.261	38.0		Fractional change in V _{c,quiz} for female		-0.169	16.0		Fractional change in F _{rel} during Induction		-0.419	4.92		Fractional change in F _{rel} during Consolidation		-0.192	15.6		Fractional change in F _{rel} during Continuation		0.418	12.5		Shape box-cox parameter for IIV on F _{rel} for AML subjects		-1.28	14.4		IIV Q _{1,quiz}	(CV)	(b) (4)	43.9	IIV CL _{quiz}	(CV)	(b) (4)	11.8	IIV V _{c,quiz}	(CV)	(b) (4)	60.2	IIV T _{lag}	(CV)	(b) (4)	44.5	IIV k _a	(CV)	(b) (4)	46.6	IIV D1	(CV)	(b) (4)	38.1	IIV F _{rel} non-AML subjects	(CV)	(b) (4)	6.58	IIV F _{rel} AML subjects	(CV)	(b) (4)	17.5	Add. 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NDA Multi-disciplinary Review and Evaluation {NDA 216993}
{VANFLYTA; quizartinib}

	Table 25: Parameter estimates of the final AC886 model. <table><tr><th colspan="5">Final model for AC886</th></tr><tr><td>Run</td><td></td><td></td><td></td><td>107</td></tr><tr><td>OFV</td><td></td><td></td><td></td><td>-6691.71</td></tr><tr><td>Condition number</td><td></td><td></td><td></td><td>25.09</td></tr></table> <table><tr><th colspan="5">Final model for AC886</th></tr><tr><th></th><th>Unit</th><th>Value</th><th>RSE (%)</th><th>SHR (%)</th></tr><tr><td>CL_{AC886}</td><td>L/h</td><td>4.61</td><td>3.75</td><td></td></tr><tr><td>V_{c,AC886}</td><td>L</td><td>8.93</td><td>6.84</td><td></td></tr><tr><td>V_{p,AC886}</td><td>L</td><td>68.5</td><td>1.78</td><td></td></tr><tr><td>Q_{AC886}</td><td>L/h</td><td>3.76</td><td>2.06</td><td></td></tr><tr><td>Fractional change in CL_{AC886} for non-AML subjects</td><td></td><td>0.843</td><td>11.0</td><td></td></tr><tr><td>Fractional change in CL_{AC886} for Black^a subjects</td><td></td><td>0.488</td><td>20.9</td><td></td></tr><tr><td>Fractional change in CL_{AC886} with strong CYP3A inhibitors</td><td></td><td>0.298</td><td>8.01</td><td></td></tr><tr><td>Fractional change in V_{c,AC886} with strong CYP3A inhibitors</td><td></td><td>2.79</td><td>7.34</td><td></td></tr><tr><td>Fractional change in t_{MET} during Induction</td><td></td><td>0.715</td><td>6.38</td><td></td></tr><tr><td>Fractional change in t_{MET} during Consolidation</td><td></td><td>0.272</td><td>13.3</td><td></td></tr><tr><td>Fractional change in t_{MET} during Continuation</td><td></td><td>-0.249</td><td>8.47</td><td></td></tr><tr><td>IIV CL_{AC886} AML</td><td>(CV)</td><td></td><td>(b) (4)</td><td>4.65</td></tr><tr><td>IIV CL_{AC886} non-AML</td><td>(CV)</td><td></td><td></td><td>1.56</td></tr><tr><td>IIV V_{c,AC886}</td><td>(CV)</td><td></td><td></td><td>13.7</td></tr><tr><td>Add. RUV log scale AML subjects</td><td>(CV)</td><td></td><td></td><td>6.61</td></tr><tr><td>Add. RUV log scale non-AML subjects</td><td>(CV)</td><td></td><td></td><td>5.09</td></tr></table> ^a Black or African American race The RSE for IIV and RUV parameters are reported on the approximate SD scale. The values for clearances and volumes of distribution are allometrically scaled with a fixed exponent of 0.75 and 1, respectively. t_{MET} was fixed to 0.5. CL_{AC886}: apparent CL of AC886; V_{c,AC886}: apparent V_c of AC886; V_{p,AC886}: apparent V_p of AC886; Q_{AC886}: apparent inter-compartmental clearance of AC886; CV: coefficient of variation; IIV: interindividual variability; OFV: objective function value; RSE: relative standard error; RUV: residual unexplained variability; SD: standard deviation; SHR: shrinkage; AML: acute myeloid leukemia; CYP3A: isoenzyme 3A of cytochrome P450	Final model for AC886					Run				107	OFV				-6691.71	Condition number				25.09	Final model for AC886						Unit	Value	RSE (%)	SHR (%)	CL _{AC886}	L/h	4.61	3.75		V _{c,AC886}	L	8.93	6.84		V _{p,AC886}	L	68.5	1.78		Q _{AC886}	L/h	3.76	2.06		Fractional change in CL _{AC886} for non-AML subjects		0.843	11.0		Fractional change in CL _{AC886} for Black ^a subjects		0.488	20.9		Fractional change in CL _{AC886} with strong CYP3A inhibitors		0.298	8.01		Fractional change in V _{c,AC886} with strong CYP3A inhibitors		2.79	7.34		Fractional change in t _{MET} during Induction		0.715	6.38		Fractional change in t _{MET} during Consolidation		0.272	13.3		Fractional change in t _{MET} during Continuation		-0.249	8.47		IIV CL _{AC886} AML	(CV)		(b) (4)	4.65	IIV CL _{AC886} non-AML	(CV)			1.56	IIV V _{c,AC886}	(CV)			13.7	Add. RUV log scale AML subjects	(CV)			6.61	Add. RUV log scale non-AML subjects	(CV)			5.09	
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Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	As shown in Tables 20 and 25, the parameters were estimated with adequate precision. The models were able to capture the general tendency of the median data as well as their variabilities across relevant subgroups of subjects. The analysis supports the use of derived individual exposure metrics for the E-R analyses.		Goodness-of-fit (GOF) plots indicate that the final PPK models adequately fit the quizartinib and AC886 PK data overall and in subgroups of subjects with newly diagnosed AML, subjects with R/R AML, and healthy volunteers (i.e., “non-AML”). The final PPK models adequately predicted variability in quizartinib and AC886 concentrations according to the VPC plots.																																																																																																													
BLQ for Parameter Accuracy	BLQ observations were excluded from the analysis. VPCs showed that the proportion of BLQ samples was adequately described by the model for quizartinib (Figure A7-10) and for AC886 (Figure A7-23).																																																																																																															
GOF, VPC	Quizartinib: Figure A7-5: Observed quizartinib concentrations versus PRED and IPRED for the final quizartinib model. The upper panel shows the data on a linear scale and the lower panel shows the same plot with logarithmic scales. Individual data points are indicated by dots and the points for each individual and visit are connected with a line. The points and lines are colored according to subjects with or without AML. The diagonal black line is the line of identity and the red line is a smooth.																																																																																																															

	The range of CWRES values was relatively

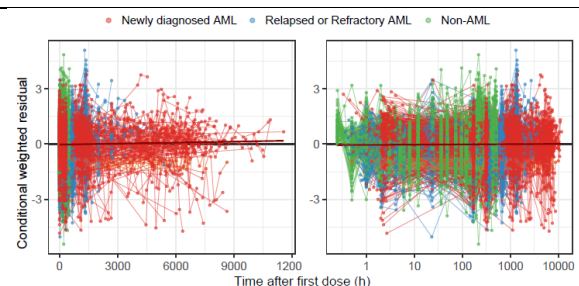


Figure A7-6: CWRES versus time since first dose of quizartinib concentrations for the final quizartinib model. The left panel shows the data with time on a linear scale and the right panel shows the same plot with time on a logarithmic scale. Individual data points are indicated by dots and the points for each individual and visit are connected with a line. The points and lines are colored according to subjects with or without AML. The horizontal black line is the zero line and the red line is a smooth.

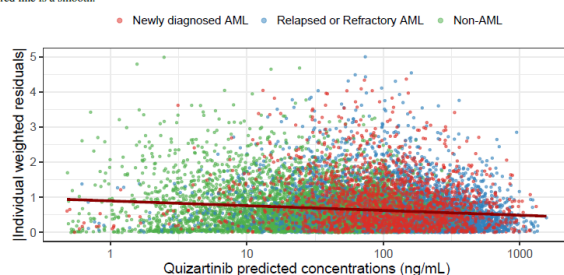


Figure A7-7: IWRES versus IPRED of quizartinib concentrations for the final quizartinib model. The x axis is on the logarithmic scale. Individual data points are indicated by dots and colored according to subjects with or without AML. The red line is a smooth.

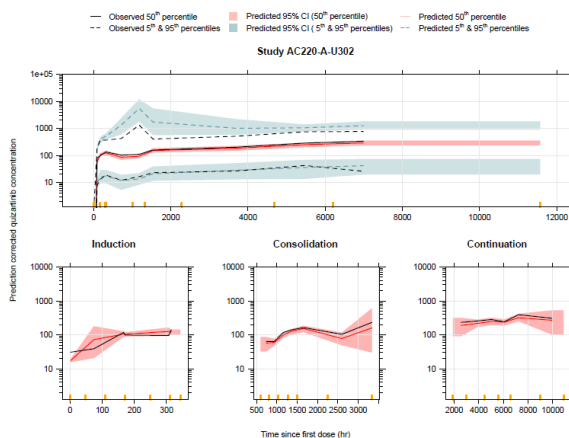


Figure 30: PcVPC of quizartinib concentrations for the final quizartinib model in study AC220-A-U302 (overall and stratified by study phase). BLQ data are included in the pcVPC. Quizartinib concentrations are displayed versus time after first dose on a semi-logarithmic scale. The solid and dashed black lines represent the median, 5th and 95th percentiles of the observations, respectively. The solid red and dashed blue lines represent the median, 5th and 95th percentiles of the predictions, respectively and the corresponding red and blue areas represent the 95% confidence interval of the percentile predicted by the model. Orange markers delimit the bins.

wide (-5.4 to 5.1) which suggests that some individual concentrations may not be accurately characterized by the model. However, the CWRES appeared evenly distributed around zero and the models are adequate for the purpose of predicting the average PK profiles of quizartinib and AC886.

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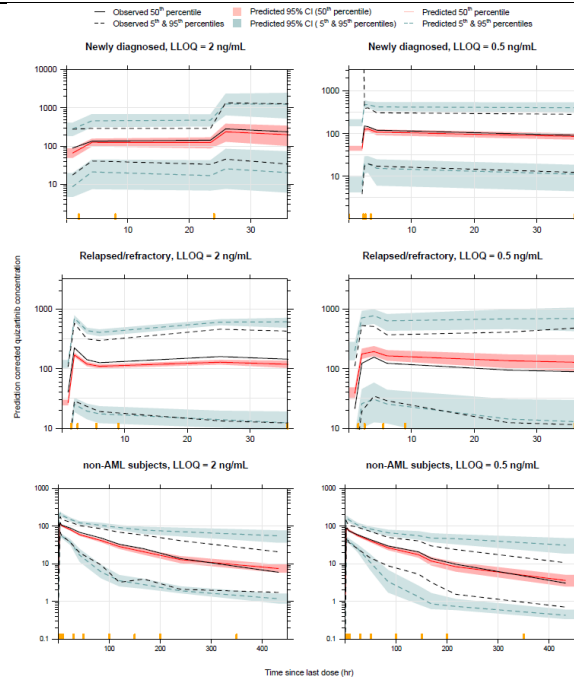


Figure 31: PcVPC of quizartinib concentrations for the final quizartinib model. BLQ data are included in the pcVPC. Quizartinib concentrations of all studies are displayed versus time after last dose on a semi-logarithmic scale and stratified by AML/non-AML subjects and study-specific LLOQ value. The solid and dashed black lines represent the median, 5th and 95th percentiles of the observations, respectively. The solid red and dashed blue lines represent the median, 5th and 95th percentiles of the predictions, respectively and the corresponding red and blue areas represent the 95% confidence interval of the percentile predicted by the model. Orange markers delimit the bins.

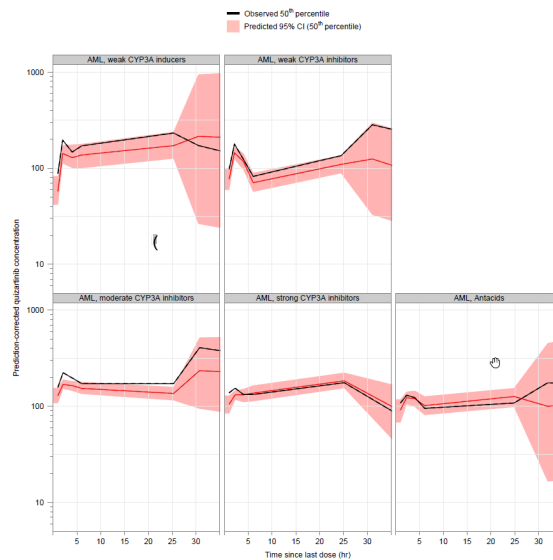


Figure A14-1: PcVPC of quizartinib concentrations for AML patients taking CYP3A inducers, CYP3A inhibitors or antacids in the analysis data set using the corrected derived data file, for the final quizartinib model. The x-axis is truncated at 35 hours. Quizartinib concentrations are displayed versus time after last dose on a semi-logarithmic scale and stratified by antacids, CYP3A inhibitors and inducers. The solid black and red lines represent the median of the observations and the predictions, respectively; the shaded red area represents the 95% confidence interval of the median predicted by the model. See [Glossary](#) for explanation of abbreviations.

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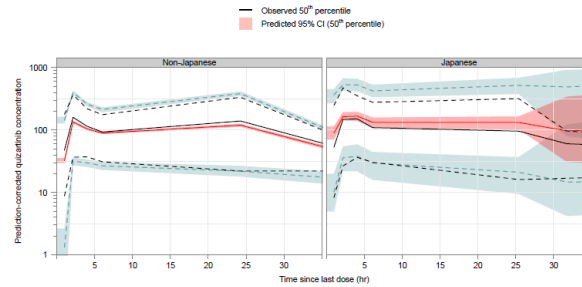


Figure 33: PcVPC of quizartinib concentrations for the final quizartinib model. Quizartinib concentrations in AML subjects are displayed versus time after last dose on a semi-logarithmic scale stratified by Japanese/non-Japanese subjects. The solid and dashed black lines represent the median, 5th and 95th percentiles of the observations, respectively. The solid red and dashed blue lines represent the median, 5th and 95th percentiles of the predictions, respectively and the corresponding red and blue areas represent the 95% confidence interval of the percentile predicted by the model.

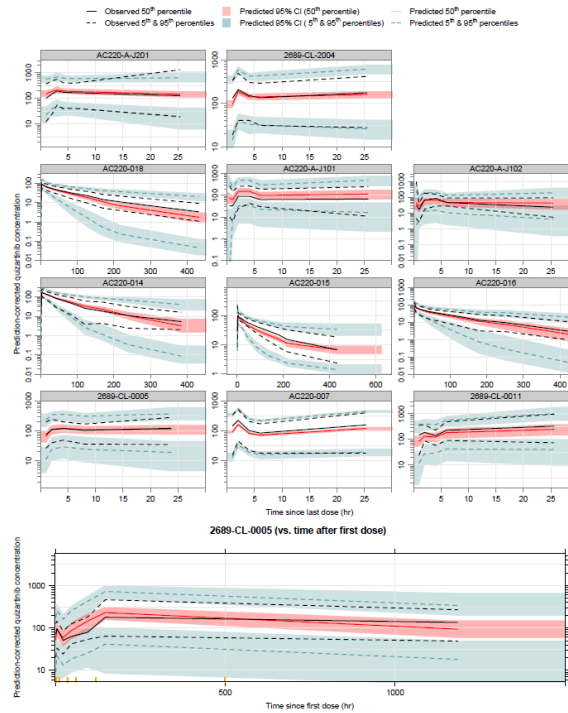


Figure A7-8: PcVPC of quizartinib concentrations for the final quizartinib model. Quizartinib concentrations of all studies (except studies AC220-A-U105 and AC220-A-U302) are displayed versus time after last dose on a semi-logarithmic scale and stratified by study. Study 2689-CL-0005 is also displayed versus time after first dose in the bottom panel (orange markers delimit the bins). The solid and dashed black lines represent the median, 5th and 95th percentiles of the observations, respectively. The solid red and dashed blue lines represent the median, 5th and 95th percentiles of the predictions, respectively and the corresponding red and blue areas represent the 95% confidence interval of the percentile predicted by the model.

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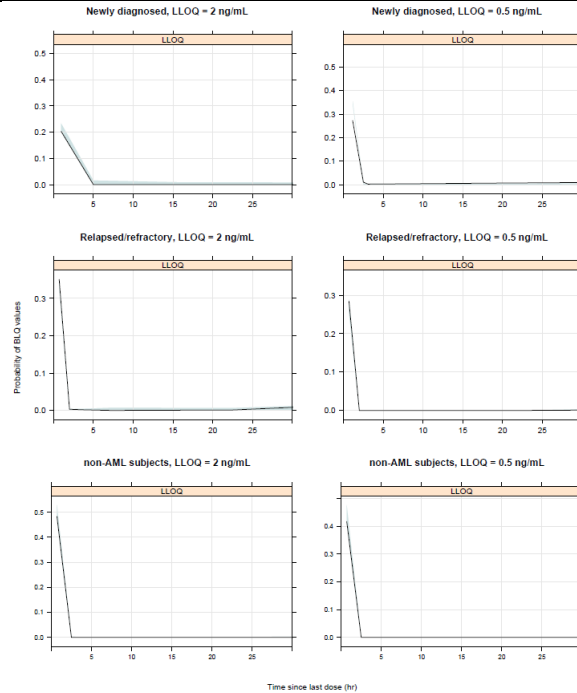


Figure A7-10: Probability of BLQ values for the final quizartinib model for all studies versus time after last dose on a semi-logarithmic scale and stratified by AML/non-AML subjects and study-specific LLOQ value. The solid black lines represent the observed probabilities and the blue areas represent the 95% confidence interval of the predicted probabilities.

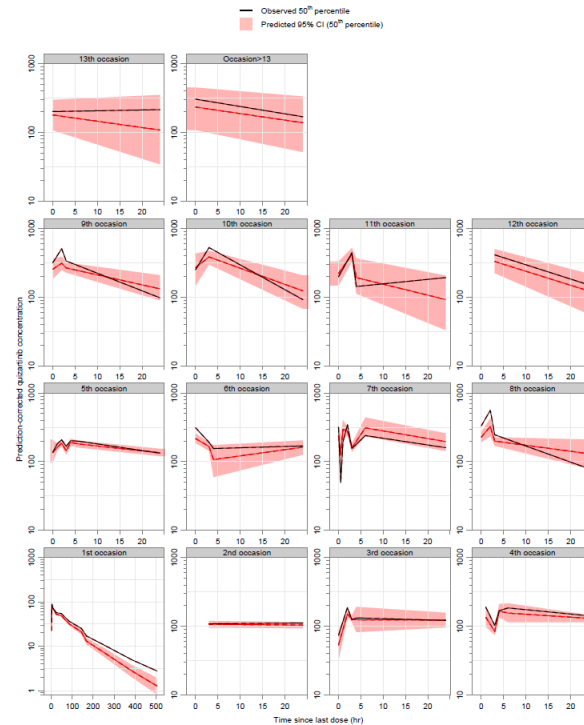


Figure A7-9: PcVPC of quizartinib concentrations for the final quizartinib model. Quizartinib concentrations of all studies are displayed versus time after last dose on a semi-logarithmic scale and stratified by occasion. The solid black and red lines represent the median of the observations and the predictions, respectively; the shaded red area represents the 95% confidence interval of the median predicted by the model.

AC886:

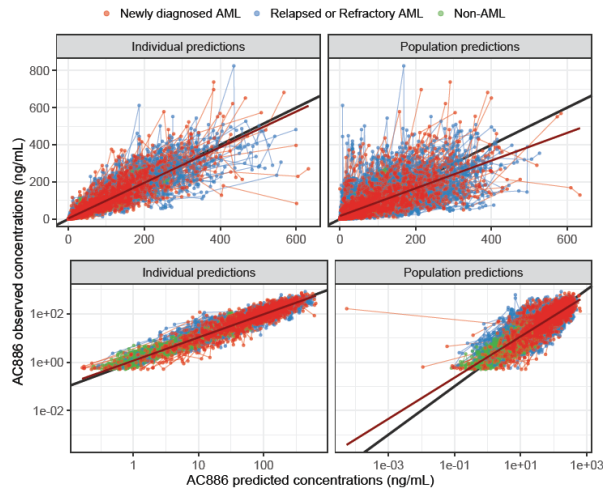


Figure A7-19: Observed AC886 concentrations versus PRED and IPRED for the final AC886 model. The upper panel shows the data on a linear scale and the lower panel shows the same plot with logarithmic scales. Individual data points are indicated by dots and the points for each individual and visit are connected with a line. The points and lines are colored according to subjects with or without AML. The diagonal black line is the line of identity and the red line is a smooth.

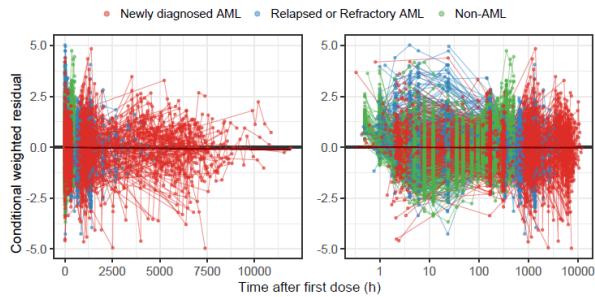


Figure A7-20: CWRES versus time since first dose of AC886 concentrations for the final AC886 model. The left panel shows the data with time on a linear scale and the right panel shows the same plot with time on a logarithmic scale. Individual data points are indicated by dots and the points for each individual and visit are connected with a line. The points and lines are colored according to subjects with or without AML. The horizontal black line is the zero line and the red line is a smooth.

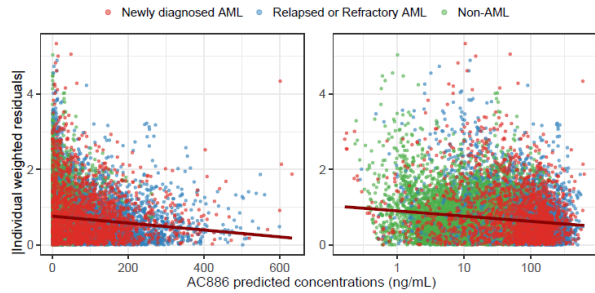


Figure A7-21: IWRES versus IPRED of AC886 concentrations for the final AC886 model. The left panel shows the data with the IPRED on a linear scale and the right panel shows the same plot with IPRED on a logarithmic scale. Individual data points are indicated by dots and colored according to subjects with or without AML. The red line is a smooth.

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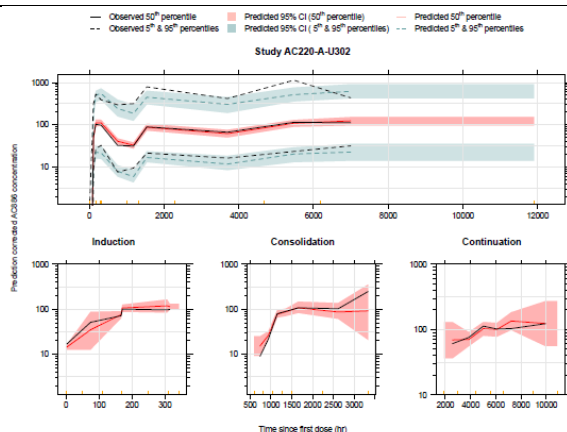


Figure 36: PcVPC of AC886 concentrations for the final AC886 model in study AC220-A-U302 (overall and stratified by study phase). BLQ data are included in the pcVPC. AC886 concentrations are displayed versus time after first dose on a semi-logarithmic scale. The solid and dashed black lines represent the median, 5th and 95th percentiles of the observations, respectively. The solid red and dashed blue lines represent the median, 5th and 95th percentiles of the predictions, respectively and the corresponding red and blue areas represent the 95% confidence interval of the percentile predicted by the model. Orange markers delimit the bins.

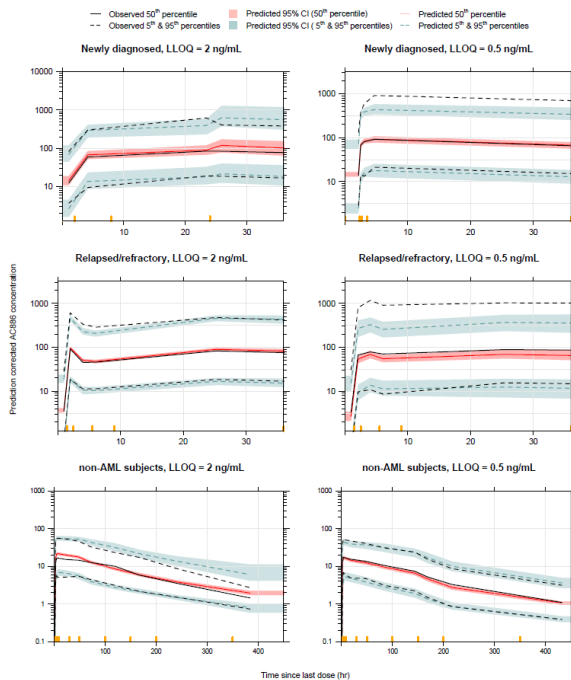


Figure 37: PcVPC of AC886 concentrations for the final AC886 model. BLQ data are included in the pcVPC. AC886 concentrations of all studies are displayed versus time after last dose on a semi-logarithmic scale and stratified by AML/non-AML subjects and study-specific LLOQ value. The solid and dashed black lines represent the median, 5th and 95th percentiles of the observations, respectively. The solid red and dashed blue lines represent the median, 5th and 95th percentiles of the predictions, respectively and the corresponding red and blue areas represent the 95% confidence interval of the percentile predicted by the model. Orange markers delimit the bins.

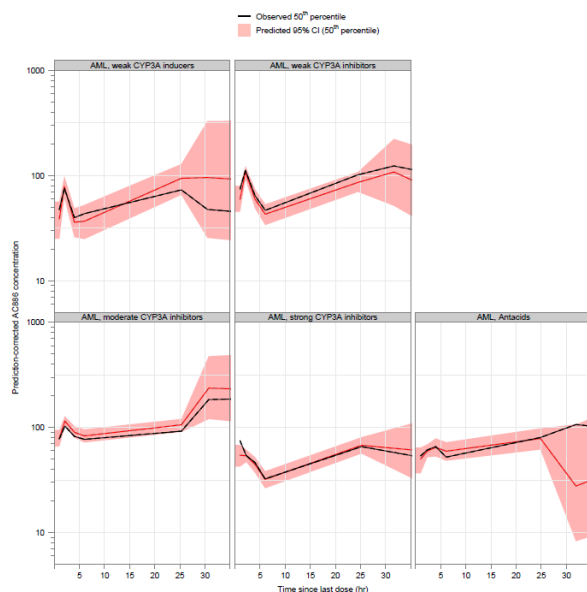


Figure A14-2: PcVPC of AC886 concentrations for AML patients taking CYP3A inducers, CYP3A inhibitors or antacids in the analysis data set using the corrected derived data file, for the final AC886 model. The x-axis is truncated at 35 hours. AC886 concentrations are displayed versus time after last dose on a semi-logarithmic scale and stratified by CYP3A inhibitors and inducers. The solid black and red lines represent the median of the observations and the predictions, respectively; the shaded red area represents the 95% confidence interval of the median predicted by the model. See [Glossary](#) for explanation of abbreviations.

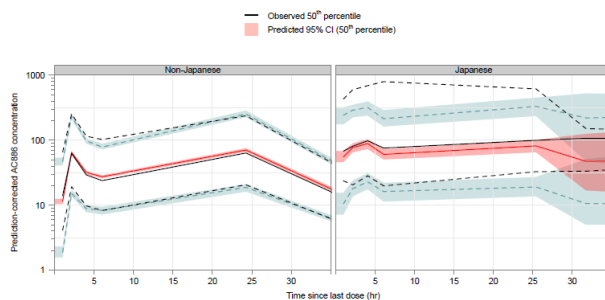


Figure 39: PcVPC of AC886 concentrations for the final AC886 model. AC886 concentrations of all studies are displayed versus time after last dose on a semi-logarithmic scale and stratified by Japanese/non-Japanese subjects. The solid and dashed black lines represent the median, 5th and 95th percentiles of the observations, respectively. The solid red and dashed blue lines represent the median, 5th and 95th percentiles of the predictions, respectively and the corresponding red and blue areas represent the 95% confidence interval of the percentile predicted by the model.

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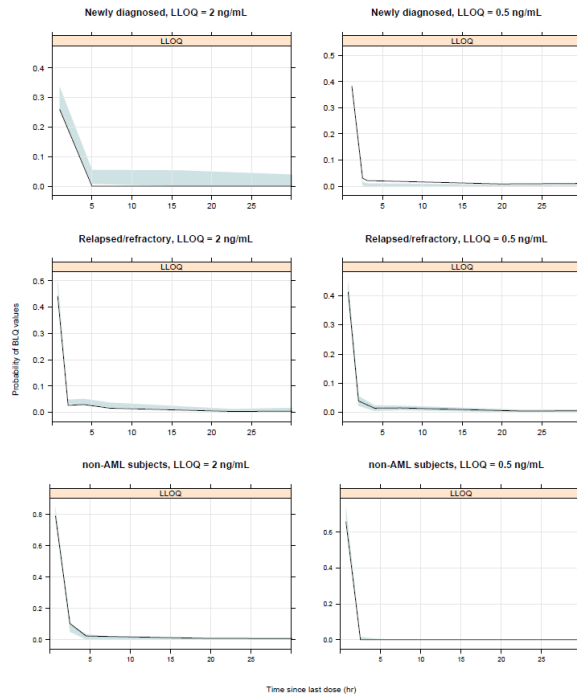


Figure A7-23: Probability of BLQ values for the final AC886 model for all studies versus time after last dose stratified by AML/non-AML subjects and study-specific LLOQ value. The solid black lines represent the observed probabilities and the blue areas represent the 95% confidence interval of the predicted probabilities.

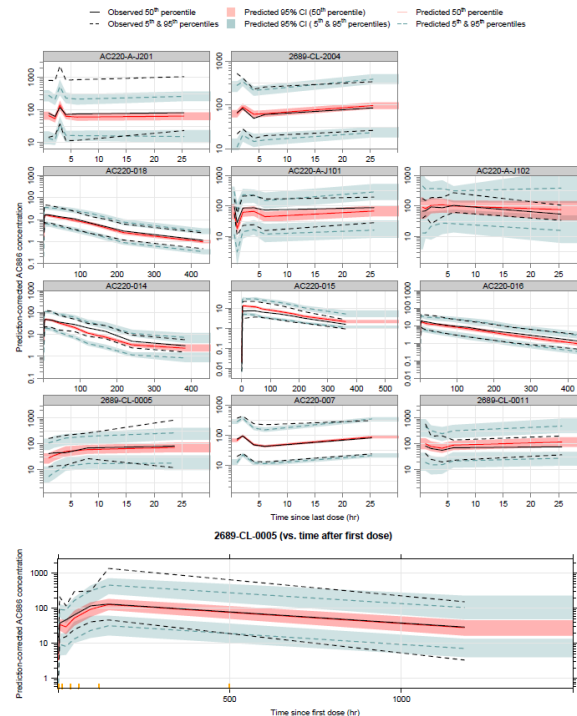


Figure A7-22: PeVPC of AC886 concentrations for the final AC886 model. AC886 concentrations of all studies (except studies AC220-A-U105 and AC220-A-U302) are displayed versus time after last dose on a semi-logarithmic scale and stratified by studies. Study 2689-CL-0005 is also displayed versus time after first dose in the bottom panel (orange markers delimit the bins). The solid and dashed black lines represent the median, 5th and 95th percentiles of the observations, respectively. The solid red and dashed blue lines represent the median, 5th and 95th percentiles of the predictions, respectively and the corresponding red and blue areas represent the 95% confidence interval of the percentile predicted by the model.

Significant
Covariates and
Clinical Relevance

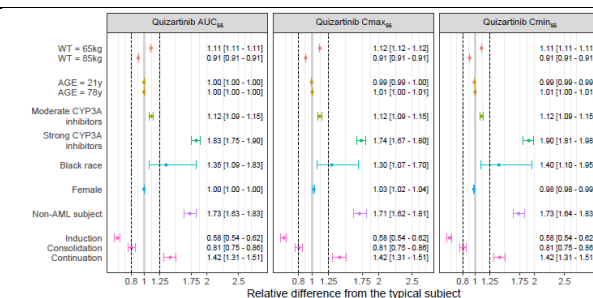


Figure 43: Forest plot of covariate effects for quizartinib PK parameters. The dots represent the median of the relative difference from the typical subject and the whiskers represent the 95% CI for AUC_{ss} , $C_{ss,max}$, and $C_{ss,min}$, colored by the covariate. The numbers are median [95% CI] of the relative difference from the typical subject (male R/R subject, WT=75 kg, AGE= 47 years, no CYP3A co-administration and not Black or African American). CI: confidence interval; AUC_{ss} : steady-state AUC in the 24-hour dosing interval; $C_{ss,max}$: maximum concentration at steady-state; $C_{ss,min}$: minimum concentration at steady-state.

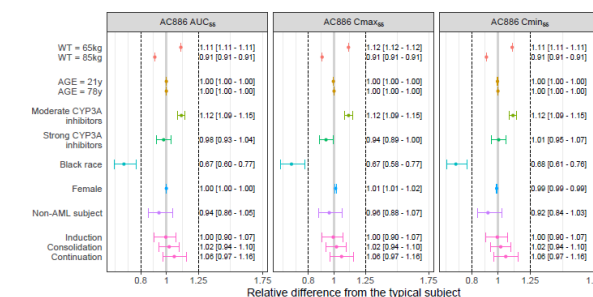


Figure 44: Forest plot of covariate effects for AC886 PK parameters. The dots represent the median of the relative difference from the typical subject and the whiskers represent the 95% CI for AUC_{ss} , $C_{ss,max}$, and $C_{ss,min}$, colored by the covariate. The numbers are median [95% CI] of the relative difference from the typical subject (male R/R subject, WT=75 kg, AGE= 47 years, albumin = 4.1 g/dL, no CYP3A co-administration, not Black or African American and not Asian). CI: confidence interval; AUC_{ss} : steady-state AUC in the 24-hour dosing interval; $C_{ss,max}$: maximum concentration at steady-state; $C_{ss,min}$: minimum concentration at steady-state.

(b) (4)

Figure 45: Forest plot of covariate effects for the sum of quizartinib and AC886 PK parameters. The dots represent the median of the relative difference from the typical subject and the whiskers represent the 95% CI for the sum of quizartinib and AC886 AUC_{ss} , $C_{ss,max}$ and $C_{ss,min}$, colored by the covariate. The numbers are median [95% CI] of the relative difference from the typical subject (male R/R subject, WT=75 kg, AGE= 47 years, albumin = 4.1 g/dL, no CYP3A co-administration, not Black or African American and not Asian). CI: confidence interval; AUC_{ss} : steady-state AUC in the 24-hour dosing interval; $C_{ss,max}$: maximum concentration at steady-state; $C_{ss,min}$: minimum concentration at steady-state.

No clinically relevant differences in quizartinib or AC886 exposure are expected according to age, weight, sex, race, weak or moderate CYP3A4 inhibitors, mild or moderate renal impairment, and mild or moderate hepatic impairment. The effect of severe renal impairment and severe hepatic impairment on quizartinib and AC886 PK has not been studied.

Exposure is expected to be significantly higher following the proposed 53 mg QD dosage during maintenance compared to the proposed 35.4 mg dosage in induction and consolidation, which is due to lower elimination CL and higher daily dose in maintenance treatment.

See Table 114 and Table 115 for a summary of quizartinib and AC886 exposure, respectively, according to treatment phase in Study AC220-A-U302. The acceptability of the proposed maintenance dosage is assessed further in Section 19.4.3.2.

Analysis Based on
Simulation
(optional)

Not applicable

		Median and 95% CI exposure values according to covariate effects are displayed in forest plots in Figure 32 and Figure 33, which correspond to the exposure ratios presented in the Applicant's Figure 43 and Figure 44 in the PPK Assessment Summary, respectively. The Applicant's Figure 45 in the PPK Assessment Summary was generated by adding quizartinib and AC886 exposure together without accounting for differences in molecular weight, which may result in errors in relative exposure difference according to covariates.
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	Specific Populations: (b) (4)	Overall, the proposed labeling language is acceptable upon the Applicant's agreement to FDA's revisions.

Note: table and figure numbering corresponds to those used in the source document.
Source: **AC220-PMx009** (eCTD 5.3.3.5)

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Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study

Note: table numbering corresponds to that used in the source document.

Source: **AC220-PMx009** (eCTD 5.3.3.5)

Table 8: Baseline continuous covariate statistics for the analysis data set including non-AML subjects.

	AC220-014 N=80	AC220-015 N=89	AC220-016 N=30	AC220-018 N=62	AC220-A-U105 N=12	Overall N=273
Age (years)						
Mean (SD)	31.3 (9.77)	33.5 (9.06)	53.7 (7.35)	34.6 (9.19)	56.2 (5.34)	36.3 (11.9)
Median (min, max)	28.0 (18.0, 55.0)	32.0 (18.0, 53.0)	55.0 (34.0, 66.0)	32.5 (18.0, 55.0)	54.0 (50.0, 66.0)	33.0 (18.0, 66.0)
Body weight (kg)						
Mean (SD)	75.3 (13.5)	79.0 (11.7)	79.9 (13.8)	75.2 (10.7)	85.5 (11.2)	77.4 (12.4)
Median (min, max)	73.4 (48.1, 112)	78.0 (50.0, 103)	81.3 (54.1, 106)	73.9 (50.0, 99.9)	87.8 (67.4, 108)	76.7 (48.1, 112)
Albumin (g/dL)						
Mean (SD)	4.57 (0.275)	4.50 (0.268)	4.14 (0.363)	4.47 (0.281)	3.97 (0.596)	4.45 (0.344)
Median (min, max)	4.55 (3.70, 5.20)	4.50 (3.90, 5.20)	4.10 (3.30, 4.70)	4.50 (3.90, 5.00)	4.20 (2.70, 4.50)	4.50 (2.70, 5.20)
Missing (N (%))	0 (0%)	9 (10%)	0 (0%)	0 (0%)	0 (0%)	9 (3.3%)
CRCL (mL/min)						
Mean (SD)	120 (24.9)	123 (22.3)	135 (45.0)	119 (19.9)	120 (39.8)	122 (27.2)
Median (min, max)	118 (79.7, 215)	120 (77.3, 169)	126 (83.9, 310)	120 (83.3, 158)	115 (61.6, 203)	120 (61.6, 310)
Missing (N (%))	0 (0%)	9 (10%)	0 (0%)	0 (0%)	0 (0%)	9 (3.3%)
Alanine aminotransferase (IU/L)						
Mean (SD)	15.5 (5.37)	22.6 (8.43)	44.4 (48.4)	15.0 (6.26)	28.3 (11.0)	21.4 (19.6)
Median (min, max)	15.0 (7.00, 33.0)	21.5 (7.00, 45.0)	24.5 (12.0, 201)	13.0 (6.00, 37.0)	29.5 (11.0, 47.0)	17.0 (6.00, 201)
Missing (N (%))	0 (0%)	9 (10%)	0 (0%)	0 (0%)	0 (0%)	9 (3.3%)
Aspartate aminotransferase (IU/L)						
Mean (SD)	17.6 (3.14)	24.2 (4.71)	50.3 (57.8)	18.0 (4.28)	31.2 (20.7)	24.0 (22.4)
Median (min, max)	17.0 (13.0, 25.0)	24.0 (16.0, 38.0)	26.5 (19.0, 261)	18.0 (10.0, 35.0)	26.0 (15.0, 92.0)	20.0 (10.0, 261)
Missing (N (%))	0 (0%)	9 (10%)	0 (0%)	0 (0%)	0 (0%)	9 (3.3%)
Alkaline phosphatase (IU/L)						
Mean (SD)	69.5 (21.7)	70.8 (20.5)	89.2 (36.3)	60.7 (13.9)	78.9 (39.7)	70.5 (24.3)
Median (min, max)	64.5 (31.0, 150)	69.0 (36.0, 172)	90.0 (38.0, 221)	58.0 (32.0, 96.0)	66.0 (42.0, 189)	66.0 (31.0, 221)
Missing (N (%))	0 (0%)	9 (10%)	0 (0%)	0 (0%)	0 (0%)	9 (3.3%)
Total bilirubin (mg/dL)						
Mean (SD)	0.522 (0.272)	0.585 (0.241)	0.747 (0.611)	0.377 (0.221)	1.45 (0.991)	0.575 (0.426)
Median (min, max)	0.526 (0.117, 1.40)	0.500 (0.200, 1.30)	0.550 (0.300, 3.40)	0.300 (0.200, 1.50)	1.20 (0.300, 3.00)	0.500 (0.117, 3.40)
Missing (N (%))	0 (0%)	9 (10%)	0 (0%)	0 (0%)	0 (0%)	9 (3.3%)

Table 9: Baseline continuous covariate statistics for the analysis data set including AML patients.

	2689-CL-0005 N=15	2689-CL-0011 N=13	2689-CL-2004 N=73	AC220-A-J101 N=15	AC220-A-J102 N=7	AC220-A-J201 N=38	AC220-007 N=239	AC220-A-U302 N=259	Overall N=659
Age (years)									
Mean (SD)	43.4 (13.9)	43.7 (14.5)	53.4 (15.0)	63.5 (15.8)	55.9 (12.5)	60.3 (14.5)	53.7 (14.3)	53.6 (13.2)	53.8 (14.2)
Median (min, max)	43.0 (22.0, 60.0)	43.0 (23.0, 61.0)	54.0 (19.0, 77.0)	68.0 (33.0, 91.0)	62.0 (34.0, 68.0)	65.5 (31.0, 81.0)	55.0 (19.0, 81.0)	56.0 (23.0, 75.0)	56.0 (19.0, 91.0)
Body weight (kg)									
Mean (SD)	77.4 (19.8)	84.9 (27.8)	75.8 (16.4)	53.5 (10.6)	59.4 (9.91)	53.1 (9.09)	73.7 (18.5)	72.2 (15.9)	71.8 (17.9)
Median (min, max)	79.5 (47.2, 114)	78.8 (53.4, 153)	76.5 (40.4, 116)	53.1 (38.8, 75.2)	57.8 (49.8, 80.7)	51.8 (38.1, 75.5)	69.6 (39.5, 147)	70.0 (36.8, 125)	69.4 (36.8, 153)
Albumin (g/dL)									
Mean (SD)	3.46 (0.452)	3.69 (0.477)	3.49 (0.610)	3.55 (0.496)	3.64 (0.621)	3.63 (0.563)	3.70 (0.517)	3.29 (0.509)	3.51 (0.556)
Median (min, max)	3.50 (2.50, 4.10)	3.60 (3.10, 4.60)	3.60 (2.10, 4.50)	3.40 (2.80, 4.60)	3.60 (2.60, 4.20)	3.73 (2.20, 4.70)	3.70 (2.10, 4.80)	3.30 (1.70, 4.90)	3.50 (1.70, 4.90)
Missing (N (%))	1 (6.7%)	0 (0%)	2 (2.7%)	0 (0%)	0 (0%)	0 (0%)	1 (0.42%)	8 (3.1%)	12 (1.8%)
CRCL (mL/min)									
Mean (SD)	128 (39.9)	129 (41.7)	113 (43.3)	72.5 (29.7)	95.0 (32.3)	88.8 (34.2)	111 (48.2)	130 (50.4)	117 (48.8)
Median (min, max)	118 (74.1, 233)	134 (57.6, 192)	104 (44.2, 273)	68.8 (25.4, 124)	94.9 (48.9, 143)	79.9 (35.2, 163)	105 (22.1, 368)	123 (52.3, 390)	112 (22.1, 390)
Missing (N (%))	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.42%)	0 (0%)	1 (0.15%)
Alanine aminotransferase (IU/L)									
Mean (SD)	29.6 (20.0)	47.2 (23.4)	35.7 (24.6)	24.9 (12.0)	24.6 (16.0)	22.5 (13.9)	30.7 (30.0)	32.5 (37.9)	31.6 (31.7)
Median (min, max)	23.0 (10.0, 76.0)	47.0 (18.0, 97.0)	29.0 (6.00, 121)	22.0 (10.0, 49.0)	20.0 (6.00, 53.0)	17.5 (5.00, 58.0)	21.0 (1.50, 224)	21.0 (3.00, 377)	22.0 (1.50, 377)
Missing (N (%))	1 (6.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.42%)	3 (1.2%)	5 (0.76%)
Aspartate aminotransferase (IU/L)									
Mean (SD)	26.1 (12.7)	31.3 (13.8)	31.1 (17.2)	25.9 (11.7)	25.4 (13.1)	24.5 (11.8)	30.6 (46.8)	22.4 (16.8)	26.9 (31.2)
Median (min, max)	23.5 (13.0, 57.0)	32.0 (3.00, 57.0)	26.0 (7.00, 95.0)	20.0 (12.0, 48.0)	20.0 (13.0, 51.0)	22.5 (9.00, 66.0)	23.0 (7.00, 688)	17.0 (5.00, 138)	21.0 (3.00, 688)
Missing (N (%))	1 (6.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.42%)	4 (1.5%)	6 (0.91%)
Alkaline phosphatase (IU/L)									
Mean (SD)	66.3 (34.0)	85.4 (18.4)	119 (68.8)	361 (193)	204 (72.2)	298 (130)	103 (65.3)	84.8 (72.1)	115 (99.1)
Median (min, max)	58.5 (37.0, 175)	77.0 (64.0, 124)	95.0 (44.0, 376)	292 (156, 786)	206 (83.0, 303)	256 (160, 823)	84.0 (28.0, 507)	60.0 (19.0, 600)	81.0 (19.0, 823)
Missing (N (%))	1 (6.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.42%)	3 (1.2%)	5 (0.76%)
Total bilirubin (mg/dL)									
Mean (SD)	0.721 (0.326)	0.480 (0.240)	0.570 (0.283)	0.516 (0.303)	0.663 (0.235)	0.423 (0.169)	0.488 (0.232)	0.881 (0.421)	0.655 (0.375)
Median (min, max)	0.800 (0.200, 1.40)	0.400 (0.220, 1.00)	0.500 (0.100, 1.30)	0.500 (0.100, 1.30)	0.600 (0.300, 1.00)	0.365 (0.200, 0.900)	0.438 (0.117, 1.64)	0.816 (0.257, 2.83)	0.585 (0.100, 2.83)
Missing (N (%))	1 (6.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.42%)	1 (0.39%)	3 (0.46%)

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Table 11: Baseline categorical covariate statistics for the analysis data set including non-AML subjects.

Covariate		AC220-014		AC220-015		AC220-016		AC220-018		AC220-A-U105	
		N	%	N	%	N	%	N	%	N	%
Sex	Female	30	38	22	25	14	47	27	44	0	0
	Male	50	62	67	75	16	53	35	56	12	100
Race ^a	American Indian	3	4	0	0	1	3	1	2	0	0
	Asian	2	2	1	1	0	0	1	2	0	0
	Black	12	15	29	33	4	13	17	27	1	8
	Native Hawaiian	1	1	0	0	0	0	0	0	0	0
	White	62	78	55	62	25	83	37	60	11	92
	Other	0	0	4	4	0	0	6	10	0	0
	Missing	0	0	0	0	0	0	0	0	0	0
Japanese	No	80	100	89	100	30	100	62	100	12	100
	Yes	0	0	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0	0	0
Chinese or Taiwanese or Hongkongese	No	80	100	89	100	30	100	62	100	12	100
	Yes	0	0	0	0	0	0	0	0	0	0
Korean	No	80	100	89	100	30	100	62	100	12	100
	Yes	0	0	0	0	0	0	0	0	0	0
Formulation	Tablet	54	68	89	100	30	100	62	100	12	100
	Solution	26	32	0	0	0	0	0	0	0	0
Type of AML	Newly diagnosed AML	0	0	0	0	0	0	0	0	0	0
	Relapsed or Refractory AML	0	0	0	0	0	0	0	0	0	0
	Non-AML	80	100	89	100	30	100	62	100	12	100
NCI-ODWG grade	Normal	80	100	79	89	22	73	61	98	6	50
	Mild	0	0	1	1	7	23	1	2	0	0
	Moderate	0	0	0	0	1	3	0	0	6	50
	Severe	0	0	0	0	0	0	0	0	0	0
	Missing	0	0	9	10	0	0	0	0	0	0
CYP3A inhibitors	No	80	100	30	34	29	97	62	100	12	100
	Weak	0	0	0	0	1	3	0	0	0	0
	Moderate	0	0	30	34	0	0	0	0	0	0
	Strong	0	0	29	33	0	0	0	0	0	0
CYP3A inducers	No	80	100	89	100	30	100	62	100	12	100
	Weak	0	0	0	0	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0	0	0	0	0
	Strong	0	0	0	0	0	0	0	0	0	0
Antacids	No	80	100	89	100	29	97	62	100	12	100
	Yes	0	0	0	0	1	3	0	0	0	0
H2 antagonists	No	80	100	89	100	30	100	62	100	12	100
	Yes	0	0	0	0	0	0	0	0	0	0
PPI	No	80	100	89	100	29	97	30	48	10	83
	Yes	0	0	0	0	1	3	32	52	2	17
Dose	30 mg	14	18	89	100	30	100	62	100	12	100
	60 mg	52	65	0	0	0	0	0	0	0	0
	90 mg	14	18	0	0	0	0	0	0	0	0

^a The full names of categories are American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other and Not Known

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Table 12: Baseline categorical covariate statistics for the analysis data set including AML patients.

Covariate		2689-CL-0005		2689-CL-0011		2689-CL-0004		AC220-A-J101		AC220-A-J102		AC220-A-J201		AC220-007		AC220-A-U302	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Sex	Female	8	53.3	6	46.2	31	42.5	6	40.0	4	57.1	23	60.5	127	53.1	139	53.7
	Male	7	46.7	7	53.8	42	57.5	9	60.0	3	42.9	15	39.5	112	46.9	120	46.3
Race ^a	American Indian	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.4	0	0.0
	Asian	0	0.0	0	0.0	3	4.1	15	100.0	7	100.0	38	100.0	24	10.0	78	30.1
	Black	2	13.3	0	0.0	3	4.1	0	0.0	0	0.0	0	0.0	9	3.8	2	0.8
	Native Hawaiian	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White	11	73.3	13	100.0	56	76.7	0	0.0	0	0.0	0	0.0	179	74.9	154	59.5
	Other	2	13.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	8	3.3	25	9.7
Japanese ^b	Missing	0	0.0	0	0.0	11	15.1	0	0.0	0	0.0	0	0.0	18	7.5	0	0.0
	No	15	100.0	13	100.0	73	100.0	0	0.0	0	0.0	0	0.0	239	100.0	243	93.8
	Yes	0	0.0	0	0.0	0	0.0	15	100.0	7	100.0	38	100.0	0	0.0	16	6.2
Chinese or Taiwanese or Hongkongese	Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	No	15	100.0	13	100.0	73	100.0	15	100.0	7	100.0	38	100.0	232	97.1	238	91.9
	Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	7	2.9	21	8.1
Korean	No	15	100.0	13	100.0	73	100.0	15	100.0	7	100.0	38	100.0	228	95.4	225	86.9
	Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	11	4.6	34	13.1
Formulation	Tablet	0	0.0	0	0.0	0	0.0	15	100.0	7	100.0	38	100.0	239	100.0	259	100.0
	Solution	15	100.0	13	100.0	73	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Type of AML	Newly diagnosed AML	15	100.0	13	100.0	0	0.0	0	0.0	7	100.0	0	0.0	0	0.0	259	100.0
	Relapsed or Refractory AML	0	0.0	0	0.0	73	100.0	15	100.0	0	0.0	38	100.0	239	100.0	0	0.0
	Non-AML	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
NCI-ODWG grade	Normal	10	66.7	9	69.2	47	64.4	11	73.3	6	85.7	29	76.3	213	89.1	190	73.4
	Mild	4	26.7	4	30.8	26	35.6	4	26.7	1	14.3	9	23.7	25	10.5	57	22.0
	Moderate	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	9	3.5
	Severe	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Missing	1	6.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.4	3	1.2
CYP3A inhibitors	No	6	40.0	0	0.0	40	54.8	14	93.3	7	100.0	22	57.9	109	45.6	76	29.3
	Weak	2	13.3	0	0.0	6	8.2	1	6.7	0	0.0	2	5.3	39	16.3	34	13.1
	Moderate	7	46.7	6	46.2	5	6.8	0	0.0	0	0.0	11	28.9	55	23.0	62	23.9
CYP3A inducers	Strong	0	0.0	7	53.8	22	30.1	0	0.0	0	0.0	3	7.9	36	15.1	87	33.6
	No	13	86.7	7	53.8	71	97.3	15	100.0	7	100.0	38	100.0	229	95.8	242	93.4
	Weak	2	13.3	6	46.2	2	2.7	0	0.0	0	0.0	0	0.0	9	3.8	17	6.6
Antacids	Moderate	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.4	0	0.0
	Strong	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	No	12	80.0	12	92.3	63	86.3	15	100.0	4	57.1	34	89.5	220	92.1	210	81.1
H2 antagonists	Yes	3	20.0	1	7.7	10	13.7	0	0.0	3	42.9	4	10.5	19	7.9	49	18.9
	No	14	93.3	11	84.6	68	93.2	13	86.7	5	71.4	32	84.2	207	86.6	197	76.1
PPI	Yes	1	6.7	2	15.4	5	6.8	2	13.3	2	28.6	6	15.8	32	13.4	62	23.9
	No	9	60.0	6	46.2	37	50.7	11	73.3	4	57.1	16	42.1	140	58.6	144	55.6
Dose	Yes	6	40.0	7	53.8	36	49.3	4	26.7	3	42.9	22	57.9	99	41.4	115	44.4
	20 mg	0	0.0	0	0.0	0	0.0	8	53.3	4	57.1	3	7.9	33	13.8	86	33.2
	30 mg	0	0.0	0	0.0	37	50.7	3	20.0	0	0.0	35	92.1	206	86.2	1	0.4
	40 mg	4	26.7	7	53.8	0	0.0	0	0.0	3	42.9	0	0.0	0	0.0	172	66.4
	60 mg	11	73.3	6	46.2	36	49.3	4	26.7	0	0.0	0	0.0	0	0.0	0	0.0

^a The full names of categories are American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other and Not Known. See [Glossary](#) for explanation of abbreviations.

^b For study AC220-A-U302, n=16 Japanese subjects is reported in this table while n=15 Japanese subjects are included in [Figures 40 to 42](#) because after finalization of the population PK analysis of quizartinib and AC886, Daiichi-Sankyo informed [\(b\) \(4\)](#) that subject [\(b\) \(6\)](#) is actually a Chinese subject who was being treated in Japan and not Japanese (see [Section 3.3](#)). The number of Chinese or Taiwanese or Hongkongese subjects was adapted accordingly.

The FDA's Assessment:

The final quizartinib and AC886 population PK models are acceptable for the purpose of characterizing the average PK profile and predicting exposure in subjects with newly diagnosed AML for use in exposure-response (E-R) analyses.

The population PK dataset contained quizartinib and AC886 concentration data from a total of 931 subjects, which included 273 healthy volunteers (29%), 293 subjects with newly-diagnosed AML (31%), and 365 subjects with R/R AML (39%). Continuous covariates are summarized in non-AML subjects and for subjects with AML in the Applicant's Table 8 and Table 9 above, respectively. Categorical covariates are summarized for non-AML subjects and for subjects with AML above in the Applicant's Table 11 and Table 12 above, respectively.

The Reviewer was able to verify the Applicant's final quizartinib and AC886 PPK models without significant discrepancies in final parameter estimates. The Applicant's Table 20 and Table 25 in the PPK Assessment Summary above report the standard deviations for inter-individual variability (IIV) and residual unexplained variability (RUV) instead of the coefficient of variation (CV%). Additionally, relative standard error (RSE) percentages in the Applicant's Table 20 and Table 25 were calculated incorrectly. The summary of the Reviewer's final parameter estimates, including corrected statistics for IIV and RUV, are presented in **Table 112** for the final quizartinib model and in **Table 113** for the final AC886 model.

Table 112. Reviewer's Parameter Estimates for the Final Quizartinib Population PK Model

Parameter	Definition	Estimate	RSE (%)	95% CI	Shrinkage
tvCL	Typical value of elimination clearance (L/h)	6.65	1.6%	6.44, 6.86	-
tvVC	Typical value of central compartment volume (L)	371	3.1%	348, 394	-
tvQP1	Typical value of distribution clearance from central compartment to first peripheral compartment (L/h)	40.7	4.7%	37, 44.4	-
tvVP1	Typical value of first peripheral compartment volume (L)	312	2.0%	300, 324	-
tvQP2	Typical value of distribution clearance from central compartment to second peripheral compartment (L/h)	0.757	3.9%	0.699, 0.815	-
tvVP2	Typical value of second peripheral compartment volume (L)	91.9	2.2%	87.9, 95.9	-
tvT _{LAG}	Typical value of absorption lag time (h)	0.196	4.2%	0.18, 0.212	-
tvKA	Typical value of absorption rate constant (1/h)	1.10	6.3%	0.96, 1.24	-
tvD1	Typical value of duration of zero-order input to depot compartment (h)	0.710	6.4%	0.621, 0.799	-
CL _{STRCP3A4}	Fractional change in CL with strong CYP3A4 inhibitor coadministration	-0.301	7.4%	-0.345, -0.257	-
F1 _{STRCP3A4}	Fractional change in F1 with strong CYP3A4 inhibitor coadministration	0.273	10.8%	0.215, 0.331	-
F1 _{non-AML}	F1 in non-AML subjects	1.73	3.0%	1.63, 1.83	-
F _{MODCYP3A4}	Fractional change in F1 with moderate CYP3A4 inhibitor coadministration	0.116	13.8%	0.085, 0.147	-
KA _{non-AML}	Absorption rate constant in non-AML subjects	-0.188	28.9%	-0.294, -0.082	-
VP1 _{age}	Age effect on VP1	0.0152	6.0%	0.0134, 0.017	-
CL _{race}	Fractional change in CL for Black or African American subjects	-0.261	38.0%	-0.455, -0.067	-
VC _{sex}	Fractional change in VC for female subjects	-0.169	16.0%	-0.222, -0.116	-
BOXCOX_F	Shape box-cox parameter for IIV on F1 _{AML}	-1.28	14.4%	-1.64, -0.92	-
F1 _{induction}	Fractional change in relative bioavailability during induction treatment	-0.419	4.9%	-0.459, -0.379	-
F1 _{consolidation}	Fractional change in relative bioavailability during consolidation treatment	-0.192	15.7%	-0.251, -0.133	-
F1 _{maintenance}	Fractional change in relative bioavailability during maintenance treatment	0.418	12.5%	0.315, 0.521	-
ETA(1)	IIV on Q (exponential)	0.478 (CV=31%)	9.2%	0.392, 0.564	43.9%
ETA(2)	IIV on CL (exponential)	0.483 (CV=31%)	4.7%	0.439, 0.527	11.8%
ETA(3)	IIV on VC (exponential)	0.0347 (CV=1.8%)	22.0%	0.02, 0.05	60.2%
ETA(5)	IIV on TLAG (exponential)	0.418 (CV=26%)	8.2%	0.351, 0.485	44.5%
ETA(6)	IIV on KA (exponential)	0.179 (CV=10%)	13.6%	0.131, 0.227	46.6%
ETA(7)	IIV on D1 (exponential)	0.674 (CV=48%)	9.0%	0.555, 0.793	38.1%
ETA(8)	IIV on F1 in non-AML subjects (exponential)	0.0655 (CV=3.4%)	8.4%	0.0547, 0.0763	6.6%
ETA(9)	IIV on F1 in subjects with AML	0.198 (CV=11%)	9.6%	0.161, 0.235	17.5%

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Parameter	Definition	Estimate	RSE (%)	95% CI	Shrinkage
RUV _{AML}	Additive RUV log scale in subjects with AML	0.193	0.7%	0.19, 0.2	8.5%
RUV _{non-AML}	Additive RUV log scale in non-AML subjects	0.0104	1.3%	0.0101, 0.0107	13.0%

CL, QP1, and QP2 are allometrically scaled by normalized body weight (i.e., weight / 75 kg) with fixed exponent of 0.75. VC, VP1, and VP2 are allometrically scaled by normalized body weight with fixed exponent of 1.0.

$tvF1 = 1 \cdot (1 + F1_{STRCYP3A4} \text{ if receiving concomitant strong CYP3A inhibitor}) \cdot F1_{non-AML} \text{ if non-AML subject} \cdot (1 + F1_{induction} \text{ if during induction treatment}) \cdot (1 + F1_{consolidation} \text{ if during consolidation treatment}) \cdot (1 + F1_{maintenance} \text{ if during maintenance treatment}).$

For non-AML subjects (i.e., healthy subjects), $F1 = tvF1 \cdot \exp(ETA(8))$.

For subjects with AML, $F1 = tvF1 \cdot \exp(\exp(ETA(9))^{BOXCOX\_F - 1} / BOXCOX\_F)$.

CV for exponential IIV calculated as $100\% \cdot (\exp(IIV) - 1)^{0.5}$.

Objective Function Value = -16373. Condition number = 983.7.

AML = acute myeloid leukemia; CI = confidence interval; CV = coefficient of variation; IIV = inter-individual variability; RSE = relative standard error; RUV = residual unexplained variability; tv = typical value; tvF1 = typical value of relative bioavailability.

Source: Reviewer's run of Applicant's final quizartinib model

Table 113. Reviewer's Parameter Estimates for the Final AC886 Population PK Model

Parameter	Definition	Estimate	RSE (%)	95% CI	Shrinkage
tvCL _M	Typical value of elimination clearance (L/h)	4.61	3.8%	4.271, 4.949	-
tvVC _M	Typical value of central compartment volume (L)	8.93	6.8%	7.73, 10.13	-
tvVP _M	Typical value of peripheral compartment volume (L)	68.5	1.8%	66.11, 70.89	-
tvQ _M	Typical value of distribution clearance to peripheral compartment (L/h)	3.76	2.1%	3.6083, 3.9117	-
CL _{M,non-AML}	Fractional change in CL _M for non-AML subjects	0.843	11.0%	0.6615, 1.0245	-
CL _{M,race}	Fractional change in CL _M for Black or African American subjects	0.488	20.9%	0.288, 0.688	-
CL _{M,STRCYP3A4}	Fractional change in CL _M with strong CYP3A4 inhibitor coadministration	0.298	8.0%	0.2512, 0.3448	-
VC _{M,STRCYP3A4}	Fractional change in VC _M with strong CYP3A4 inhibitor coadministration	2.79	7.3%	2.388, 3.192	-
f _{MET,induction}	Fractional change in f _{MET} during induction	0.715	6.4%	0.626, 0.804	-
f _{MET,consolidation}	Fractional change in f _{MET} during consolidation	0.272	13.3%	0.201, 0.343	-
f _{MET,maintenance}	Fractional change in f _{MET} during maintenance	-0.249	8.5%	-0.29, -0.208	-
ETA(1)	IIV on CL _M in subjects with AML (exponential)	0.547 (CV=4.5%)	4.5%	0.499, 0.595	4.7%
ETA(2)	IIV on CL _M in non-AML subjects (exponential)	1.84 (CV=7%)	7.1%	1.58, 2.1	13.7%
ETA(3)	IIV on VC _M (exponential)	0.266 (CV=11%)	10.6%	0.211, 0.321	1.6%
RUV _{AML}	Additive RUV log scale in subjects with AML	0.205	0.7%	0.202, 0.208	6.6%
RUV _{non-AML}	Additive RUV log scale in non-AML subjects	0.0975	0.8%	0.096, 0.099	5.1%

CL_M and VC_M are allometrically scaled by normalized body weight (weight / 75 kg) with fixed exponents of 0.75 and 1.0, respectively.

$f_{MET} = 0.5 \cdot (1 + f_{MET,induction} \text{ if during induction treatment}) \cdot (1 + f_{MET,consolidation} \text{ if during consolidation treatment}) \cdot (1 + f_{MET,maintenance} \text{ if during maintenance treatment})$.

CV for exponential IIV calculated as $100\% \cdot (\exp(IIV) - 1)^{0.5}$.

Objective Function Value = -6691.7. Condition number = 25.08.

AML = acute myeloid leukemia; CI = confidence interval; CV = coefficient of variation; f_{MET} = fraction of quizartinib dose that is metabolized into AC886; IIV = inter-individual variability; RSE = relative standard error; RUV = residual unexplained variability; tv = typical value.

Source: Reviewer's run of Applicant's final AC886 model

The final AC886 model included typical values of quizartinib PK parameters that were fixed to the final estimates from the final quizartinib model. Individual values of IIV for quizartinib parameters were set to the individual posthoc IIV from the quizartinib PPK model. However, the AC886 PPK model structure did not include quizartinib T_{LAG} or quizartinib relative bioavailability (F_1). Although the AC886 model estimated the fraction of quizartinib that was metabolized into AC886 (f_{MET}) and included covariate effects of treatment phase on f_{MET} , the AC886 model did not incorporate the effects of moderate and strong CYP3A inhibitors on F_1 which were included in the final quizartinib model. Therefore, the AC886 model assumed that subjects receiving concomitant CYP3A inhibitors would have the same proportion of quizartinib metabolized into AC886 compared with subjects without concomitant CYP3A inhibitors.

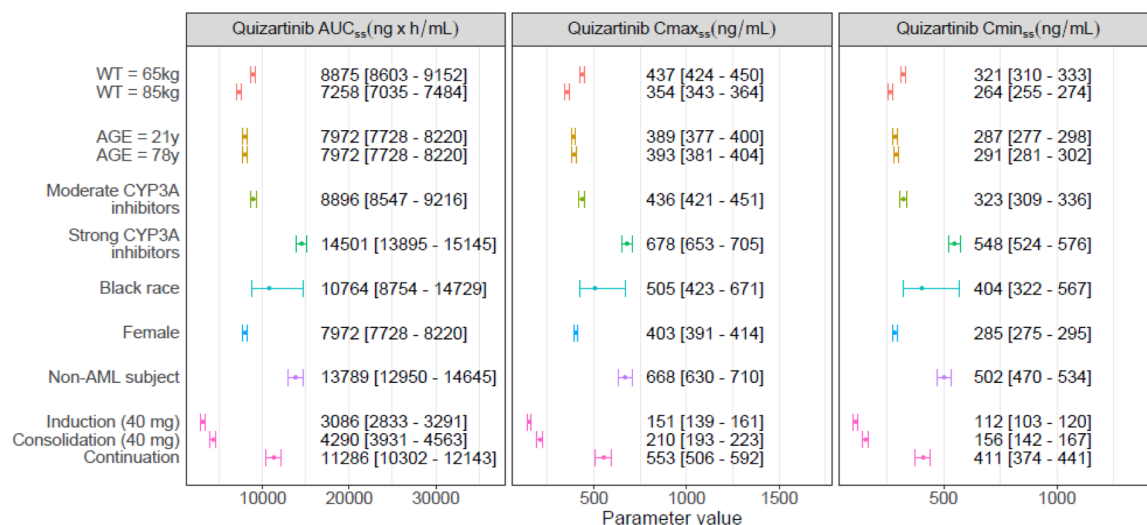
The quizartinib and AC886 goodness of fit plots (Figures A7-5, A7-6, A7-7 for quizartinib and Figures A7-19, A7-20, and A7-21 for AC886 in the Applicant's PPK Assessment Summary) indicate adequate model fit. Although the relatively even distribution of CWRES around zero in both models indicates relatively small bias, some observed quizartinib and AC886 observed concentrations had relatively high absolute values of CWRES. The range of CWRES was -5.4 to 5.1, and no significant associations between any covariates and CWRES were identified. The final PPK models are adequate for characterizing average quizartinib and AC886 concentrations but may not accurately characterize individual concentrations.

Covariate Effects

The predicted impacts of covariates on exposure are displayed in the Applicant's Figure 43 and Figure 44 in the PPK Assessment Summary for quizartinib and AC886, respectively. **Figure 31** and **Figure 32** display the median exposure values corresponding to the Applicant's Figure 43 and Figure 44, respectively. Of note, the Applicant's forest plot of the sum of quizartinib and AC886 exposure (Figure 45 in the PPK Assessment Summary) was generated by adding quizartinib and AC886 exposure together without accounting for differences in molecular weight, which may result in errors in relative exposure difference according to covariates.

Figure 31. Forest plot of covariate effects on quizartinib steady state exposure

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{VANFLYTA; quizartinib}

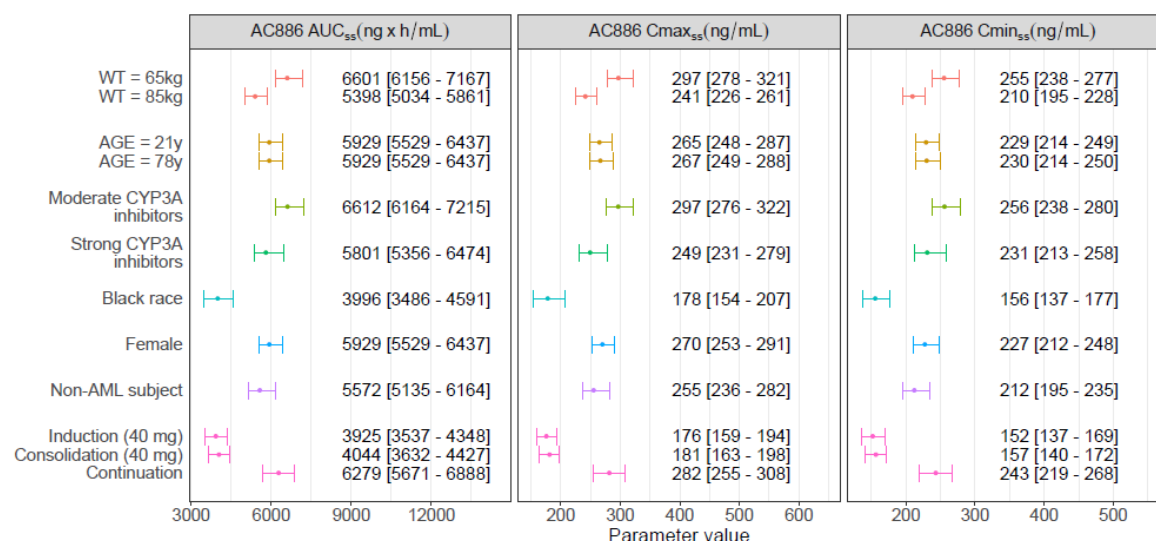


Exposure is shown for 60 mg of the salt form of quizartinib (i.e., 53 mg quizartinib free base), except for Induction and Consolidation which are shown for 40 mg of the salt form of quizartinib (i.e., 35.4 mg quizartinib free base). The dots and the whiskers represent the median and the 95% confidence intervals of AUC_{ss}, C_{max,ss}, and C_{min,ss}. The typical subject is a male subject with R/R AML who weighs 75 kg and is 47 years of age, has no concomitant CYP3A inhibitors, is not Black or African American, and has no treatment phase effect unless specified (i.e., Induction, Consolidation, or Continuation). Continuation refers to maintenance treatment. Non-AML subject refers to healthy subject. Steady state is achieved at Day 15.

AML = acute myeloid leukemia; AUC_{ss} = steady state area under the concentration-versus-time curve during one dosing interval; C_{max,ss} = steady state maximum concentration; C_{min,ss} = steady state trough concentration; R/R = relapsed or refractory.

Source: Figure 1 in Applicant's response (dated 15 December 2022) to 8 December 2022 Information Request

Figure 32. Forest plot of covariate effects on AC886 steady state exposure



Exposure is shown for 60 mg of the salt form of quizartinib (i.e., 53 mg quizartinib free base), except for Induction and Consolidation which are shown for 40 mg of the salt form of quizartinib (i.e., 35.4 mg quizartinib free base).

The dots and the whiskers represent the median and the 95% confidence intervals of AUC_{ss} , $C_{max,ss}$, and $C_{min,ss}$. The typical subject is a male subject with R/R AML who weighs 75 kg and is 47 years of age, has no concomitant CYP3A inhibitors, is not Black or African American, and has no treatment phase effect unless specified (i.e., Induction, Consolidation, or Continuation). Continuation refers to maintenance treatment. Non-AML subject refers to healthy subject. Steady state is achieved at Day 15.

AML = acute myeloid leukemia; AUC_{ss} = steady state area under the concentration-versus-time curve during one dosing interval; $C_{max,ss}$ = steady state maximum concentration; $C_{min,ss}$ = steady state trough concentration; R/R = relapsed or refractory.

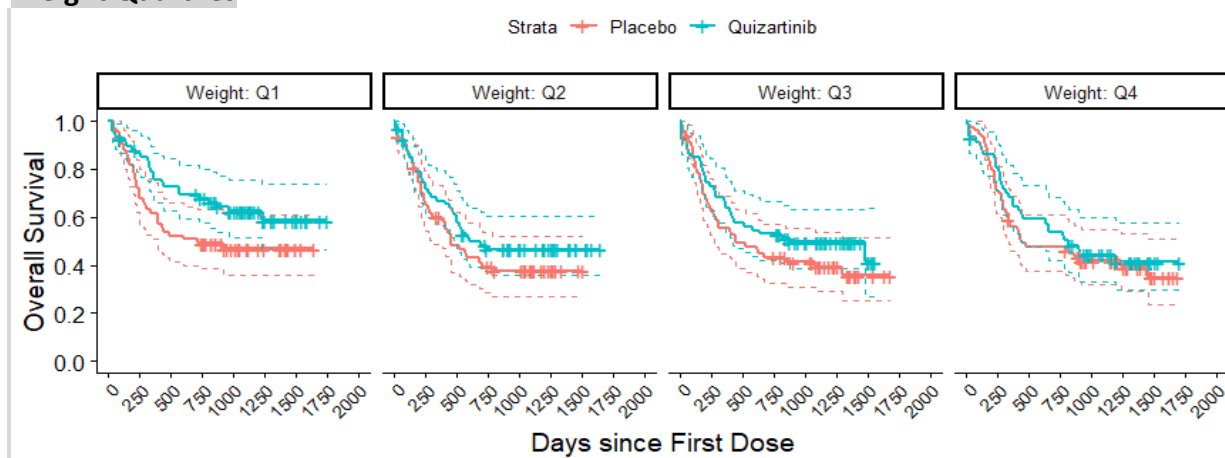
Source: Figure 2 in Applicant's response (dated 15 December 2022) to 8 December 2022 Information Request

Body Weight

In the final quizartinib PPK model, higher body weight was associated with higher clearance and higher volume with allometric scaling (see **Table 112**). The median quizartinib AUC_{ss} , $C_{max,ss}$, and $C_{min,ss}$ are 22 to 23% higher in a typical patient weighing 65 kg compared to a typical patient weighing 85 kg, as shown in **Figure 31**.

The observed OS appeared better in the quizartinib arm compared to the placebo arm across all weight quartiles, as displayed in **Figure 33**. The difference in exposure according to body weight is not expected to have clinically relevant impact on clinical outcomes, and no dose adjustments based on body weight are warranted based on current data.

Figure 33. Study AC220-A-U302 Overall Survival versus Treatment Arm Across Baseline Body Weight Quartiles



Weight quartile 1 = 36.8 to 61.6 kg (n=67 quizartinib; n=65 placebo). Weight quartile 2 = 61.8 to 70.2 kg (n=68 quizartinib; n=64 placebo). Weight quartile 3 = 70.3 to 82 kg (n=66 quizartinib; n=66 placebo). Weight quartile 4 = 82.1 to 151.6 kg (n=58 quizartinib; n=73 placebo). Q = quartile.

Source: Reviewer's analysis of Applicant's exposure-response efficacy dataset

Renal Impairment

After accounting for body weight, CL_{cr} was not associated with any clinically significant

differences in quizartinib or AC886 exposure. The PPK analysis supports the recommendation that no dose adjustment is needed in patients with mild to moderate renal impairment. The effect of severe renal impairment (CL_{cr} <30 mL/min) on quizartinib pharmacokinetics has not been studied.

Hepatic Impairment

In the PPK dataset, 139/931 (15%) of subjects had baseline mild hepatic dysfunction and 16/931 (1.7%) subjects had baseline moderate hepatic dysfunction according to NCI-ODWG classification. Quizartinib exposure did not differ significantly according to hepatic dysfunction category. In Study AC220-A-U302, subjects with moderate hepatic dysfunction had 25% lower AC886 AUC_{ss} following planned dosing of 35.4 mg quizartinib daily during induction compared to subjects with normal hepatic function. The difference in AC886 exposure is not expected to be clinically significant.

The PPK analysis of hepatic function is consistent with the dedicated hepatic impairment studies AC220-016 and AC220-A-U105, which are described in Section 6.3.2.3. No dose adjustment is needed in patients with mild or moderate hepatic impairment. The pharmacokinetics of quizartinib have not been studied in patients with severe hepatic impairment.

Race and Ethnicity

In the PPK analysis, PK parameters did not significantly differ according to Caucasian race category or Asian race category (Caucasian [n=603] compared to not Caucasian [n=328]; Asian [n=169] compared to not Asian [n=762]). However, the PPK model identified statistically significant impacts of Black or African American race (Black or African American [n=79] compared to not Black or African American [n=852]) on quizartinib and AC886 clearance. Black or African American subjects had 35% higher median quizartinib AUC_{ss} (95% CI = 9 to 83% higher AUC_{ss}), 30% higher median quizartinib C_{max,ss} (95% CI = 7 to 70% higher C_{max,ss}), 33% lower median AC886 AUC_{ss} (95% CI = 23 to 40% lower AUC_{ss}), and 33% lower median AC886 C_{max,ss} (95% CI = 23 to 42% lower C_{max,ss}) compared to subjects who did not identify as Black or African American (see **Figure 31** and **Figure 32**).

Study AC220-A-U302 only included 2 Black or African American subjects in the quizartinib arm and so the subgroup analysis could not adequately evaluate whether identifying as Black or African American race was associated with differences in clinical safety due to potentially higher exposure. However, E-R analyses did not find any E-R safety associations where 30 to 35% higher quizartinib exposure would result in higher risk of TEAEs (see Section 19.4.3.4). Therefore, Black and African American patients with previously untreated AML are not expected to have clinically significant differences in quizartinib exposure compared to patients

of other races.

Regarding ethnicity, the PPK analysis did not identify any differences in PK parameters in Asian patients according to Japanese, Korean, Chinese, Taiwanese, or Hongkongese subgroups. Potential PK parameter differences in subjects with Hispanic/Latino ethnicity were not evaluated due to lack of Hispanic/Latino ethnicity data.

Treatment Phase

The model fit was improved when a Study AC220-A-U302 treatment phase effect was included. The Applicant included a treatment phase effect on F1 in the final quizartinib model, which resulted in a statistically significant improvement in objective function value (OFV) compared to a treatment phase effect on CL or no treatment phase effect at all.

The increase in quizartinib dose-normalized concentrations from induction to consolidation and then from consolidation to continuation may be due to changes in disease characteristics over the course of treatment. Although the PPK model adequately fits the current data, the apparent effect of treatment phase on F1 is likely explained by a correlated mechanism that is more physiologically plausible than an impact on F1. For instance, time-dependent clearance or a time-varying disease characteristic effect on quizartinib clearance may characterize PK differences more accurately than the model's treatment phase effect on F1. The model-predicted F1 of quizartinib should not be used in place of absolute bioavailability determined from clinical bioavailability data.

Median exposure following 35.4 mg once daily is 1.4-fold higher during consolidation compared to induction ($AUC_{ss} = 4290$ versus 3086 ng·hr/mL). $C_{max,ss}$ is strongly impacted by F1 even though the treatment phase effect on F1 is physiologically unlikely, and so the PPK model may over-predict the impact of treatment phase on $C_{max,ss}$.

Quizartinib and AC886 exposure is higher during maintenance treatment compared to induction or consolidation due to lower clearance during maintenance as well as the higher proposed dose during maintenance. Median AUC_{ss} is 3.7-fold higher following the proposed 53 mg dose during continuation versus the proposed 35.4 mg dose during induction ($AUC_{ss} = 11286$ versus 3086 ng·hr /mL).

Based on E-R analysis of safety (Section 19.4.3.4) and E-R analysis of efficacy according to maintenance exposure (Section 19.4.3.2), the proposed quizartinib maintenance dose of 53 mg daily may result in worse QTcF prolongation and other safety events without improving survival compared to lower quizartinib maintenance dosages. The PMR in Section 6.2.2.3 addresses these concerns with the quizartinib maintenance dose and exposure.

CYP3A Inhibitor Coadministration

The PPK analysis supports the conclusion that no dosage adjustment is needed for concomitant weak or moderate CYP3A inhibitor coadministration. The PPK analysis also supports the proposed dosage reductions in patients with concomitant use of CYP3A inhibitors (see Section 6.3.2.4).

The quizartinib PPK model predicted 12% higher median quizartinib exposure (95% CI = 9 to 15%) with coadministration of a moderate CYP3A inhibitor (see **Figure 31**). This difference in quizartinib exposure is consistent with the results of Study AC220-015, which found that moderate CYP3A inhibitor coadministration resulted in 11% higher quizartinib C_{max} and 20% higher quizartinib AUC in healthy subjects. The difference in quizartinib exposure following coadministration with a moderate CYP3A inhibitor is $\leq 20\%$ and is not expected to be clinically relevant.

The quizartinib PPK model predicted that coadministration of a strong CYP3A inhibitor will result in 74% higher (95% CI = 67 to 80% higher) median quizartinib $C_{max,ss}$ and 83% higher (95% CI = 75 to 90% higher) median quizartinib AUC_{ss}. The predicted difference in AUC is consistent with the results of Study AC220-015, which found that strong CYP3A inhibitor coadministration resulted in 17% higher quizartinib C_{max} and 94% higher quizartinib AUC in healthy subjects. The PPK model may overpredict the impact on C_{max} because the model included strong CYP3A inhibitor administration impacts on both CL and F1. Although this may have resulted in better model fit, there is no clear physiologic mechanism explaining why CYP inhibitor administration would impact quizartinib F1. However, the model-predicted impact on AUC supports the degree of exposure difference observed in Study AC220-015.

CYP3A Inducer Coadministration

Only 36/931 (3.9%) subjects with PPK data had any recorded coadministration of a weak CYP3A inducer, and 1/931 (0.1%) subject had recorded coadministration of a moderate or strong CYP3A inducer. PPK data is inadequate to assess the impact of weak, moderate, or strong CYP3A inducer coadministration on quizartinib or AC886 PK. Due to the potential for concomitant CYP3A inducer administration to decrease quizartinib exposure and impact effectiveness, the recommendation to avoid coadministration of quizartinib with moderate or strong CYP3A inducers is reasonable.

Predicted Exposure

Study AC220-A-U302 quizartinib (**Table 114**) and AC886 (**Table 115**) exposures following planned dosage were calculated from individual predicted PK parameters for each treatment phase. Study AC220-A-U302 elimination half-lives and accumulation ratios during maintenance

treatment are summarized in **Table 116**.

Table 114. Summary of Individual Predicted Quizartinib Exposure in Study AC220-A-U302 According to Treatment Phase and Dose

Exposure metric	Statistic	Induction 35.4 mg QD (n=259)	Consolidation 35.4 mg QD (n=164)	Maintenance 26.5 mg QD (n=115)	Maintenance 53 mg QD (n=115)
Quizartinib AUC _{ss} (ng·hr/mL)	Geometric mean (CV%)	2676.4 (84.9%)	3934 (77.6%)	5076.6 (74.7%)	10153.2 (74.7%)
	95% confidence interval of the geometric mean	2445.6 to 2929	3538.7 to 4373.5	4489 to 5741.1	8977.9 to 11482.3
	Median (5 th , 95 th percentile)	2994.6 (706.2, 7427.5)	4252.5 (1000.5, 9902)	5459.9 (1324.8, 11901.9)	10919.7 (2649.7, 23803.8)
	Min, max	250, 11870	451.1, 13823.9	594.1, 18204.2	1188.2, 36408.5
Quizartinib C _{max,ss} (ng/mL)	Geometric mean (CV%)	139.6 (71.1%)	204 (63.4%)	264 (59.7%)	527.9 (59.7%)
	95% confidence interval of the geometric mean	129.1 to 150.9	186.5 to 223.1	238.4 to 292.3	476.7 to 584.6
	Median (5 th , 95 th percentile)	149.1 (42.8, 352.4)	216.5 (69.5, 465.1)	270.4 (94.2, 569.3)	540.9 (188.4, 1138.6)
	Min, max	11.7, 546	42.6, 587.7	67.9, 746	135.8, 1492.1
Quizartinib T _{max,ss} (hr)	Median (5 th , 95 th percentile)	2.7 (2.3, 4)	2.7 (2.3, 4)	2.7 (2.3, 4.7)	2.7 (2.3, 4.7)
	Min, max	1.5, 7.3	1.7, 6	1.7, 6	1.7, 6

The exposure metrics were obtained from empirical Bayes estimates of primary PK parameters based on the final population PK models for quizartinib and AC886, assuming nominal dosing without reductions/interruptions, as well as no concomitant administration of CYP3A inhibitors. Steady state is achieved at Day 15.

Quizartinib AUC_{ss} = 1000 • DOSE • F1/CL where DOSE is the dose in milligrams of quizartinib free base (i.e., 35.4 mg free base in 40 mg of the quizartinib salt form).

AUC_{ss} = steady state area under the concentration-versus-time curve during one dosing interval; CL = elimination clearance of quizartinib; C_{max,ss} = steady state maximum concentration; CV = coefficient of variation;

F1 = bioavailability of quizartinib; QD = once daily; T_{max,ss} = time to maximum concentration at steady state.

Source: Table A10-1 in Applicant's Population PK Report and Reviewer's analysis of "app_individualparameters.r" code provided in response to 26 October 2022 information request.

Table 115. Summary of Individual Predicted AC886 Exposure in Study AC220-A-U302 According to Treatment Phase and Dose

Exposure metric	Statistic	Induction 35.4 mg QD (n=259)	Consolidation 35.4 mg QD (n=164)	Maintenance 26.5 mg QD (n=115)	Maintenance 53 mg QD (n=115)
AC886 AUC _{ss} (ng·hr/mL)	Geometric mean (CV%)	3593.2 (51.1%)	3798.8 (45.8%)	2893.9 (46.1%)	5787.8 (46.1%)
	95% confidence interval of the geometric mean	3387.7 to 3811.2	3551.5 to 4063.3	2668.5 to 3138.3	5337.1 to 6276.7
	Median (5 th , 95 th percentile)	3973.2 (1389.3, 6156.7)	4178.3 (1567.2, 6321.6)	3108.2 (1203.6, 4969.5)	6216.4 (2407.3, 9939.1)
	Min, max	253.7, 8780.5	764.3, 9048.6	594.2, 7034.4	1188.3, 14068.8
AC886 C _{max,ss}	Geometric mean (CV%)	162.6 (52%)	171.5 (47.1%)	130.8 (48%)	261.6 (48%)
	95% confidence interval of	153.2 to 172.6	160.1 to 183.8	120.2 to 142.3	240.5 to 284.5

Exposure metric	Statistic	Induction 35.4 mg QD (n=259)	Consolidation 35.4 mg QD (n=164)	Maintenance 26.5 mg QD (n=115)	Maintenance 53 mg QD (n=115)
(ng/mL)	the geometric mean				
	Median (5 th , 95 th percentile)	178.5 (60.9, 270.8)	187.8 (65.6, 280.7)	140.2 (50, 228.8)	280.4 (100, 457.5)
	Min, max	11.2, 417.2	32.7, 429.9	25.4, 334.2	50.8, 668.4
AC886	Median (5 th , 95 th percentile)	4.6 (3.1, 8.5)	4.6 (3.1, 8.2)	4.8 (3.1, 8.2)	4.8 (3.1, 8.2)
Tmax _{ss} (hr)	Min, max	1.6, 9.7	2.3, 9.7	2.3, 9.7	2.2, 9.7

The exposure metrics were obtained from empirical Bayes estimates of primary PK parameters based on the final population PK models for quizartinib and AC886, assuming nominal dosing without reductions/interruptions, as well as no concomitant administration of CYP3A inhibitors. Steady state is achieved at Day 15.

AC886 AUC_{ss} = 1000 • DOSE • 576.67/560.68 • F1 • f_{MET}/CL_M where DOSE is the dose in milligrams of quizartinib free base (i.e., 35.4 mg free base in 40 mg of the quizartinib salt form), 560.68 g/mol is the molecular weight of quizartinib, and 576.67 g/mol is the molecular weight of AC886.

AUC_{ss} = steady state area under the concentration-versus-time curve during one dosing interval; CL_M = elimination clearance of AC886; C_{max,ss} = steady state maximum concentration; CV = coefficient of variation; F1 = bioavailability of quizartinib; f_{MET} = fraction of quizartinib dose that is metabolized into AC886; QD = once daily; Tmax_{ss} = time to maximum concentration at steady state.

Source: Table A10-1 in Applicant's Population PK Report and Reviewer's analysis of "app_individualparameters.r" code provided in response to 26 October 2022 information request.

Table 116. Summary statistics of half-life and accumulation ratios in the maintenance phase for quizartinib and AC886 in study AC220-A-U302.

	N	Mean	SD	Median	5th percentile	95th percentile
Quizartinib						
t1/2 _{eff} (h)	115	81.0	73.3	61.8	23.0	219
Accumulation ratio	115	5.39	4.40	4.24	1.94	13.6
AC886						
t1/2 _{eff} (h)	115	136	113	103	45.7	368
Accumulation ratio	115	8.69	6.80	6.72	3.28	22.6

The effective half-life (t_{1/2eff}) was calculated as $24 \cdot \ln(2) / (\ln(R_{ac} / R_{ac} - 1))$.

The accumulation ratio (R_{ac}) was calculated as AUC_{ss} / AUC₀₋₂₄. Individual values of AUC_{ss} and AUC₀₋₂₄ were calculated following 53 mg quizartinib daily during maintenance treatment without dose reductions or interruptions, as well as no concomitant administration of CYP3A inhibitors. Steady state is achieved at Day 15.

AUC₀₋₂₄ = area under the concentration-versus-time curve from time zero to 24 hours following a single dose of quizartinib; AUC_{ss} = steady state area under the concentration-versus-time curve during one dosing interval; h = hours; ln=natural log; R_{ac} = accumulation ratio; SD = standard deviation; t_{1/2eff} = effective half-life.

Source: Table A13-1 in Applicant's Population PK Report

Model-predicted exposures in Phase 2 Study AC220-007 subjects with R/R AML are summarized in **Table 117**. Unlike Study AC220-A-U302, Study AC220-007 did not include treatment phases and quizartinib was only administered as monotherapy. Individual predicted clearance did not vary according to nominal dose in Study AC220-007.

Table 117. Summary statistics of model-predicted Exposure in Subjects with R/R AML in Study AC220-007, grouped by nominal dose.

Dose	Subjects N	Quizartinib			AC886		
		AUC _{ss} ^a ng·h/mL (CV%)	C _{ss,max} ^a ng/mL (CV%)	T _{max,ss} ^b h	AUC _{ss} ^a ng·h/mL (CV%)	C _{ss,max} ^a ng/mL (CV%)	T _{max,ss} ^b h
20 mg	238	2730 (93.3)	141 (75.5)	2.56 (1.65, 9.46)	1910 (46.3)	86.8 (45.2)	4.13 (1.99, 11.5)
30 mg	238	4090 (93.3)	212 (75.5)	2.56 (1.65, 9.46)	2870 (46.3)	130 (45.2)	4.13 (1.99, 11.5)
60 mg	238	8190 (93.3)	424 (75.5)	2.56 (1.65, 9.46)	5730 (46.3)	261 (45.2)	4.13 (1.99, 11.5)

^a Reported as geometric mean (CV%).

^b Reported as median (min, max)

^c One subject with estimated duration of zero-order input to depot compartment over 24 hours was excluded from the summary statistics.

The exposure metrics were obtained from empirical Bayes estimates of primary PK parameters based on the final population PK models for quizartinib and AC886, assuming nominal dosing without dose reductions or interruptions, as well as no concomitant administration of CYP3A inhibitors. Nominal dose is described in mg of the quizartinib dihydrochloride salt, and 20 mg quizartinib dihydrochloride salt contains 17.7 mg quizartinib free base. Steady state is achieved at Day 15.

Quizartinib AUC_{ss} = 1000 • DOSE • F1/CL where DOSE is the dose in milligrams of quizartinib free base (i.e., 35.4 mg free base in 40 mg of the quizartinib salt form).

AC886 AUC_{ss} = 1000 • DOSE • 576.67/560.68 • F1 • f_{MET}/CL_M where DOSE is the dose in milligrams of quizartinib free base, 560.68 g/mol is the molecular weight of quizartinib, and 576.67 g/mol is the molecular weight of AC886.

AML = acute myeloid leukemia; AUC_{ss} = steady-state area under the concentration-versus-time curve during one dosing interval; CL = elimination clearance of quizartinib; CL_M = elimination clearance of AC886; CV = coefficient of variation; C_{ss,max} = steady state maximum concentration; F1 = bioavailability of quizartinib; f_{MET} = fraction of quizartinib dose that is metabolized into AC886; R/R = relapsed or refractory; T_{max,ss} = time to maximum concentration at steady state.

Source: Table A10-2 in Applicant's Population PK Report

19.4.3. Exposure-Response Analysis

19.4.3.1. E-R Efficacy Executive Summary

The FDA's Assessment:

E-R analysis identified that improvement in OS may be associated with treatment arm (quizartinib versus placebo) or with higher quizartinib induction exposure (AUC_{ss}) following planned dosing of 35.4 mg daily. The data do not adequately support the conclusion that there is an E-R association with OS due to the high level of uncertainty. No E-R associations were identified between quizartinib induction exposure and EFS or CR rate.

The Reviewer also assessed OS and EFS according to maintenance exposure in subjects who received at least one maintenance dose. Maintenance exposure was not associated with any clear differences in OS or EFS. Due to confounding factors such as a potential carryover effect from quizartinib induction and consolidation as well as the QTcF-dependent maintenance dosage in the protocol, E-R analysis cannot support the conclusion that quizartinib maintenance

treatment has a clinical benefit.

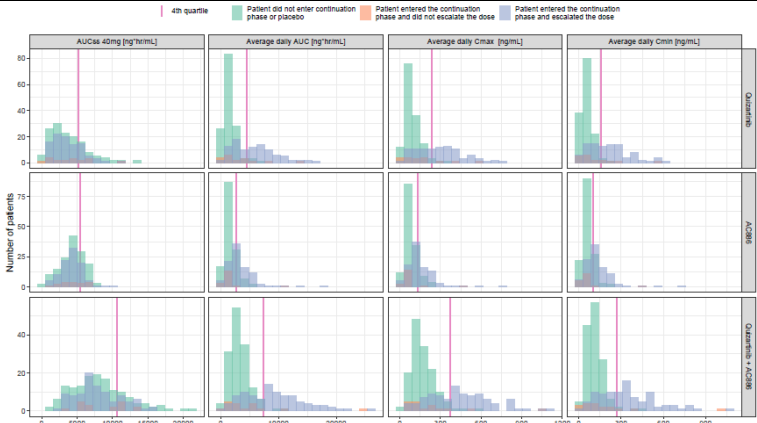
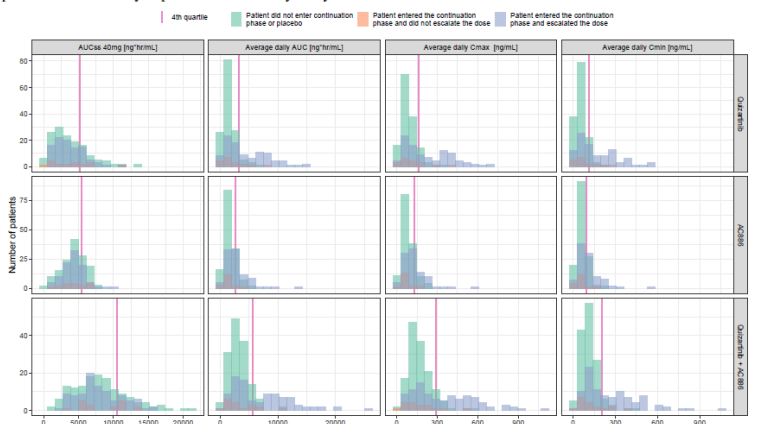
Importantly, E-R analysis indicates that the proposed 53 mg daily maintenance dosage may expose patients to unnecessary toxicity such as QT prolongation and other safety events without an improvement in survival compared to lower maintenance doses. The need for additional data to determine an appropriate quizartinib maintenance dose is addressed by the PMR in Section 6.2.2.3.

19.4.3.2. E-R Efficacy Assessment Summary

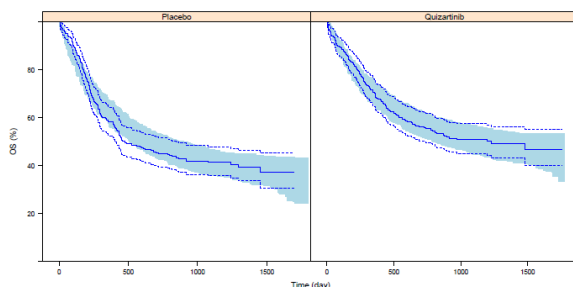
The Applicant's Position:

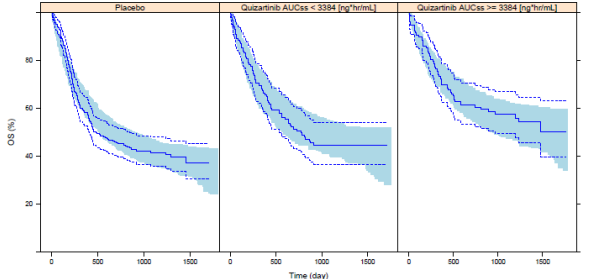
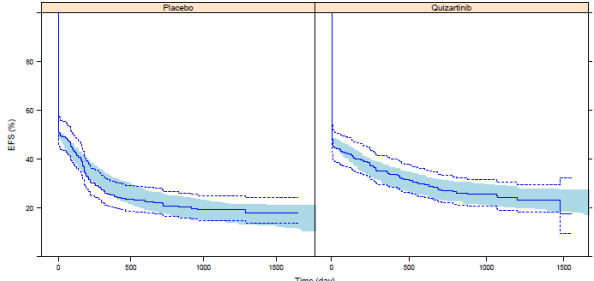
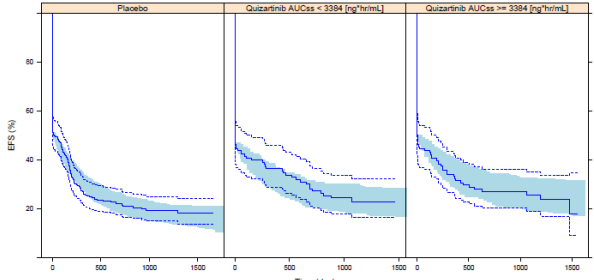
General Information		
Goal of E-R analysis		To support the quizartinib dosing regimen tested in Study AC220-A-U302 based on the identified E-R relationships in newly diagnosed AML patients
Study Included		E-R analyses were based on the data from Study AC220-A-U302 only.
Endpoint		Primary: OS Secondary: EFS (based on the definition of ITF as failure to achieve CR within 42 days from the start of the last cycle of induction chemotherapy), remission rates, and remission rates with MRD negativity
No. of Subjects (total, and with individual PK)		Total 265 quizartinib-treated, 259 with PK
Population Characteristics (Tables 12 and 13 in E-R report AC220-PMx010)	General	Including both placebo- and quizartinib-treated: Age median (range): 56.0 years (20.0, 75.0) Weight median (range): 70.3 kg (36.8, 152) Sex: male 243 (45.8%) Race: 1 (0.2%) American Indian 156 (29.4%) Asian 7 (1.3%) Black 316 (59.5%) White 51 (9.6%) Other
	Pediatrics (if any)	Not applicable
Dose(s) Included		20 mg, 30 mg, 40 mg, 60 mg
Exposure Metrics Explored (range)		AUCss 40 mg in induction, average daily AUC, Cmax and Cmin. Ranges provided in E-R Report Figures A6-1 (OS) and A6-2 (EFS)

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	 Figure A6-1: Histograms of exposure metrics for patients in the OS dataset, colored by dose escalation during continuation phase and stratified by exposure metric and by analyte.  Figure A6-2: Histograms of exposure metrics for patients in the EFS dataset, colored by dose escalation during continuation phase and stratified by exposure metric and by analyte.
Covariates Evaluated	<i>OS and EFS: WBC count at the time of diagnosis, FLT3-ITD AR, NPM1 mutation, AML cytogenetic risk score, ECOG score, sex, race, age, and body weight</i> <i>Remission rates: WBC count at the time of diagnosis, FLT3-ITD AR, NPM1 mutation, AML cytogenetic risk score, ECOG score, sex, race, age, and body weight</i>

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	<i>For primary and major secondary endpoints</i> <i>OS: A parametric TTE model where the baseline hazard followed a Gompertz distribution</i> <i>EFS: a parametric TTE model with time-varying hazard according to a Gompertz distribution. A separate hazard term was included for subjects with refractory disease (treatment failures)</i>	OS appeared to be associated with age and quizartinib induction AUC_{ss}, based on the Applicant's OS model. Parameter estimates with 95%
Model Parameter Estimates	OS:	Parameter estimates with 95%

	Table 20: Parameter estimates for the final OS model. <table><tr><th colspan="4">Final OS model</th></tr><tr><td>Run</td><td></td><td>208</td><td></td></tr><tr><td>OFV</td><td></td><td>4467.8</td><td></td></tr><tr><td>Condition number</td><td></td><td>7.7</td><td></td></tr></table> <table><tr><th></th><th>Unit</th><th>Value</th><th>RSE (%)</th></tr><tr><td>Baseline hazard</td><td>year⁻¹</td><td>0.669</td><td>9.13</td></tr><tr><td>Gompertz shape parameter</td><td>year⁻¹</td><td>-0.619</td><td>11.1</td></tr><tr><td>Age on baseline hazard</td><td>year⁻¹</td><td>0.0288</td><td>17.2</td></tr><tr><td>Slope for linear effect of quizartinib AUC_{ss}</td><td>(ng*hr/mL)⁻¹</td><td>-0.0690</td><td>37.2</td></tr></table> EFS: Table 22: Parameter estimates for the final EFS model. <table><tr><th colspan="4">Final EFS model</th></tr><tr><td>Run</td><td></td><td>25</td><td></td></tr><tr><td>OFV</td><td></td><td>-1479.00</td><td></td></tr><tr><td>Condition number</td><td></td><td>8.74</td><td></td></tr></table> <table><tr><th></th><th>Unit</th><th>Value</th><th>RSE (%)</th></tr><tr><td>Baseline hazard</td><td>year⁻¹</td><td>0.795</td><td>14.0</td></tr><tr><td>Gompertz shape parameter</td><td>year⁻¹</td><td>-0.684</td><td>16.1</td></tr><tr><td>Baseline hazard for RD</td><td>year⁻¹</td><td>1000</td><td>(FIX)</td></tr><tr><td>Treatment effect^a</td><td></td><td>-0.395</td><td>43.6</td></tr></table> ^a Defined as binary yes/no variable. See Glossary for definitions.	Final OS model				Run		208		OFV		4467.8		Condition number		7.7			Unit	Value	RSE (%)	Baseline hazard	year ⁻¹	0.669	9.13	Gompertz shape parameter	year ⁻¹	-0.619	11.1	Age on baseline hazard	year ⁻¹	0.0288	17.2	Slope for linear effect of quizartinib AUC _{ss}	(ng*hr/mL) ⁻¹	-0.0690	37.2	Final EFS model				Run		25		OFV		-1479.00		Condition number		8.74			Unit	Value	RSE (%)	Baseline hazard	year ⁻¹	0.795	14.0	Gompertz shape parameter	year ⁻¹	-0.684	16.1	Baseline hazard for RD	year ⁻¹	1000	(FIX)	Treatment effect ^a		-0.395	43.6	CI for the Applicant’s OS model are summarized in Table 119. EFS was associated with treatment arm and refractory disease. Quizartinib AUC_{ss} during induction did not have a statistically significant effect on EFS. The Reviewer also conducted E-R efficacy analysis for the maintenance treatment phase, as described in the FDA assessment.
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Model Evaluation	OS:  Figure 23: Visual predictive check of the final OS model, stratified according to treatment arm. The solid and dashed blue lines represent the Kaplan-Meier point estimate and 95% confidence interval, based on observed placebo and quizartinib data; the shaded areas represent the 95% confidence interval of the Kaplan-Meier point estimate, based on 200 replicate simulations.	The data do not adequately support the conclusion that higher quizartinib exposure during induction is associated with better OS. The OS model fit did not differ significantly																																																																								

	 Figure 24: Visual predictive check of the final OS model for placebo or quizartinib-treated subjects, stratified according to AUC_{ss} levels below or equal and above the median AUC_{ss} calculated for quizartinib. The solid and dashed blue lines represent the Kaplan-Meier point estimate and 95% confidence interval, based on observed placebo and quizartinib data; the shaded areas represent the 95% confidence interval of the Kaplan-Meier point estimate, based on 200 replicate simulations. EFS:  Figure 27: Visual predictive check of the final EFS model, stratified according to treatment arm. The solid and dashed blue lines represent the Kaplan-Meier point estimate and 95% confidence interval, based on observed placebo and quizartinib data; the shaded areas represent the 95% confidence interval of the Kaplan-Meier point estimate, based on 200 replicate simulations.  Figure 28: Visual predictive check of the final EFS model for placebo or quizartinib-treated subjects, stratified according to AUC_{ss} levels below or equal and above the median AUC_{ss} calculated for quizartinib. The solid and dashed blue lines represent the Kaplan-Meier point estimate and 95% confidence interval, based on observed placebo and quizartinib data; the shaded areas represent the 95% confidence interval of the Kaplan-Meier point estimate, based on 200 replicate simulations.	when the induction AUC_{ss} effect was replaced with a treatment effect (quizartinib versus placebo), as described in the FDA assessment. It is uncertain if the apparent improvement in OS is due to treatment arm or induction quizartinib AUC_{ss}. No difference in EFS was observed according to quizartinib AUC_{ss} following 35.4 mg daily during induction. In subjects who received at least one maintenance dose, OS was not clearly associated with induction AUC_{ss}, average daily maintenance exposure, or
Covariates and Clinical Relevance	OS: Age was a statistically significant covariate on the baseline hazard for OS, with older subjects being at higher risk.	

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	Figure 36: Univariate forest plot of hazard ratios based on the final OS model. The dots and the whiskers represent the median and the 95% CI of the hazard ratio, respectively, displayed numerically as median [95% CI] on the right of each panel. The vertical black line represents the hazard ratio for a typical patient in placebo arm in the analysis data set, aged 56 years.	quizartinib treatment (versus placebo).
Simulation for Specific Population	Not applicable	
Visualization of E-R relationships	See E-R Report Figure 36	
Overall Clinical Relevance for E-R	A modest but statistically significant E-R relationship in OS, where higher quizartinib exposure was associated with longer OS, provided support for dose escalation to 60 mg in continuation treatment.	The data do not adequately support the conclusion that higher quizartinib exposure during induction is associated with better OS. The E-R analyses do not provide evidence supporting the proposed maintenance dosage of 53 mg daily. The lack of association between maintenance exposure and OS suggests that the proposed 53 mg daily maintenance dosage could expose patients to unnecessary toxicity without clinical

		benefit in survival.
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	<i>Not applicable</i>	The E-R relationship and time course of pharmacodynamic response for the safety and effectiveness of quizartinib have not been fully characterized.

Note: table and figure numbering corresponds to those used in the source document.

Source: **AC220-PMx010** (eCTD 5.3.3.5)

Summary of Baseline Characteristics and Laboratory Values in the Dataset

Note: table numbering corresponds to that used in the source document.

Source: **AC220-PMx010** (eCTD 5.3.3.5)

Table 12: Baseline continuous covariate statistics in any of the 5 analysis data sets.

	Placebo N=268	Quizartinib N=263	Overall N=531
Age (years)			
Mean (SD)	54.3 (12.8)	53.6 (13.2)	53.9 (13.0)
Median (min, max)	56.0 (20.0, 75.0)	56.0 (23.0, 75.0)	56.0 (20.0, 75.0)
Body weight (kg)			
Mean (SD)	74.3 (17.8)	72.3 (16.0)	73.3 (16.9)
Median (min, max)	71.0 (42.0, 152)	70.0 (36.8, 125)	70.3 (36.8, 152)
Potassium (mM)			
Mean (SD)	3.95 (0.464)	4.00 (0.408)	3.98 (0.437)
Median (min, max)	4.00 (2.40, 5.70)	4.00 (2.80, 5.20)	4.00 (2.40, 5.70)
Calcium (mM)			
Mean (SD)	2.23 (0.130)	2.21 (0.158)	2.22 (0.145)
Median (min, max)	2.22 (1.65, 2.71)	2.22 (1.00, 2.60)	2.22 (1.00, 2.71)
Missing (N (%))	1 (0.37%)	2 (0.76%)	3 (0.56%)
Magnesium (mM)			
Mean (SD)	0.858 (0.126)	0.859 (0.128)	0.859 (0.127)
Median (min, max)	0.860 (0.410, 1.93)	0.860 (0.560, 2.08)	0.860 (0.410, 2.08)

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Table 13: Baseline categorical covariate statistics in any of the 5 analysis data sets.

Covariate		Placebo		Quizartinib		Overall	
		N	%	N	%	N	%
Sex	Female	148	55.2	140	53.2	288	54.2
	Male	120	44.8	123	46.8	243	45.8
Race	American Indian	1	0.4	0	0.0	1	0.2
	Asian	77	28.7	79	30.0	156	29.4
	Black	5	1.9	2	0.8	7	1.3
	White	161	60.1	155	58.9	316	59.5
	Other	24	9.0	27	10.3	51	9.6
White blood cell count (cells/L)	<40 10 ⁹	133	49.6	131	49.8	264	49.7
	≥40 10 ⁹	135	50.4	132	50.2	267	50.3
FLT3-ITD allelic ratio	3-25%	98	36.6	93	35.4	191	36.0
	26-50%	136	50.7	141	53.6	277	52.2
	>50%	34	12.7	28	10.6	62	11.7
	Missing	0	0.0	1	0.4	1	0.2
NPM1 mutation	Absent	120	44.8	115	43.7	235	44.3
	Present	137	51.1	138	52.5	275	51.8
	Missing	11	4.1	10	3.8	21	4.0
AML cytogenetic risk score	Favorable	19	7.1	13	4.9	32	6.0
	Intermediate	190	70.9	193	73.4	383	72.1
	Unfavorable	27	10.1	19	7.2	46	8.7
	Unknown	31	11.6	38	14.4	69	13.0
	Missing	1	0.4	0	0.0	1	0.2
ECOG Performance status	0	97	36.2	85	32.3	182	34.3
	1	134	50.0	133	50.6	267	50.3
	2	36	13.4	45	17.1	81	15.3
	Missing	1	0.4	0	0.0	1	0.2

The FDA's Assessment:

E-R analysis was conducted for OS, EFS, and CR rate using induction exposure (AUC_{ss} following planned dosage of 35.4 mg daily during induction). A separate E-R analysis was conducted in subjects with at least one maintenance dose using maintenance exposure from actual dosing records

E-R Efficacy Analysis using Induction Steady State Exposure

The E-R analysis of induction exposure contained data from 259 subjects with newly diagnosed FLT3-ITD(+) AML who received at least one dose of quizartinib and 268 subjects with newly diagnosed FLT3-ITD(+) AML who received at least one dose of placebo in Study AC220-A-U302. **Table 118** summarizes the individual predicted exposures for subjects with E-R efficacy data who received quizartinib.

Table 118. Study AC220-A-U302 Individual Predicted Exposure in the E-R Efficacy Dataset

Statistic	Quizartinib AUC _{ss} (ng·hr/mL)	AC886 AUC _{ss} (ng·hr/mL)
N	259	259
Geometric Mean (CV%)	2676.4 (84.9%)	3493.6 (51.1%)
95% CI of the Geometric Mean	2445.6 to 2929	3293.8 to 3705.5
Median	2994.6	3863
5 th , 95th percentile	706.2, 7427.5	1350.8, 5986
Min, Max	250, 11870	246.7, 8537

Individual predicted exposure was determined following planned dosage of 35.4 mg daily during induction treatment in subjects with newly diagnosed FLT3-ITD(+) AML and assuming no CYP3A inhibitor coadministration. Steady state is achieved at Day 15.

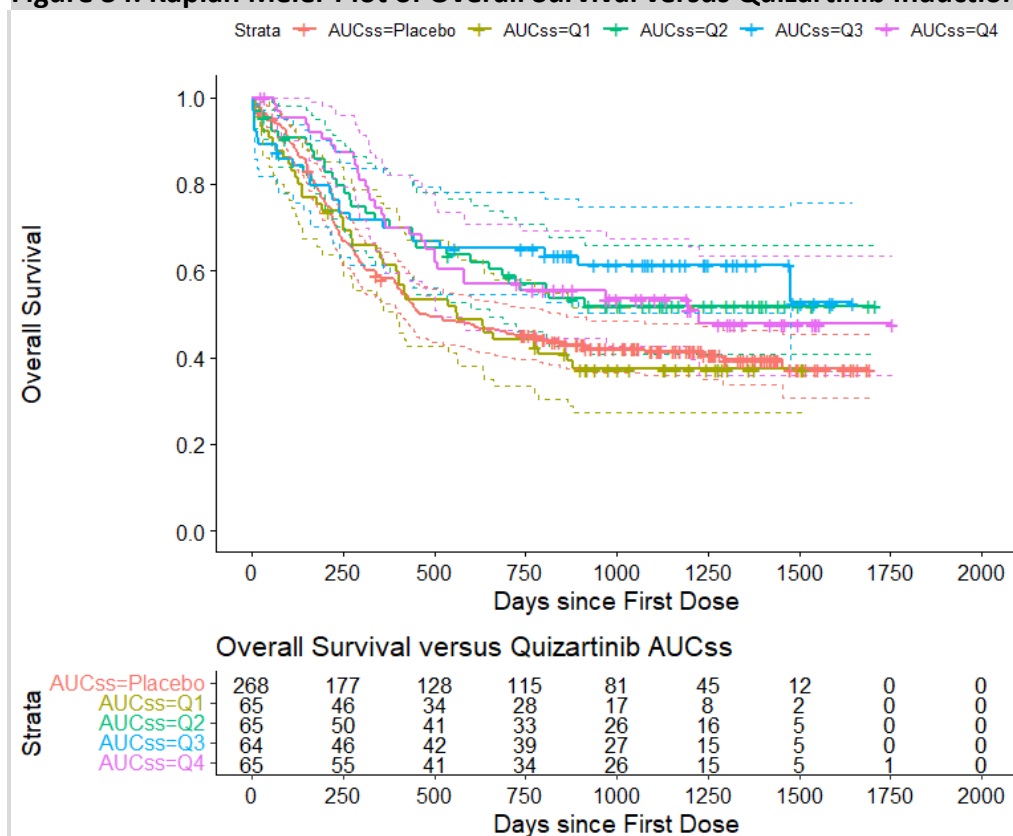
AML = acute myeloid leukemia; AUC_{ss} = steady state area under the concentration-versus-time curve during one dosing interval; CI = confidence interval; CV = coefficient of variation; E-R = exposure-response.

Source: Reviewer's analysis

Multivariate E-R modeling did not identify any clear associations between EFS or CR rate and quizartinib AUC_{ss} following planned dosage of 35.4 mg once daily.

Observed OS according to quizartinib exposure quartile is displayed in **Figure 34**. The lowest quizartinib AUC_{ss} quartile did not appear to have significantly different OS compared to placebo. Quizartinib quartiles Q2, Q3, and Q4 generally had better OS than placebo or Q1. However, the 95% CIs for all quartiles overlap with each other and there is no clear association between AUC_{ss} and OS.

Figure 34. Kaplan Meier Plot of Overall Survival versus Quizartinib Induction AUCss Quartile



Individual predicted exposure was determined following planned dosage of 35.4 mg daily during induction treatment in subjects with newly diagnosed FLT3-ITD(+) AML and assuming no CYP3A inhibitor coadministration. AML = acute myeloid leukemia; AUC_{ss}= steady state area under the concentration-versus-time curve during one dosing interval; Q = quartile.

Source: Reviewer's analysis

Several confounding factors may impact OS, such as age or baseline disease characteristics, and so multivariate E-R modeling was performed to account for potential confounding. The final OS model used a time-varying hazard function according to a Gompertz distribution, and both lower age and increased induction AUC_{ss} were associated with better OS. The final model parameter estimates from the Reviewer's run of the final model are summarized in **Table 119**. The value of the estimated AUC_{ss} slope is slightly different than the value in the Applicant's Table 20 in the E-R Efficacy Assessment Summary above due to discovery of a calculation error; however, conclusions from the model did not differ.

Table 119. Applicant's Final Overall Survival Model Parameter Estimates

	Estimate	RSE	95% CI
Baseline Hazard (1/year)	0.669	9.1%	0.549 to 0.789
Gompertz shape parameter (1/year)	-0.619	11.1%	-0.753 to -0.485

	Estimate	RSE	95% CI
Age (year) effect	0.0288	17.2%	0.019 to 0.038
Slope for linear effect of quizartinib AUC _{ss} (ng·hr/mL)	-0.0779	37.3%	-0.135 to -0.021

Individual predicted exposure was determined following planned dosage of 35.4 mg daily during induction treatment in subjects with newly diagnosed FLT3-ITD(+) AML and assuming no CYP3A inhibitor coadministration. AML = acute myeloid leukemia; AUC_{ss} = steady state area under the concentration-versus-time curve during one dosing interval; CI = confidence interval; RSE = relative standard error.

Source: Table 20 in Applicant's Exposure-Response Report and Reviewer's analysis of Applicant's run208 model file

The VPC plots in the Applicant's Figure 23 and Figure 24 in the E-R Efficacy Assessment Summary display the variability in OS according to the Applicant's final model. However, VPC plots do not display uncertainty of model parameters or predictions, which is a critical consideration in model selection. Although the Applicant's final OS model included a statistically significant effect of quizartinib exposure on OS, reviewer analysis found that the exposure effect could be replaced by a treatment arm effect (i.e., quizartinib versus placebo) without a significant difference in model fit (OFV 4467.8 versus 4471.4, difference of 3.6 points). Therefore, it is uncertain whether the apparent effect on overall survival is truly due to quizartinib AUC_{ss} or due to treatment cohort (i.e., quizartinib or placebo). The use of exposure following planned dosing rather than actual dosing records also contributed to the uncertainty of an exposure effect on OS. The data do not adequately support the conclusion that higher quizartinib exposure is associated with better OS.

Maintenance E-R Efficacy in Subjects who Received at least one Maintenance Dose

The maintenance E-R analysis contained data for 116 subjects who received at least one maintenance dose of quizartinib and 92 subjects who received at least one maintenance dose of placebo in Study AC220-A-U302.

Subjects receiving quizartinib were less likely to receive a maximum individual dose of 53 mg, which is the full proposed once daily maintenance dose, compared to placebo. Subjects who received quizartinib had significantly higher rates of dose modifications during the maintenance phase than subjects who received placebo. The maximum individual maintenance dose and rates of dose modifications are summarized in **Table 120** and **Table 121**, respectively.

Table 120. Summary of Maximum Individual Dose During Maintenance Treatment in Study AC220-A-U302

	Quizartinib n=116 (%)	Placebo n=92 (%)
Subjects who received at least one maintenance dose (any strength)	100%	100%
Subjects who received a maximum individual maintenance dose of 26.5 mg	19.8%	10.9%
Subjects who received a maximum individual maintenance dose of 53 mg	74.1%	89.1%

In the quizartinib arm, 2 subjects had maximum individual dose of 17.7 mg during maintenance treatment and 5 subjects had maximum individual dose of 35.4 mg during maintenance treatment.

Source: Table 14.3.2.2.6 in the Applicant's response (dated 27 January 2023) to 12 January 2023 information request

Table 121. Summary of TEAE leading to Dose Modification by Treatment Arm and Individual Dose During Maintenance Treatment in Study AC220-A-U302

	Quizartinib n=116 n (%)	Placebo n=92 n (%)
Subjects who received at least one maintenance dose (any strength)	116	92
TEAE leading to any dose modification during maintenance treatment*	87 (75.0)	33 (35.9)
TEAE leading to dose reduction during maintenance treatment	42 (36.2)	14 (15.2)
TEAE leading to dose interruption or delay during maintenance treatment	65 (56.0)	22 (23.9)
TEAE leading to discontinuation during maintenance treatment	18 (15.5)	7 (7.6)
Subjects who received a maximum individual maintenance dose of 26.5 mg	23	10
TEAE leading to any dose modification during maintenance treatment*	17 (73.9)	4 (40.0)
TEAE leading to dose reduction during maintenance treatment	3 (13.0)	1 (10.0)
TEAE leading to dose interruption or delay during maintenance treatment	15 (65.2)	1 (10.0)
TEAE leading to discontinuation during maintenance treatment	5 (21.7)	2 (20.0)
Subjects who received a maximum individual maintenance dose of 53 mg	86	82
TEAE leading to any dose modification during maintenance treatment*	64 (74.4)	29 (35.4)
TEAE leading to dose reduction during maintenance treatment	37 (43.0)	13 (15.9)
TEAE leading to dose interruption or delay during maintenance treatment	46 (53.5)	21 (25.6)
TEAE leading to discontinuation during maintenance treatment	11 (12.8)	5 (6.1)

*Dose modification = dose reduction, dose interruption or delay, or discontinuation

In the quizartinib arm, 2 subjects had maximum individual dose of 17.7 mg during maintenance treatment and 5 subjects had maximum individual dose of 35.4 mg during maintenance treatment.

TEAE = treatment emergent adverse event

Source: Table 14.3.2.2.6 in the Applicant's response (dated 27 January 2023) to 12 January 2023 information request

Individual predicted exposure calculated from actual maintenance dosage records are summarized in **Table 122**. Average concentration from first maintenance dose to time of event ($C_{avg,TTE}$) was the primary exposure metric for E-R maintenance analysis. However, results and conclusions were similar when average concentration from first maintenance dose to last dose or time of event, whichever occurred first ($C_{avg,lastdose}$), was used as the maintenance exposure metric instead.

Table 122. Study AC220-A-U302 Individual Predicted Exposure During Maintenance Treatment in Subjects with at least one Maintenance Dose

	Quizartinib		AC886	
	$C_{avg,TTE}$ (ng/mL)	$C_{avg,lastdose}$ (ng/mL)	$C_{avg,TTE}$ (ng/mL)	$C_{avg,lastdose}$ (ng/mL)
N	115	115	115	115

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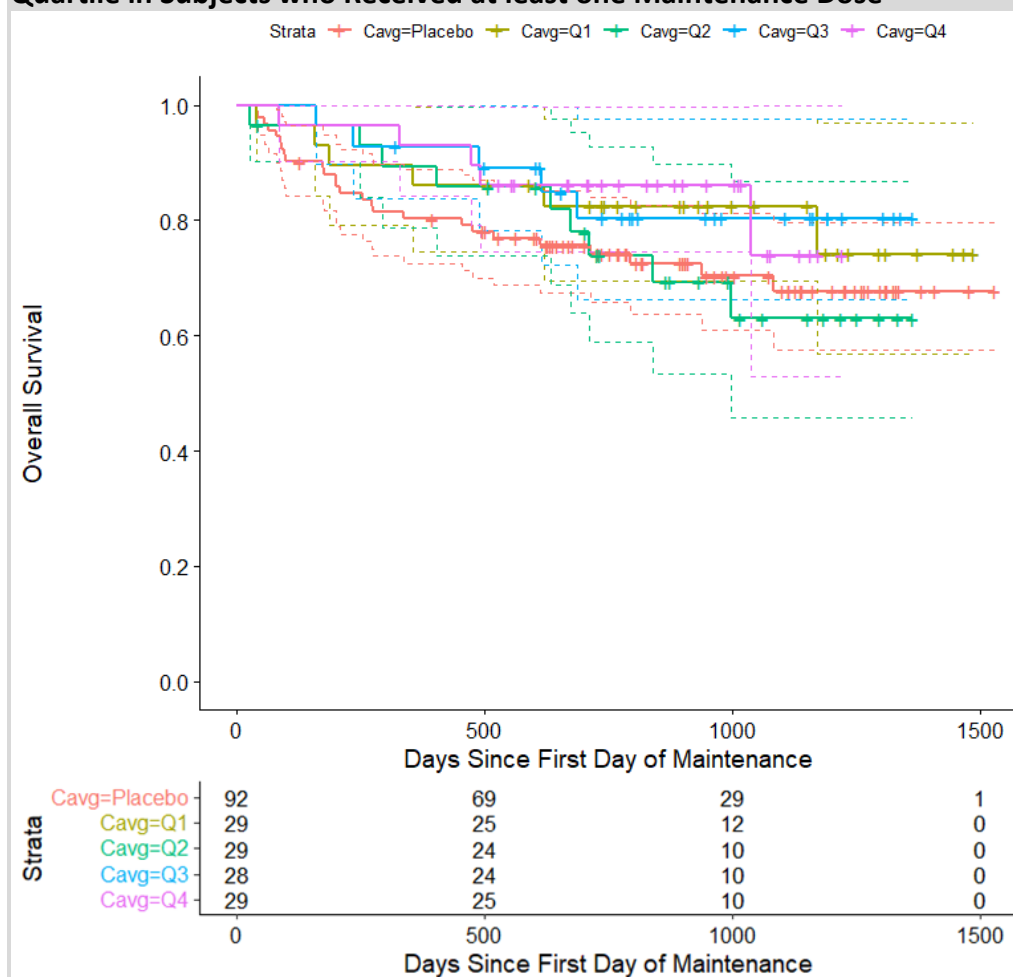
	Quizartinib		AC886	
	$C_{avg,TTE}$ (ng/mL)	$C_{avg,lastdose}$ (ng/mL)	$C_{avg,TTE}$ (ng/mL)	$C_{avg,lastdose}$ (ng/mL)
Geometric mean (CV%)	118.4 (248.5%)	257.8 (86.8%)	66.3 (225.2%)	142.3 (80.1%)
95% CI of the geometric mean	91.3 to 153.4	224.5 to 296.1	51.7 to 84.9	125 to 162.1
Median	177.8	299.9	85.2	147.5
5 th , 95 th percentile	5.8, 632.5	57.6, 699	4.6, 370.5	44.9, 450.3
Min, Max	1, 880.6	33.2, 879.6	0.7, 968.7	15.5, 967.1

Individual predicted exposure was determined following actual maintenance dosage records during maintenance treatment in subjects with newly diagnosed FLT3-ITD(+) AML and assuming no CYP3A inhibitor coadministration. AML = acute myeloid leukemia; $C_{avg,lastdose}$ = average concentration from first maintenance dose to day of last maintenance dose or time of survival event/censoring, whichever occurred first; $C_{avg,TTE}$ = average concentration from first maintenance dose to time of survival event/censoring. CI = confidence interval; CV = coefficient of variation.

Source: Reviewer's analysis of data provided in the Applicant's response (dated 27 January 2023) to 12 January 2023 information request.

Observed OS did not differ significantly across maintenance $C_{avg,TTE}$ quartiles, as shown in **Figure 35**. The confidence intervals for $C_{avg,TTE}$ quartiles and placebo also overlap greatly in **Figure 35**, suggesting that quizartinib maintenance treatment is not clearly associated with better OS compared to placebo.

Figure 35. Study AC220-A-U302 Observed Overall Survival versus Maintenance Exposure Quartile in Subjects who Received at least one Maintenance Dose



Dashed lines represent 95% confidence intervals. Strata refer to maintenance quizartinib C_{avg} exposure quartiles. C_{avg} = average concentration from first maintenance dose to time of survival event/censoring; Q = quartile; Q1 = 1st quartile (i.e., lowest C_{avg} quartile).

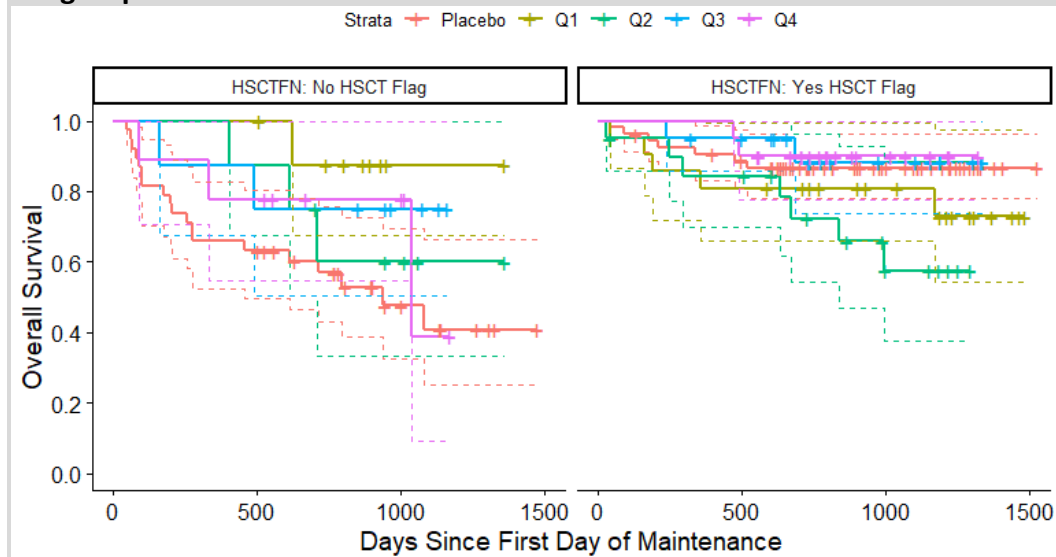
Source: Reviewer's analysis of data provided in the Applicant's response (dated 27 January 2023) to 12 January 2023 information request.

OS and maintenance $C_{avg,TTE}$ were also compared after stratifying by HSCT status, as shown in **Figure 36**, due to the potential impact of HSCT on OS. Observed OS did not differ significantly across maintenance $C_{avg,TTE}$ quartiles in subjects without HSCT or in subjects with HSCT, which is consistent with the overall analysis.

In subjects with HSCT, observed OS in the placebo arm also overlapped greatly with the quizartinib arm which suggests that quizartinib maintenance treatment may not provide a survival benefit in subjects with HSCT. In subjects without HSCT, all quartiles of maintenance $C_{avg,TTE}$ appeared to have generally better OS compared to placebo although this finding is

uncertain due to overlapping confidence intervals between treatment arms. Additionally, all subjects who received quizartinib maintenance also received quizartinib induction and consolidation, and therefore any apparent survival benefit in subjects who received quizartinib maintenance may be due to a carryover effect from quizartinib induction and consolidation.

Figure 36. Study AC220-A-U302 Observed Overall Survival versus Maintenance Exposure Quartile in Subjects who Received at least one Maintenance Dose Stratified by HSCT Subgroup



Dashed lines represent 95% confidence intervals. Strata refer to maintenance quizartinib $C_{avg,TTE}$ exposure quartiles.

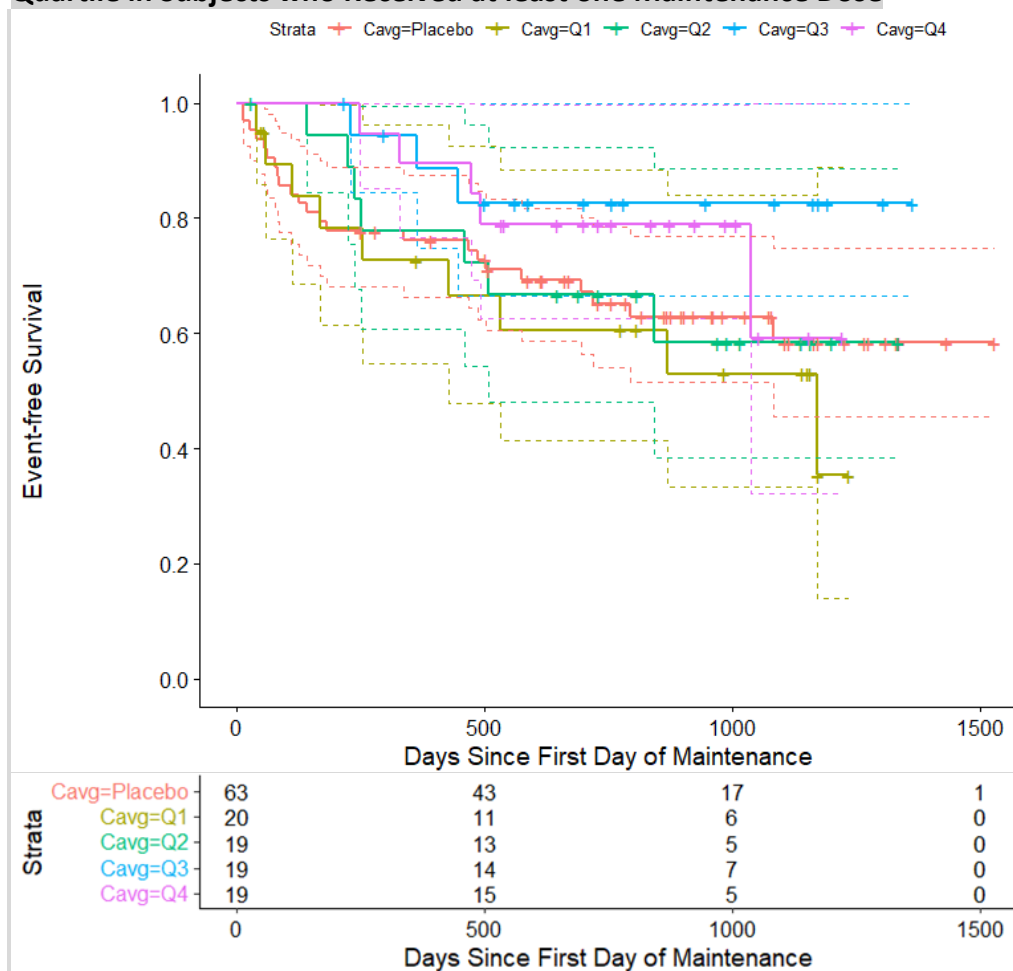
$C_{avg,TTE}$ = average concentration from first maintenance dose to time of survival event/censoring;

HSCTFN = hematopoietic stem cell transplantation status; Q = quartile; Q1 = 1st quartile (i.e., lowest $C_{avg,TTE}$ quartile).

Source: Reviewer's analysis of data provided in the Applicant's response (dated 27 January 2023) to 12 January 2023 information request

Although observed EFS appeared better in the two highest maintenance $C_{avg,TTE}$ quartiles (i.e., Q3 and Q4) compared to the two lowest quartiles (i.e., Q1 and Q2), confidence intervals overlapped across all exposure quartiles as shown in **Figure 37**. The Kaplan-Meier plot does not adequately support an association between $C_{avg,TTE}$ and EFS. Additionally, EFS in maintenance $C_{avg,TTE}$ Q1 and Q2 overlap with EFS in the placebo arm. The confidence intervals of all $C_{avg,TTE}$ quartiles overlap with the placebo arm as well.

Figure 37. Study AC220-A-U302 Observed Event-Free Survival versus Maintenance Exposure Quartile in Subjects who Received at least one Maintenance Dose

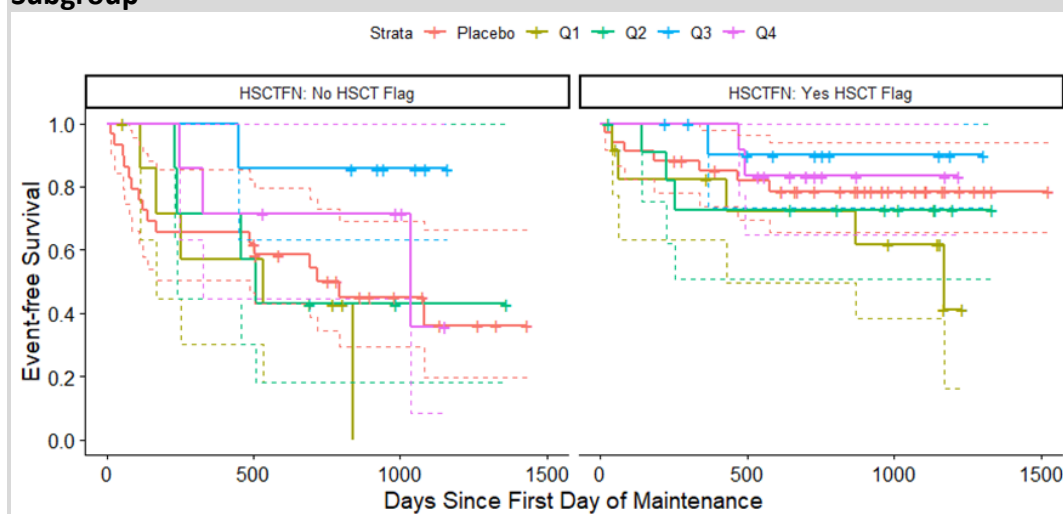


Dashed lines represent 95% confidence intervals. Strata refer to maintenance quizartinib Cavg exposure quartiles. Cavg= average concentration from first maintenance dose to time of survival event/censoring; Q = quartile; Q1 = 1st quartile (i.e., lowest Cavg quartile).

Source: Reviewer's analysis of data provided in the Applicant's response (dated 27 January 2023) to 12 January 2023 information request.

Observed EFS was also compared across maintenance $C_{avg,TTE}$ quartiles after stratifying by HSCT status, as shown in **Figure 38**. Maintenance $C_{avg,TTE}$ Q3 and Q4 still appeared to have generally better EFS compared to Q1 and Q2, although the overlap in confidence intervals indicates uncertainty of this difference. In the subgroup with HSCT, observed EFS did not appear to differ significantly across $C_{avg,TTE}$ exposure quartiles or the placebo arm which suggests that quizartinib maintenance treatment may not provide an EFS benefit in subjects with HSCT.

Figure 38. Study AC220-A-U302 Observed Event-Free Survival versus Maintenance Exposure Quartile in Subjects who Received at least one Maintenance Dose Stratified by HSCT Subgroup



Dashed lines represent 95% confidence intervals. Strata refer to maintenance quizartinib C_{avg} exposure quartiles. C_{avg} = average concentration from first maintenance dose to time of survival event/censoring; HSCTFN = hematopoietic stem cell transplantation status; Q = quartile; Q1 = 1st quartile (i.e., lowest C_{avg} quartile).

Source: Reviewer's analysis of data provided in the Applicant's response (dated 27 January 2023) to 12 January 2023 information request

Because the potential impact of quizartinib $C_{avg,TTE}$ on survival may be confounded by other patient characteristics, the Reviewer conducted multivariate Cox proportional hazard modeling for the primary efficacy endpoint of OS in subjects with at least one maintenance dose. Actual maintenance dosage records were used to calculate maintenance $C_{avg,TTE}$.

Potential effects from the following covariates were investigated: *treatment arm, quizartinib maintenance $C_{avg,TTE}$, AC886 maintenance $C_{avg,TTE}$, quizartinib induction AUC_{ss} following nominal dosing of 35.4 mg QD, baseline body weight, baseline ECOG score, sex, age, race, maintenance dose escalation status, AML cytogenetic risk score (favorable versus intermediate versus unfavorable), NPM1 mutation status, baseline white blood cell count ($<40 \times 10^9/L$ versus $\geq 40 \times 10^9/L$), HSCT status, choice of anthracycline during induction, and region.*

The model with the best fit, presented in **Table 123**, included effects from age and HSCT. Lower age and HSCT were associated with improved OS.

Table 123. Final Cox Proportional Hazard Model of Overall Survival

Characteristic	Hazard Ratio	95% CI	p-value
Age (years)	1.03	1.01, 1.06	0.012
HSCT (yes versus no)	0.49	0.27, 0.89	0.018

CI = confidence interval; HSCT = hematopoietic stem cell transplantation.

Source: Reviewer's analysis of data provided in the Applicant's response (dated 27 January 2023) to 12 January 2023 information request

The model fit did not significantly differ when $C_{avg,TTE}$ was included in the model, and $C_{avg,TTE}$ was not a statistically significant covariate as shown in **Table 124**. Treatment arm (quizartinib versus placebo) did not improve model fit either, as shown in **Table 125**.

Table 124. Cox Proportional Hazard Model of Overall Survival including Maintenance Quizartinib $C_{avg,TTE}$

Characteristic	Hazard Ratio	95% CI	p-value
Age (years)	1.03	1.00, 1.06	0.020
HSCT (yes versus no)	0.47	0.26, 0.85	0.013
Maintenance quizartinib $C_{avg,TTE}$ (ug/mL)	0.22	0.03, 1.51	0.12

$C_{avg,TTE}$ = average concentration from first maintenance dose to time of survival event/censoring; CI = confidence interval; HSCT = hematopoietic stem cell transplantation.

Source: Reviewer's analysis of data provided in the Applicant's response (dated 27 January 2023) to 12 January 2023 information request

Table 125. Cox Proportional Hazard Model of Overall Survival including Treatment Arm

Characteristic	Hazard Ratio	95% CI	p-value
Age (years)	1.03	1.00, 1.06	0.015
HSCT (yes versus no)	0.50	0.28, 0.90	0.021
Quizartinib treatment (versus placebo)	0.82	0.47, 1.42	0.5

CI = confidence interval; HSCT = hematopoietic stem cell transplantation.

Source: Reviewer's analysis of data provided in the Applicant's response (dated 27 January 2023) to 12 January 2023 information request

Evaluation of effectiveness associated with the maintenance dosage is complicated by several issues. Due to the study design of Study AC220-A-U302 and lack of re-randomization prior to maintenance treatment, the effects of quizartinib exposure and treatment during induction and consolidation phases could not be isolated from the effect of quizartinib exposure and treatment during maintenance. Subjects with higher maintenance $C_{avg,TTE}$ tended to have higher induction exposure as well. It is not certain how survival after initiation of maintenance treatment is impacted by quizartinib maintenance independent of the impact of quizartinib induction and consolidation. Additionally, QTcF and related patient characteristics may confound the analysis because of the QTcF-dependent dose escalation during maintenance treatment.

After accounting for age and HSCT, no clear association was identified between OS and maintenance exposure or maintenance treatment (quizartinib versus placebo). The E-R

maintenance analysis did not find evidence that quizartinib maintenance treatment has a clinical benefit. Clinical analyses determined that quizartinib maintenance was beneficial (see Section 8), but the E- E-R maintenance analysis did not find evidence that higher maintenance exposure is associated with improved effectiveness. Given the significantly higher exposure in maintenance treatment compared to induction or consolidation (refer to Section 19.4.1.2) and the potential for higher exposures to result in worse QTcF prolongation (refer to Section 19.4.3.4) and worse tolerability, the proposed quizartinib maintenance dosage of 53 mg QD may expose patients to toxicity without providing a survival benefit compared to lower maintenance dosages. Evaluation of lower maintenance dosages is warranted in order to evaluate this significant safety concern. The PMR in Section 6.2.2.3 addresses the need for additional data to adequately evaluate maintenance quizartinib dosage.

19.4.3.3. E-R Safety Executive Summary

The FDA's Assessment:

Worse QTcF prolongation was associated with higher quizartinib concentrations. Individual observed QTcF prolongations varied widely in subjects receiving quizartinib, and QTcF measurements over +100 ms were observed in Study AC220-A-U302. The median QTcF prolongation for $C_{max,ss}$ in the typical subject is +18.4 ms following 26.5 mg daily maintenance treatment and +24.1 ms following 53 mg daily maintenance treatment.

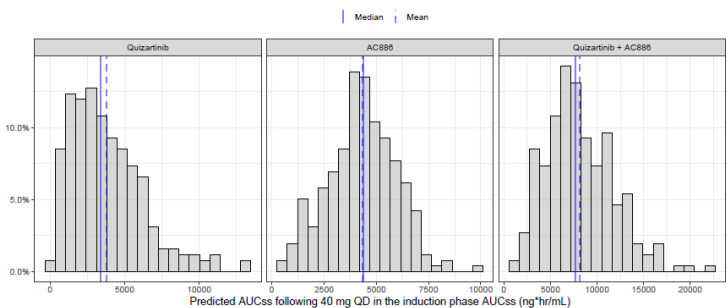
Higher quizartinib induction exposure may result in higher incidence of TEAE leading to dose interruption. Although E-R safety analysis was limited by use of exposure calculated with planned dosing rather than actual dosage records, no E-R associations were identified with infection, TEAE leading to dose reduction, TEAE leading to drug withdrawn, or Grade ≥ 3 cytopenia incidence from the lab dataset.

19.4.3.4. E-R Safety Assessment Summary

The Applicant's Position:

General Information	
Goal of E-R analysis	<i>To support the quizartinib dosing regimen tested in Study AC220-A-U302 based on the identified E-R relationships in newly diagnosed AML patients</i>
Study Included	<i>Justify the data pooling if any Not applicable. E-R analyses were based on the data from Study AC220-A-U302 only.</i>
Population Included	<i>Newly diagnosed AML subjects in Study AC220-A-U302</i>
Endpoint	<i>Major common AE/SAE, AE of interest QTcF (C-QTcF), TEAEs of any grade, TEAEs of Grade ≥ 3, serious TEAEs, TEAEs leading to dose reduction/interruption, TEAEs leading to dose discontinuation, events in the TdP/QT prolongation SMQ, infection, hemorrhages, hepatotoxicity, and myelosuppression</i>

NDA Multi-disciplinary Review and Evaluation {NDA 216993}
{VANFLYTA; quizartinib}

No. of Subjects (total, and with individual PK)		Total 265 quizartinib-treated, 259 with PK
Population Characteristics (Tables 12 and 13 in AC220-PMx010)	General	Including both placebo- and quizartinib-treated: Age median (range): 56.0 years (20.0, 75.0) Weight median (range): 70.3 kg (36.8, 152) Sex: Male 243 (45.8%) Race: 1 (0.2%) American Indian 156 (29.4%) Asian 7 (1.3%) Black 316 (59.5%) White 51 (9.6%) Other
	Organ impairment	Hepatic (NCI, Child-Pugh, etc): n (%) in each category Renal (CrCL, etc): n (%) in each category Not included in E-R analysis
	Pediatrics (if any)	Not applicable
	Geriatrics (if any)	Not applicable
Dose(s) Included		20 mg, 30 mg, 40 mg, 60 mg
Exposure Metrics Explored (range)		AUCss 40 mg in induction (E-R Report Figure 19), average daily AUC, C_{max}, and C_{min}  Figure 19: Distribution of the exposure metrics in the OS and EFS analysis data sets, shown by analyte (quizartinib and AC886) or the sum of analytes.
Covariates Evaluated		QTcF: Hypokaliemia, serum calcium and magnesium concentrations, age, body weight, sex, race, QT-prolonging drug, beta-blocker drug, anthracycline AEs: ECOG score, age, sex, race

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	For primary and major secondary endpoints C-QTcF: A direct-response E_{max} model AEs: Logistic regression model	The change in QTcF was characterized by an

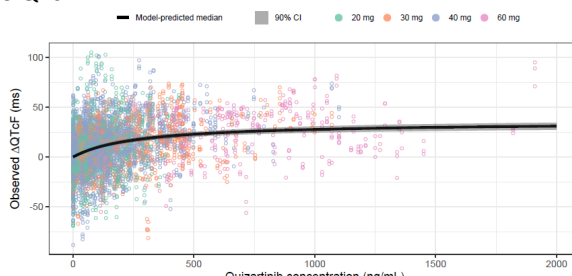
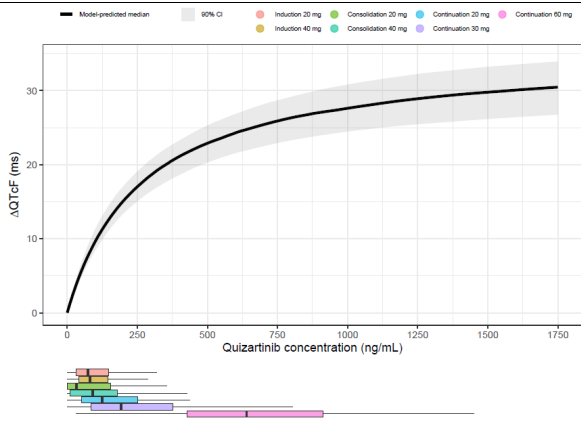
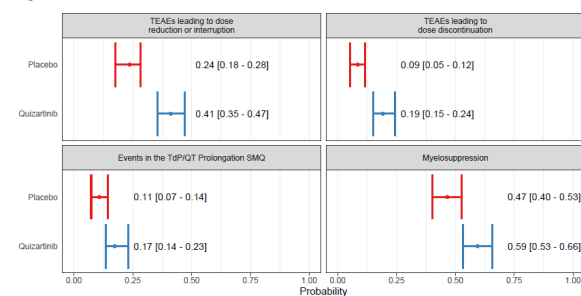
Model Parameter Estimates	C-QTcF: Table 28: Parameter estimates of the final model for QTcF. <table><thead><tr><th colspan="5">Final model for QTcF</th></tr><tr><th>Run</th><th></th><th>39</th><th></th><th></th></tr><tr><th>OFV</th><th></th><th>144957.09</th><th></th><th></th></tr><tr><th>Condition number</th><th></th><th>8.67</th><th></th><th></th></tr></thead><tbody><tr><th colspan="5">Final model for QTcF</th></tr><tr><th></th><th>Unit</th><th>Value</th><th>RSE (%)</th><th>SHR (%)</th></tr><tr><td>Baseline</td><td>ms</td><td>409</td><td>0.192</td><td></td></tr><tr><td>Fixed time effect for 3rd decile of clock time</td><td>ms</td><td>-1.68</td><td>33.9</td><td></td></tr><tr><td>Fixed time effect for 10th decile of clock time</td><td>ms</td><td>-1.18</td><td>54.7</td><td></td></tr><tr><td>E_{max}</td><td>ms</td><td>35.2</td><td>8.56</td><td></td></tr><tr><td>EC₅₀</td><td>ng/mL</td><td>260</td><td>14.2</td><td></td></tr><tr><td>Age effect on Baseline</td><td>year⁻¹</td><td>0.000800</td><td>17.7</td><td></td></tr><tr><td>Hypokalemia effect on Baseline</td><td></td><td>0.00997</td><td>21.2</td><td></td></tr><tr><td>IIV Baseline</td><td>(CV)</td><td colspan="2">(b) (4)</td><td>1.22</td></tr><tr><td>IIV EC₅₀</td><td>(CV)</td><td colspan="2"></td><td>46.2</td></tr><tr><td>IIV E_{max}</td><td>ms</td><td colspan="2"></td><td>15.9</td></tr><tr><td>IIV RUV</td><td>(CV)</td><td colspan="2"></td><td>4.49</td></tr><tr><td>Additive RUV</td><td>ms</td><td colspan="2"></td><td>0.307</td></tr></tbody></table> The RSE for IIV and RUV parameters are reported on the approximate SD scale. AEs: Table 31: Parameter estimates for the final model for AEs. <table><thead><tr><th colspan="3">Final model for AEs</th></tr><tr><th>Run</th><th></th><th>83</th></tr><tr><th>OFV</th><th></th><th>4362</th></tr><tr><th>Condition number</th><th></th><th>0</th></tr></thead><tbody><tr><th></th><th>Value</th><th>RSE (%)</th></tr><tr><td>Base probability for serious TEAE</td><td>0.497</td><td>4.38</td></tr><tr><td>Base probability for TEAE leading to dose reduction/interruption</td><td>0.235</td><td>11.0</td></tr><tr><td>Base probability for TEAE leading to dose discontinuation</td><td>0.0858</td><td>19.9</td></tr><tr><td>Base probability for events in the TdP/QT prolongation SMQ</td><td>0.107</td><td>17.9</td></tr><tr><td>Base probability for infection</td><td>0.727</td><td>2.99</td></tr><tr><td>Base probability for hemorrhages</td><td>0.351</td><td>6.51</td></tr><tr><td>Base probability for hepatotoxicity</td><td>0.277</td><td>7.37</td></tr><tr><td>Base probability for myelosuppression</td><td>0.463</td><td>7.52</td></tr><tr><td>Treatment effect on TEAE leading to dose reduction/interruption^a</td><td>0.829</td><td>23.1</td></tr><tr><td>Treatment effect on TEAE leading to dose discontinuation^a</td><td>0.960</td><td>27.9</td></tr><tr><td>Treatment effect on events in the TdP/QT prolongation SMQ ^a</td><td>0.579</td><td>44.9</td></tr><tr><td>Treatment effect on myelosuppression^a</td><td>0.512</td><td>39.8</td></tr></tbody></table> ^aEstimated on the logit scale.	Final model for QTcF					Run		39			OFV		144957.09			Condition number		8.67			Final model for QTcF						Unit	Value	RSE (%)	SHR (%)	Baseline	ms	409	0.192		Fixed time effect for 3rd decile of clock time	ms	-1.68	33.9		Fixed time effect for 10th decile of clock time	ms	-1.18	54.7		E _{max}	ms	35.2	8.56		EC ₅₀	ng/mL	260	14.2		Age effect on Baseline	year ⁻¹	0.000800	17.7		Hypokalemia effect on Baseline		0.00997	21.2		IIV Baseline	(CV)	(b) (4)		1.22	IIV EC ₅₀	(CV)			46.2	IIV E _{max}	ms			15.9	IIV RUV	(CV)			4.49	Additive RUV	ms			0.307	Final model for AEs			Run		83	OFV		4362	Condition number		0		Value	RSE (%)	Base probability for serious TEAE	0.497	4.38	Base probability for TEAE leading to dose reduction/interruption	0.235	11.0	Base probability for TEAE leading to dose discontinuation	0.0858	19.9	Base probability for events in the TdP/QT prolongation SMQ	0.107	17.9	Base probability for infection	0.727	2.99	Base probability for hemorrhages	0.351	6.51	Base probability for hepatotoxicity	0.277	7.37	Base probability for myelosuppression	0.463	7.52	Treatment effect on TEAE leading to dose reduction/interruption ^a	0.829	23.1	Treatment effect on TEAE leading to dose discontinuation ^a	0.960	27.9	Treatment effect on events in the TdP/QT prolongation SMQ ^a	0.579	44.9	Treatment effect on myelosuppression ^a	0.512	39.8	Emax model which included effects from clock time, age, hypokalemia, and individual predicted induction AUC_{ss} following planned dosage of 35.4 mg once daily (see Table 126). Higher induction exposure was associated with a higher rate of TEAE leading to dose interruption. Logistic regression did not identify E-R associations with the investigated safety events, and the additional E-R safety analysis comparing rates of select TEAEs across induction exposure quartiles did not identify E-R associations with infection, TEAE leading to dose reduction, TEAE leading to drug withdrawn, or Grade ≥3 cytopenia.
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Model Evaluation	C-QTcF:  Figure 31: Individual observed ΔQTcF colored by dose (open circles) overlaid with the median model prediction (solid line) +/- 90% CI (shaded area) obtained from simulations with uncertainty (n=250).	The QTcF model was able to adequately predict the median change in QTcF in subjects who received quizartinib.																																																																																																																																													

	Figure 32: Prediction corrected visual predictive check for the final QTcF model, stratified by study phase. Prediction corrected QTcF is shown versus quizartinib concentration. Data with unknown phase are excluded from the plot. Figure 33: Prediction corrected visual predictive check for the final QTcF model. Prediction-corrected QTcF is shown versus time since last dose (left panel, data up to 40 hours since last dose are shown) and clock time (right panel, data between 7 and 20 o'clock are shown). AEs: Figure 35: Visual predictive check of the proportion of subjects with AEs versus treatment group for the final AEs model.	Variability in QTcF prolongation with quizartinib treatment is relatively wide. QTcF prolongations over 100 ms were observed in subjects receiving quizartinib. Both the predicted and observed QTcF in the VPC plots (Applicant's Figure 32) show the 95th percentile of QTcF exceeding 450 ms even at quizartinib concentrations below 100 ng/mL. Higher quizartinib concentration, older age, and hypokalemia were associated with greater QTcF prolongation. The E-R analysis did not identify a significant effect of QT prolonging drugs on the QTcF interval. However, this may be due to limitations in the dataset.
Covariates and Clinical Relevance	C-QTcF: Age and hypokalemia had an effect on the baseline QTcF, with older age and hypokalemia leading to longer baseline QTcF. AEs: No covariate effect identified	
Simulation for Specific Population	Not applicable	Not applicable.
Visualization of E-R relationships	C-QTcF:	In a typical subject, the median QTcF prolongation at time of $C_{max,ss}$ is +18.4 ms following 26.5 mg daily maintenance treatment and +24.1 ms following

	 Figure 34: Predicted $\Delta QTcF$ versus quizartinib concentrations. The shaded area represents the 90% CI for the prediction in newly diagnosed subjects obtained from simulations with uncertainty ($n=250$). The horizontal boxplots depict the distribution of the observed quizartinib concentrations in study AC220-A-U302, colored by phase and dose. It should be noted that lower doses during continuation had similar exposures as higher doses during induction/consolidation because of the “phase effect” on quizartinib PK identified in the population PK analysis (20 mg was taken by patients concomitantly treated with strong CYP3A inhibitors). AEs:  Figure 38: Forest plot of probabilities for different AEs, based on the final AEs model. The dots and the whiskers represent the median and the 95% CI of the probability, respectively, displayed numerically as median (95% CI) on the right of each panel.	53 mg daily maintenance treatment. Higher quizartinib induction exposure was associated with a higher rate of TEAE leading to dose interruption (23% in AUC_{ss} quartile 1 compared to 34% in quartile 4; Table 128). The ability to identify E-R safety associations may be limited by the use of AUC_{ss} following planned induction dosage rather than actual dosage.
Overall Clinical Relevance for E-R	<i>Quizartinib prolongs QT in a concentration-dependent manner. No E-R relationship was identified for the probability of the first occurrence of the investigated AEs.</i>	Higher quizartinib concentrations are associated with greater increases in QTcF interval.
Labeling Language	Description	Acceptability [FDA’s comments]
12.2 Pharmacodynamics	<i>The exposure-response analysis predicted a concentration-dependent</i> (b) (4)	The E-R analysis predicted a concentration-dependent QTcF interval median prolongation of 18 and 24 ms (upper bound of two-sided 90% CI: 21 and 27 ms) at the median C_{max,ss} of quizartinib at the 26.5 mg and 53 mg dose level

	during maintenance therapy.

Note: table and figure numbering corresponds to those used in the source document.
Source: **AC220-PMx010** (eCTD M5.3.3.5)

The FDA's Assessment:

QTcF Prolongation

The E-R analysis of QTcF prolongation included data from 531 subjects with newly-diagnosed AML in Study AC220-A-U302, which included 256 subjects with at least one pair of time-matched QTcF and PK measurements after first treatment dose.

The change in QTcF was characterized by an Emax model which included effects from clock time, age, hypokalemia, and individual predicted induction AUC_{ss} following planned dosage of 35.4 mg once daily as described in the Applicant's Table 28 in the E-R Safety Assessment Summary above and with 95% confidence intervals in **Table 126**. Of note, the Applicant's Table 28 in the E-R Safety Assessment contains an error in CV and RSE calculation; see final parameter estimates with corrected variance and RSE values in **Table 126**. The model fit was adequate for the purpose of predicting median change in QTcF according to quizartinib concentration.

Table 126. Final QTcF Model Parameter Estimates

	Estimate	RSE	95% CI	Shrinkage
Baseline (ms)	409	0.20%	407.46 to 410.54	-
Fixed time effect for 3 rd decile of clock time (ms)	-1.68	33.8%	-2.791 to -0.569	-
Fixed time effect for 10 th decile of clock time (ms)	-1.18	54.4%	-2.438 to 0.078	-
Emax (ms)	35.2	8.6%	29.3 to 41.1	-
EC50 (ng/mL)	260	14.2%	187.68 to 332.32	-
Age effect on baseline (1/year)	0.000799	17.8%	0.000521 to 0.001275	-
Hypokalemia effect on baseline	0.00997	21.2%	0.00583 to 0.01411	-
IIV Baseline (exponential)	0.0017 (CV = 4.1%)	6.7%	0.0015 to 0.0019	1.2%
IIV EC50 (exponential)	0.549 (CV = 85.5%)	35.2%	0.1707 to 0.9273	46.2%
IIV Emax (additive)	945 (SD = 30.1)	19.6%	582.4 to 1307.6	15.9%
Exponential RUV	0.0975 (CV = 32%)	8.5%	0.0812 to 0.1138	4.5%
Additive RUV	173 (SD = 13.2)	3.1%	162.6 to 183.4	0.3%

Condition number = 8.67.

QTcF = Baseline + EFF_{drug}(t) where

$$\text{Baseline}_i = \left[409 + \begin{cases} -1.68 & \text{if } 10 : 18 < \text{clock time} \leq 10 : 54 \\ -1.18 & \text{if clock time} > 15 : 36 \end{cases} \right] \cdot \begin{cases} 1 + 0.00997 & \text{with hypokalemia} \\ 1 & \text{without hypokalemia} \end{cases} \cdot e^{0.000800 \cdot (\text{age} - 56)} \cdot e^{\eta_{\text{Baseline},i}}$$

$$\text{EFF}_{\text{drug}_i}(t) = (35.2 + \eta_{\text{Emax},i}) \cdot \frac{C_{\text{quiz}}(t)}{C_{\text{quiz}}(t) + 260 \cdot e^{\eta_{\text{EC50},i}}}$$

CI = confidence interval; $C_{\text{quiz}}(t)$ = observed quizartinib concentration at time t ; EC50 = quizartinib concentration at which 50% of maximum effect is achieved; IIV = interindividual variability; QTcF = absolute QT interval corrected for heart rate by Fridericia's formula; RSE = relative standard error; RUV = residual unexplained variability; SD = standard deviation.

Source: Table 28 in Applicant's Exposure-Response Report and Reviewer's analysis of Applicant's run39-mod-cqt model file

Higher quizartinib concentration was associated with greater change in QTcF. The median predicted change in QTcF according to quizartinib concentration is compared to observed data in the Applicant's Figure 31 in the E-R Safety Assessment Summary, which shows that variability in QTcF prolongation with quizartinib treatment is relatively wide. QTcF prolongations over 100 ms were observed in subjects receiving quizartinib. Both the predicted and observed QTcF in the VPC plots (Applicant's Figure 32 in the E-R Safety Assessment Summary) show the 95th percentile of QTcF exceeding 450 ms even at quizartinib concentrations below 100 ng/mL.

The model did not identify any significant associations between time-varying concomitant QT prolonging drugs and QTcF prolongation. The model also did not identify any association between time-varying concomitant beta blocker use and QTcF prolongation, but the lack of apparent association may be due to the small number of subjects with any recorded beta blocker use (49 out of 531 subjects total).

Quizartinib exposure is expected to be higher during maintenance treatment compared to induction or consolidation (see Section 19.4.1.2). Therefore, exposure during maintenance treatment is likely to result in the highest QTcF prolongation. **Table 127** summarizes the median model-predicted QTcF prolongation at the $C_{\text{max,ss}}$ of a typical Study AC220-A-U302 patient (i.e., 70.3 kg, 56 year old male) following the proposed maintenance dosages of 26.5 mg or 53 mg once daily.

The $C_{\text{max,ss}}$ in the typical patient (293 ng/mL following nominal maintenance dosing of 26.5 mg QD; 586 ng/mL following nominal maintenance dosing of 53 mg QD) was slightly higher than the median $C_{\text{max,ss}}$ of the Study AC220-A-U302 population with at least one maintenance dose of quizartinib ($n=115$) (270 ng/mL following nominal maintenance dosing of 26.5 mg QD; 541 ng/mL following nominal maintenance dosing of 53 mg QD). The predicted $C_{\text{max,ss}}$ in the typical subject during maintenance treatment adequately represents average exposure in Study AC220-A-U302.

Table 127. Predicted Exposure and QTcF Prolongation in the Typical Patient in Study AC220-A-U302 (QuANTUM-F)

Treatment Phase	Quizartinib Dose	Predicted $C_{max,ss}$	Predicted Increase in QTcF	
			Median	90% CI
Maintenance	26.5 mg daily	293 ng/mL	+18.4 ms	16.3 to 20.5
Maintenance	53 mg daily	586 ng/mL	+24.1 ms	21.4 to 26.6

Typical patient in Study AC220-A-U302 was male, 70.3 kg, 56 years old.

CI = confidence interval; $C_{max,ss}$ = steady state maximum concentration; QTcF = absolute QT interval corrected for heart rate by Fridericia's formula.

Source: Table 29 in Applicant's Exposure-Response Report

Overall, the E-R analysis characterizes the median QTcF prolongation with quizartinib treatment. The median QTcF prolongation for $C_{max,ss}$ in the typical subject is +18.4 ms following 26.5 mg daily and +24.1 ms following 53 mg daily during maintenance.

Incidence of Adverse Events

The E-R safety analysis of TEAE incidence included data from 258 subjects with newly-diagnosed AML who received quizartinib and 267 subjects with newly-diagnosed AML who received placebo from Study AC220-A-U302

As summarized in the Applicant's Table 31 in the E-R Safety Assessment Summary, the Applicant's E-R analysis did not identify any associations between quizartinib AUC_{ss} following planned dosage of 35.4 mg once daily during induction and incidence of serious TEAE, TEAE leading to dose reduction or interruption, TEAE leading to discontinuation, infection, hemorrhage, hepatotoxicity, or myelosuppression in the adverse event dataset ("adae.xpt"). In the Applicant's Table 31, the term myelosuppression refers to one or more of the following adverse events in the adverse event dataset (adae.xpt): *febrile neutropenia, anemia, thrombocytopenia, neutropenia, leukopenia, platelet count decreased, white blood cell count decreased, neutrophil count decreased, pancytopenia, lymphocyte count decreased, hemoglobin decreased, hematocrit decreased, lymphopenia, or red blood cell count decreased*.

Table 128 summarizes the Reviewer's additional E-R safety analysis of select TEAEs of interest across quizartinib induction AUC_{ss} quartiles. Higher induction AUC_{ss} was associated with a higher incidence of TEAE leading to drug interruption. No other TEAEs in **Table 128** appeared to have higher incidence in higher quizartinib AUC_{ss} quartiles. Overall, subjects who received quizartinib had higher rates of TdP/QT prolongation, TEAE leading to drug interruption, TEAE leading to dose reduction, TEAE leading to drug discontinuation, and TEAE leading to any dose modification compared to placebo in all exposure quartiles.

Table 128. Incidence of Select TEAEs in Study AC220-A-U302 According to Quizartinib Induction Exposure Quartile

Safety Event	Grade	Placebo (n=267)	Quizartinib AUCss Q1 (n=65)	Quizartinib AUCss Q2 (n=65)	Quizartinib AUCss Q3 (n=64)	Quizartinib AUCss Q4 (n=64)
Serious TEAE	Any Grade	124 (46.4 %)	39 (60 %)	37 (56.9 %)	33 (51.6 %)	26 (40.6 %)
TEAE leading to drug interruption	Any Grade	50 (18.7 %)	15 (23.1 %)	20 (30.8 %)	23 (35.9 %)	22 (34.4 %)
TEAE leading to dose reduction	Any Grade	9 (3.4 %)	10 (15.4 %)	10 (15.4 %)	9 (14.1 %)	9 (14.1 %)
TEAE leading to drug withdrawn	Any Grade	17 (6.4 %)	14 (21.5 %)	9 (13.8 %)	14 (21.9 %)	8 (12.5 %)
TEAE leading to dose modification ^a	Any Grade	71 (26.6 %)	29 (44.6 %)	32 (49.2 %)	34 (53.1 %)	32 (50 %)
Infections and infestations	Any Grade	202 (75.7 %)	51 (78.5 %)	59 (90.8 %)	51 (79.7 %)	49 (76.6 %)
	Grade ≥3	111 (41.6 %)	34 (52.3 %)	21 (32.3 %)	33 (51.6 %)	16 (25 %)
TdP/QT prolongation SMQ (broad)	Any Grade	24 (9 %)	12 (18.5 %)	8 (12.3 %)	10 (15.6 %)	14 (21.9 %)
Hepatotoxicity ^b	Any Grade	99 (37.1 %)	31 (47.7 %)	39 (60 %)	22 (34.4 %)	21 (32.8 %)
Low hemoglobin ^c	Grade ≥3	238 (88.8 %)	58 (89.2 %)	57 (87.7 %)	55 (85.9 %)	55 (84.6 %)
	Grade ≥3 and worse than baseline grade	174 (64.9 %)	44 (67.7 %)	43 (66.2 %)	31 (48.4 %)	33 (50.8 %)
Low leukocytes ^c	Grade ≥3	268 (100 %)	65 (100 %)	65 (100 %)	64 (100 %)	65 (100 %)
	Grade ≥3 and worse than baseline grade	130 (48.5 %)	27 (41.5 %)	27 (41.5 %)	33 (51.6 %)	30 (46.2 %)
Low lymphocytes ^c	Grade ≥3	247 (92.2 %)	60 (92.3 %)	62 (95.4 %)	56 (87.5 %)	62 (95.4 %)
	Grade ≥3 and worse than baseline grade	130 (48.5 %)	40 (61.5 %)	31 (47.7 %)	23 (35.9 %)	25 (38.5 %)
Low neutrophils ^c	Grade ≥3	261 (97.4 %)	63 (96.9 %)	65 (100 %)	61 (95.3 %)	65 (100 %)
	Grade ≥3 and worse than baseline grade	160 (59.7 %)	37 (56.9 %)	30 (46.2 %)	36 (56.2 %)	37 (56.9 %)
Low platelets ^c	Grade ≥3	268 (100 %)	65 (100 %)	65 (100 %)	63 (98.4 %)	65 (100 %)
	Grade ≥3 and worse than baseline grade	188 (70.1 %)	40 (61.5 %)	46 (70.8 %)	40 (62.5 %)	39 (60 %)

^a dose modification = drug interruption, dose reduction, or drug withdrawn.

^b All preferred terms in the following SMQs: cholestasis and jaundice of hepatic origin (SMQ) (narrow); hepatic failure, fibrosis and cirrhosis and other liver damage related conditions (SMQ) (narrow); hepatitis, non-infectious (SMQ) (narrow); liver related investigations, signs and symptoms (SMQ) (narrow)

^c derived from Study AC220-A-U302 lab dataset ("adlb.xpt").

Individual predicted quizartinib exposure was determined following planned dosage of 35.4 mg daily during induction treatment in subjects with newly diagnosed FLT3-ITD(+) AML and assuming no CYP3A inhibitor coadministration. Steady state is achieved at Day 15.

AML = acute myeloid leukemia; AUC_{ss} = steady state area under the concentration-versus-time curve during one dosing interval; Q = quartile; SMQ = standardized MedDRA query; TEAE = treatment emergent adverse event. Source: Reviewer's analysis of Applicant's Exposure-Response dataset and Study AC220-A-U302 clinical datasets

Although rates of cytopenias and other TEAEs were not associated with induction quizartinib AUC_{ss}, the E-R analysis did not investigate TEAE incidence according to exposure following actual dosage records in induction or other treatment phases. E-R analysis using actual exposure instead of planned exposure may be more likely to identify safety associations, and so the current E-R analysis is relatively limited. The exposure-response relationships for the safety of quizartinib have not been fully characterized.

19.4.3.5. Overall Benefit-risk Evaluation Based on E-R Analyses

The Applicant's Position:

The E-R analyses support the overall favorable benefit-risk for quizartinib. The E-R analysis on OS predicted a median (95% CI) HR for quizartinib compared to the placebo of 0.790 (0.690, 0.933) at the median quizartinib exposure and thus further demonstrated survival benefit from quizartinib treatment in combination with standard chemotherapy followed by continuation monotherapy in newly diagnosed AML subjects with *FLT3*-ITD (+) AML. Quizartinib prolongs QTcF in a concentration-dependent manner, which was appropriately managed in Study AC220-A-U302 through dose modification, including QTcF-based dosing, correction of electrolyte abnormalities, and dose adjustments for concomitant use with strong CYP3A inhibitors.

The FDA's Assessment:

Overall, the concentration-dependent increase in QTcF interval has been characterized and the proposed dose modifications for QTcF prolongation are appropriate. The PPK and E-R analyses support a positive benefit-risk profile for the proposed dosage of 35.4 mg once daily for induction and consolidation treatment in subjects with newly diagnosed *FLT3*-ITD (+) AML.

The E-R analyses identified significant known risk and unclear benefit with the proposed maintenance dosage of 53 mg once daily. In subjects who received at least one maintenance dose, quizartinib exposure during maintenance treatment was not associated with improvements in OS or EFS after accounting for the effects of age and HSCT. Higher quizartinib concentrations are associated with greater QTcF prolongation, and quizartinib treatment can increase risk of safety events. Therefore, the E-R analysis indicates that 53 mg once daily during maintenance may expose patients to unnecessary toxicity without an improvement in survival. Additional data is required to determine an appropriate maintenance dose of quizartinib, and the known risk of quizartinib maintenance is addressed by the PMR in Section 6.2.2.3. Additionally, E-R analysis did not provide supportive evidence of the effectiveness of quizartinib maintenance treatment.

19.4.4. Physiology Based Pharmacokinetics (PBPK) Analyses

19.4.4.1. PBPK Executive Summary

The aim of this review is to evaluate the adequacy of the Applicant's PBPK report titled "development of a PBPK model for quizartinib in Simcyp population-based simulator and evaluation of DDI risk as a perpetrator of UGT1A1" to support the intended uses. Specifically, the Applicant applied the PBPK modeling approach to assess the DDI potential of quizartinib as an inhibitor of UGT1A1 and specifically, the effects of quizartinib on the exposure of raltegravir (a UGT1A1 substrate), following single dose administration of raltegravir.

The Division of Pharmacometrics has reviewed the PBPK report, supporting modeling files and concluded the following:

- 1) The submitted PBPK models are adequate to assess the inhibitory potential of quizartinib on the exposure of raltegravir (a UGT1A1 substrate) in the healthy volunteer.
- 2) The effect of quizartinib on a UGT1A1 substrate (such as raltegravir) is expected to be not clinically significant.

19.4.4.2. Methods

The Applicant's Position:

PBPK model structure

The PBPK analyses were performed using the population based PBPK software Simcyp® (V20 Simcyp Ltd., a Certara Company, Sheffield, United Kingdom). The PBPK models for quizartinib were developed based on in vitro and in vivo information and clinical PK data. The final input parameters and the method to obtain the values of input parameters for PBPK model of quizartinib are summarized in **Table 129**.

Table 129. Final input parameters for quizartinib PBPK models

PARAMETER	Value	Reference
Physicochemical and Binding Parameters		
Molecular Weight (g/mol)	560.7	Ver.15, IB
log P	2.33	Reported, Ambit_102052-00
Compound type	Dipropic basic	Ver.15, IB
pKa	3.16, 4.75	Reported, Ambit_102052-00
B:P (Healthy subjects)	1.17	PPD_RMWK_report
B:P (AML patients)	1.10	PPD_RMWK_report
fu	0.0088	Reported, AM17-C0020-R01

PARAMETER	Value	Reference
KD (μM)	5.96	Predicted (Simcyp)
Main binding protein	Albumin	NR0046 report
Absorption model – first-order model		
fugut	0.0380	Predicted (Simcyp)
Qgut (L/h)	8.37	Predicted using villous blood flow and permeability. Permeability was estimated by comparing observed DDI between quizartinib and dabigatran etexilate
ka (1/h)	0.420	Optimised, Clinical Study AC220-A-U107
fa	0.737	Estimated based on the absolute bioavailability study (Study AC220-A-U107) and predicted F_G value
tlag (h)	0	Clinical Study AC220-A-U107
FG	0.992	Predicted using Qgut model
Distribution model – full PBPK model		
VSS (L/kg)	3.42	Predicted, Simcyp Method 1
Kp scalar	5.6	Optimised
Kp,adipose	7	Optimised
Elimination parameters		
CLiv (L/h)	2.31	Clinical Study AC220-A-U107 (IV dose)
fmCYP3A	0.652	AM17-C0021-R01(PBC315-608)
CLR (L/h)	0.000684	Clinical Study AC220-A-U107
Interaction parameters		
UGT1A1 Ki (μM)	0.78	Reported, AM19-C0002-R01(AE8335-E)
fumic	0.985	Predicted given microsomal protein concentration of 0.05 mg/mL at pH7.4.
P-gp Ki (μM)	9.55	Reported, 2689-ME-0003

Source: Tables 4 of quizartinib PBPK report

The FDA's Assessment:

In the PBPK model of quizartinib, the first-order absorption model was used. The fugit value was estimated using the build-in function provided by Simcyp. The upper bound and lower bound of fu is likely between 0.0088 and 1. Permeability of quizartinib was estimated by comparing the simulated and observed DDI between quizartinib and dabigatran etexilate. Thus, the confidence in the estimated permeability value is subjected, not limited to, to the PBPK model of dabigatran etexilate and the assigned ki value of P-gp for quizartinib. Sensitivity of Qgut on the effect of quizartinib on exposure of raltegravir should be conducted.

PBPK model refinement and validation

The Applicant's Position:

The PBPK model was validated against the adult PK studies following single oral dose of 30 mg, 60 mg and 90 mg Quizartinib respectively in healthy subjects (AC220-014, AC220-015, AC220-018, AC220-019 and AC220-A-U106) and multiple oral doses of 30 mg and 60 mg quizartinib QD respectively in AML patients (2689-CL-2004).

The FDA's Assessment:

The Applicant's PBPK model were verified with the PK dataset relevant to clinical conditions. The proposed initial dosing for quizartinib is 35.4 mg QD for two weeks for patients taking standard chemotherapy. Different dosing regimens are proposed for patients at different stages (for example, patients who achieved complete remission (CR)). The proposed doses range from 26.5 mg QD to 53 mg QD. Ideally, the PBPK model should be verified with a wide range of clinical PK dataset which covered the full range of clinical dosing regimens. Given the PPK analysis concludes that quizartinib showed linear pharmacokinetics in the dose range of 26.5 mg to 79.5 mg in healthy subjects and 17.7 mg to 53 mg QD in AML patients. The Applicant's modeling development and verification approach is acceptable.

Raltegravir PBPK model

The Applicant's Position:

The default compound library file for raltegravir was used. Prediction performance of SV-Raltegravir model was verified with clinically observed data following 400 mg SD and 400 mg BID raltegravir treatment, respectively. A developer's summary of development and validation of the PBPK model of raltegravir is provided by the applicant.

The FDA's Assessment:

The applicability of raltegravir PBPK model as a UGT1A substrate was discussed in PBPK review for asciminib (NDA 215358). The Reviewer noted there is a limited validation of the DDI predictive performance of raltegravir model as it was conducted using clinical DDI data of a single inhibitor, atazanavir. Raltegravir PBPK model is considered acceptable as a UGT1A substrate for purpose of risk assessment.

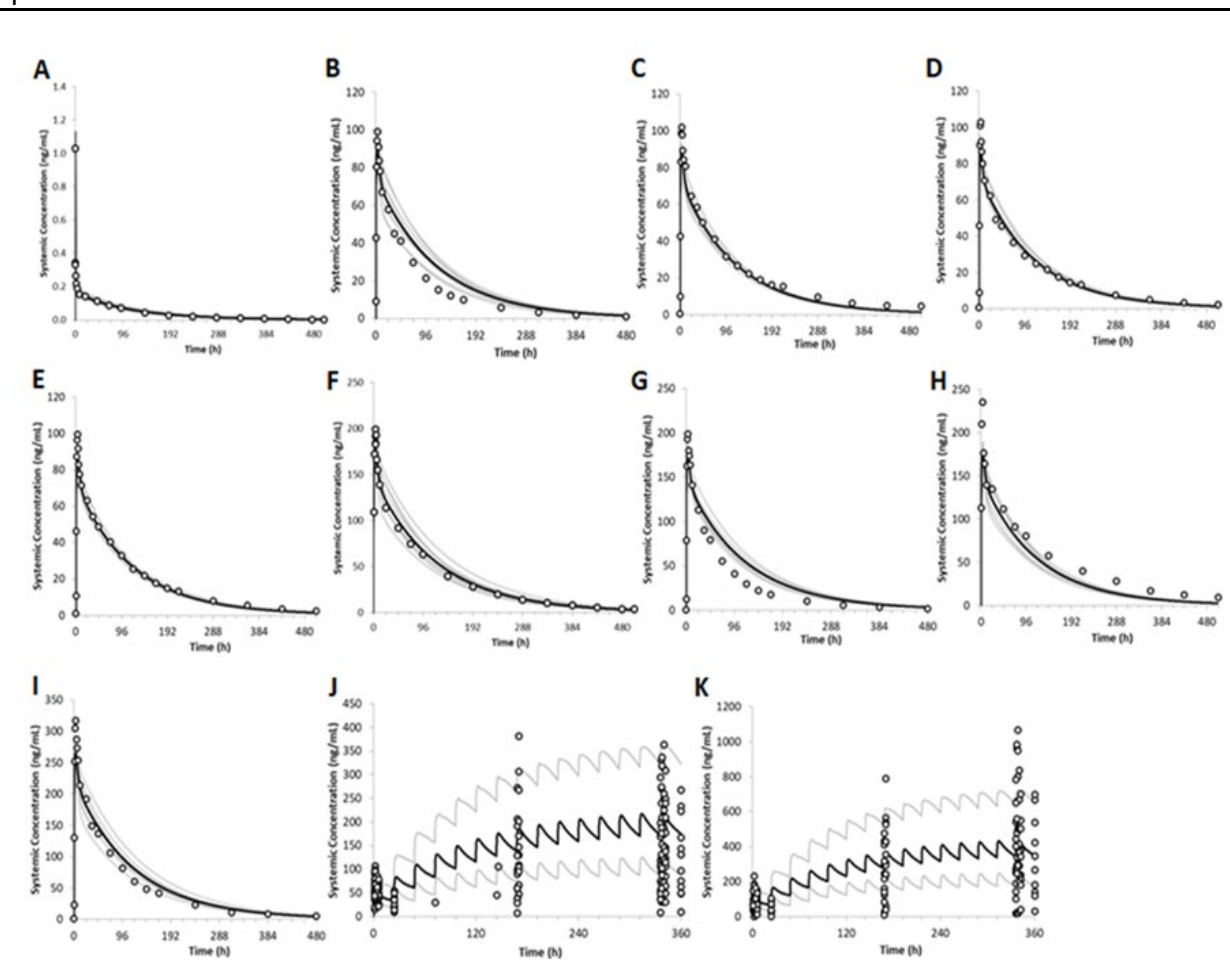
19.4.4.3. Results

Can the PBPK model adequately describe the PK profiles of quizartinib?

The Applicant's Position:

The final PBPK model for quizartinib, based on both in vitro and in vivo data was able to generate plasma concentration-time profiles and exposure levels of quizartinib after a single oral dose of quizartinib 60 mg and an intravenous dose of 14C-quizartinib 50 µg in healthy male subjects that were within 1.5-fold of observed data, respectively. The model was validated against 7 sets of PK data following a single oral dose of quizartinib (30 - 90 mg). Plasma concentration-time profiles were recovered and AUC_{inf} and C_{max} were within 2-fold of the observed data. In addition, 2 sets of PK data in AML patients (30 mg QD and 60 mg QD) were used to validate the model to simulate multiple dosing. The ability of PBPK modeling to describe the clinical PK dataset at various dosing levels is presented in Figure 39.

Figure 39. PBPK Predicted and observed PK profiles of quizartinib healthy subjects and AML patients



PBPK predicted (bold lines) and observed (circle symbols) plasma concentration-time profiles of quizartinib following single intravenous dose of 50 µg (A, Study AC220-A-U107), single oral doses of 30 mg (B-E, Studies of AC220-014, AC220-015, AC220-018 and AC220-019), 60 mg (F-H, Studies of AC220-A-U107, AC220-014 and AC220-A-U106) and 90 mg (Study AC220-014) respectively in healthy subjects and multiple (QD) oral doses of 30 mg and 60 mg respectively in AML patients (Study 2689-CL-2004). The grey lines represent the 5th and 95th percentiles and the solid black lines the mean data for the simulated population. (Source: PBPK report Figures 3-11, Figures 13-14).

The FDA's Assessment:

The submitted PBPK model can describe the PK profiles of quizartinib and adequate to support the DDI analysis with a substrate of enzyme pathway (such as UGT1A1). The f_a of quizartinib was calculated to be 0.737 by dividing the observed F (0.7147) by F_G (0.992) and F_H (0.977). However, to recover the lower plasma exposure of quizartinib in AML patients, the f_a was modified by using the ratio of simulated and observed C_{max} (1.86) on the first day of the 60 mg

QD dosing (Study 2689-CL-2004) and reduced to 0.396. To simulate the effect of quizartinib on the exposure of raltegravir, the analysis was conducted in healthy virtual population where the original f_a value of 0.737 was used. Thus, a higher plasma exposure of quizartinib at steady state compared to those observed in clinical were used to conduct PBPK DDI assessment.

Is the inhibitory effect of quizartinib on Raltegravir (an UGT1A1 substrate) is expected to be clinically significant?

The Applicant's Position:

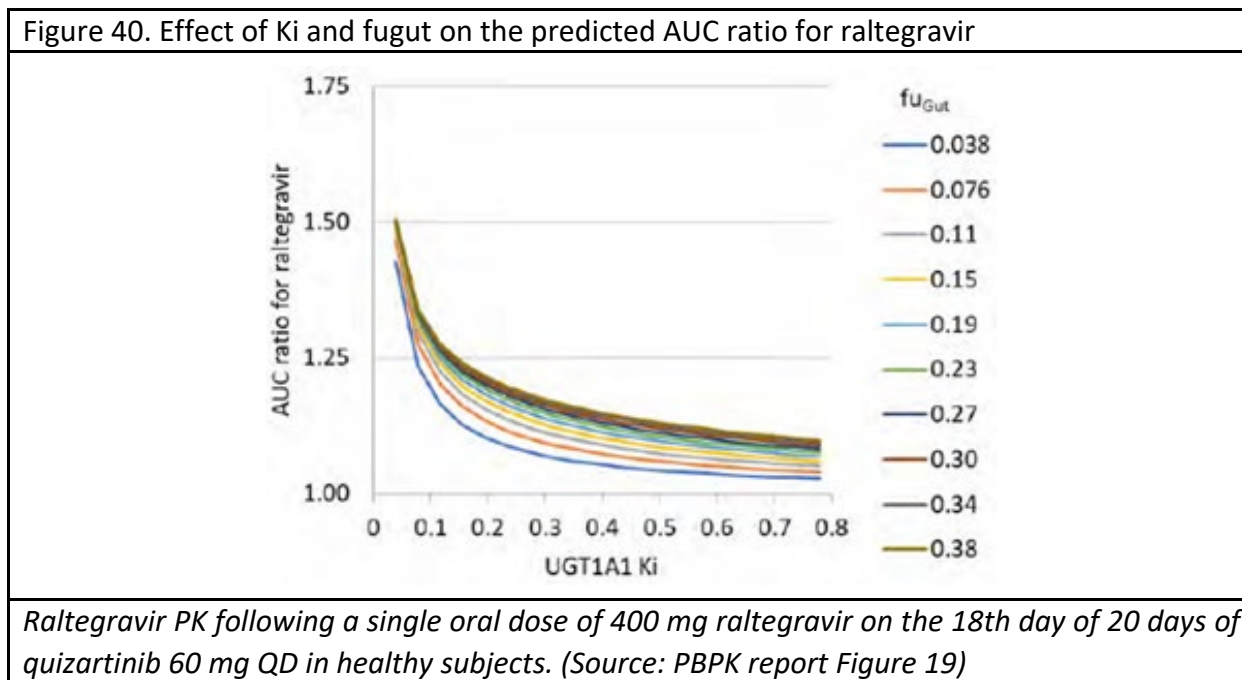
Sensitivity analysis of quizartinib K_i for UGT1A1 inhibition and f_{gut} were performed by the Applicant respectively. Briefly, plasma raltegravir PK following a single oral dose of 400 mg in the absence of quizartinib (Day 1) and on the 18th day of 20 days of dosing of quizartinib (60 mg QD) to healthy subjects were simulated using 10-fold and 20-fold reduced K_i values of quizartinib for UGT1A1 (0.078 and 0.039 μM). The impacts of different K_i values on the simulated AUC_{inf} and C_{max} ratios of raltegravir are shown in **Table 130**.

Table 130. Effect of K_i for UGT1A1 on the simulated GMRs for raltegravir in the absence and presence of quizartinib in healthy subjects.

K_i (μM)	AUC _{inf} ratio	C _{max} ratio
0.78 (in vitro K_i)	1.03 (1.02 – 1.03)	1.03 (1.02 – 1.03)
0.078 (10-fold reduction)	1.24 (1.18 – 1.27)	1.21 (1.16 – 1.24)
0.039 (20-fold reduction)	1.43 (1.32 – 1.49)	1.36 (1.27 – 1.41)

GMR: Geometric mean ratio; AUC_{inf}: simulated AUC_{408-480h}; Range of trial geometric means are shown in parentheses (Source: PBPK report Table 19).

Next, sensitivity analysis of f_{gut} was performed to evaluate the impact on the prediction of AUC_{inf} ratio for raltegravir by increasing f_{gut} by 10-fold. As shown in Figure 40, higher f_{gut} values predicted higher AUC_{inf} ratios and under the worst-case scenario using 20-fold reduced K_i (0.039 μM) and 10-fold increased f_{gut} (0.38) the predicted AUC ratio for raltegravir was approximately 1.5.



The FDA's Assessment:

As discussed in the **Methods** section (19.4.4.2), permeability of quizartinib was estimated by comparing the simulated and observed DDI between quizartinib and dabigatran etexilate. The estimated permeability was then used to derive the Q_{gut} value. Thus, the reviewer conducted additional sensitivity analysis to evaluate the effect of Q_{gut} on the predicted inhibitory effect of quizartinib on raltegravir. The results of sensitivity analysis (not presented) showed that there are minimal changes in the predicted AUC ratio for raltegravir (<2% change) when different Q_{gut} (1-20 L/hr) were used in the simulations.

Reviewer also conduct a simulation of worst-case scenario using K_i of 0.039 μM , f_{uGut} of 1 and Q_{gut} of 20 L/h. The predicted AUC ratio for raltegravir was approximately 1.5 (**Table 131**). Reviewer concluded that the effect of quizartinib on a UGT1A1 substrate (such as raltegravir) is expected to be not clinically significant or weak.

Table 131. Simulation of worst-case scenario for the effect of quizartinib on the simulated PKs for raltegravir in the absence and presence of quizartinib in healthy subjects

Alternative parameters different than the submitted model	G.M. of AUCinf ratio [Confidence Interval]	G.M. of Cmax ratio [Confidence Interval]

Ki of 0.039 μ M, fugut of 1 and Qgut of 20 L/h	1.48 [1.43,1.53]	1.43 [1.37, 1.47]

Source: Reviewer's analysis. Simulated using the submitted a4-dai-ddi-ralte-quiz-60mgqd-asg.wks with alternative model parameters.

19.5. Additional Statistical Analyses

19.5.1. Subgroup analyses

Table 132 presents subgroup analyses of OS by various landmark times. The magnitude of OS detriment within the first 3 months varies across subgroups, with no clear trend. No clear detriment in OS is present for any subgroup for overall OS, except for patients with favorable cytogenetics, for which the same size was small, limiting firm conclusions.

Table 132: Subgroup analysis of OS by landmark time in QuANTUM-First (ITT Analysis Set)

Baseline Covariate	Subgroup	n	OS by 3 months HR (95% CI)	OS by 6 months HR (95% CI)	OS by any time HR (95% CI)
Age	<65	323	1.58 (0.68, 3.66)	0.77 (0.45, 1.33)	0.68 (0.49, 0.95)
	$\geq$ 65	216	1.83 (0.84, 3.99)	0.99 (0.56, 1.74)	0.91 (0.66, 1.26)
Sex	Female	294	2.44 (1.06, 5.61)	0.93 (0.55, 1.59)	0.69 (0.50, 0.96)
	Male	245	1.17 (0.53, 2.62)	0.79 (0.44, 1.40)	0.86 (0.62, 1.19)
Race	Asian	158	0.98 (0.28, 3.39)	0.72 (0.30, 1.71)	0.80 (0.51, 1.26)
	Black Or AA	7	NE (NE, NE)	0.00 (0.00, Inf)	1.14 (0.19, 6.95)
	Other	52	0.91 (0.06, 14.51)	0.60 (0.10, 3.59)	0.61 (0.27, 1.39)
	White	322	2.08 (1.06, 4.06)	1.00 (0.63, 1.58)	0.80 (0.60, 1.06)
Region	Asia/Other	179	1.20 (0.40, 3.56)	0.75 (0.35, 1.58)	0.83 (0.55, 1.26)
	Europe	326	1.92 (0.98, 3.77)	0.96 (0.60, 1.53)	0.73 (0.55, 0.97)
	North America	34	NE (NE, NE)	0.00 (0.00, Inf)	1.03 (0.38, 2.73)
WBC count at AML diag.	$<40 \times 10^9/L$	267	2.12 (0.95, 4.73)	1.20 (0.70, 2.06)	0.94 (0.67, 1.31)
	$\geq 40 \times 10^9/L$	270	1.31 (0.57, 2.99)	0.59 (0.33, 1.06)	0.62 (0.45, 0.85)
NPM1 Mutation	N	236	1.18 (0.56, 2.49)	0.79 (0.46, 1.36)	1.01 (0.73, 1.41)
	Y	282	3.10 (1.13, 8.52)	1.03 (0.57, 1.85)	0.64 (0.46, 0.89)
Anthracycline type	Daunorubicin	219	1.11 (0.47, 2.60)	0.77 (0.42, 1.40)	0.77 (0.54, 1.10)
	Idarubicin	317	2.26 (1.04, 4.90)	0.94 (0.56, 1.58)	0.77 (0.57, 1.05)
FLT3 Category	≥ 3 to $\leq 25\%$	192	1.87 (0.73, 4.74)	1.09 (0.56, 2.14)	0.87 (0.58, 1.30)
	$>25\%$ to $\leq 50\%$	281	1.88 (0.84, 4.22)	0.85 (0.50, 1.46)	0.77 (0.56, 1.07)
	$>50\%$	65	0.76 (0.13, 4.56)	0.49 (0.15, 1.58)	0.53 (0.29, 0.95)
Risk status	Favorable	33	4.42 (0.46, 42.55)	2.10 (0.47, 9.38)	2.07 (0.72, 5.97)
	Intermediate	390	1.50 (0.72, 3.11)	0.83 (0.51, 1.34)	0.76 (0.58, 1.00)

	Unfavorable	46	1.49 (0.37, 5.97)	0.80 (0.27, 2.40)	0.45 (0.19, 1.04)
	Unknown Risk	70	2.62 (0.53, 12.99)	0.88 (0.31, 2.52)	0.79 (0.43, 1.44)
ECOG	0	185	1.46 (0.55, 3.93)	0.61 (0.30, 1.23)	0.76 (0.50, 1.16)
	1	270	1.81 (0.76, 4.32)	0.95 (0.55, 1.66)	0.76 (0.56, 1.04)
	2	83	1.61 (0.48, 5.35)	1.16 (0.44, 3.04)	0.79 (0.43, 1.44)

Source: FDA analysis

19.5.2. Additional Analyses of Efficacy in the Continuation Phase

Applicant's Analyses

To address the potential confounding issues arising from the unbalance in the prognostic factors between two treatment arms during the Continuation Phase, the sponsor provided additional analysis based on propensity scores per FDA's request. By accounting for any differences in measured baseline characteristics, the propensity score analysis mimics what would have been achieved through randomization in a randomized clinical trial. In contrast to true randomization, it should be emphasized that the propensity score can only account for measured confounders, not for any unmeasured confounders. The variables that the Applicant started with for the propensity score analysis are listed below:

- (at study baseline) age, sex, race, geographical region, ECOG performance status, choice of anthracycline, AML cytogenetic risk score, FLT3-ITD allelic burden, NPM1 mutational status, percentage of bone marrow blasts, and WBC count at the time of diagnosis of AML.
- (at the initiation of the Continuation Phase): number of induction cycles, time from randomization to start of Continuation Phase, receipt of HSCT, best response in the Induction phase, ECOG performance status, WBC count (as a continuous variable) and choice of conditioning regimen.

The Applicant chose two sets of covariates from above by selecting any unbalanced variables between two arms (1) at study baseline or the initiation of the Continuation Phase, or (2) at the initiation of the Continuation Phase, and then applied four commonly used propensity score methods to evaluate the treatment effect in the Continuation Phase for OS and RFS: stratification, matching, inverse probability treatment weighting (IPTW) and covariate adjustment based on propensity score. The corresponding results of OS overall and by HSCT status are displayed in Table 133 based on unbalanced variables between two arms at study baseline or initiation of Continuation. HR estimations for OS in the Continuation Phase from propensity score methods range from 0.72 to 0.77, which are slightly greater than the unadjusted HR of 0.68. Among 119 patients who initiated continuation with HSCT, the

estimated HR from propensity score methods range from 1.61 to 1.83 in favor of placebo. Among 89 patients who initiated continuation without HSCT, the estimated HR from propensity score methods range from 0.4 to 0.46 in favor of quizartinib. These results are supportive of the previous conclusion that the benefit of quizartinib after HSCT as continuation therapy is questionable.

Table 133: HR estimations from propensity score-based analyses of OS by HSCT status based on unbalanced variables between arms at study baseline or initiation of Continuation (Continuation Analysis Set)

	With HSCT prior to Continuation N = 119	Without HSCT prior to Continuation N = 89	Total N = 166
Crude (no adjustment)	1.62 (0.62, 4.22)	0.4 (0.19, 0.84)	0.68 (0.4, 1.18)
Stratification	1.83 (0.7, 1.81)	0.46 (0.21, 0.98)	0.77 (0.44, 1.35)
Matching	1.65 (0.63, 4.32)	0.4 (0.16, 0.99)	0.72 (0.4, 1.32)
IPTW	1.67 (0.65, 4.28)	0.41 (0.2, 0.87)	0.76 (0.43, 1.34)
Covariate adjustment	1.61 (0.61, 4.23)	0.43 (0.2, 0.93)	0.74 (0.42, 1.3)

Source: Applicant's response to information request dated 9 January 2023

Table 134 displays the HR estimations of RFS from the propensity score methods based on unbalanced variables between two arms at study baseline or the initiation of the Continuation Phase, which are generally consistent with unadjusted results.

Table 134: HR estimations from propensity score-based analyses of RFS by HSCT status based on unbalanced variables between arms at study baseline or initiation of Continuation (Continuation Analysis Set who achieved CR at end of Induction)

	With HSCT prior to Continuation N = 89	Without HSCT prior to Continuation N = 77	Total N = 166
Crude (no adjustment)	1.2 (0.47, 3.05)	0.63 (0.34, 1.17)	0.74 (0.44, 1.23)
Stratification	1.18 (0.46, 3.03)	0.66 (0.34, 1.26)	0.83 (0.49, 1.4)
Matching	0.74 (0.24, 2.27)	0.54 (0.25, 1.2)	0.59 (0.32, 1.1)
IPTW	1.36 (0.53, 3.55)	0.61 (0.33, 1.14)	0.84 (0.5, 1.42)
Covariate adjustment	1.19 (0.46, 3.06)	0.61 (0.32, 1.18)	0.79 (0.47, 1.34)

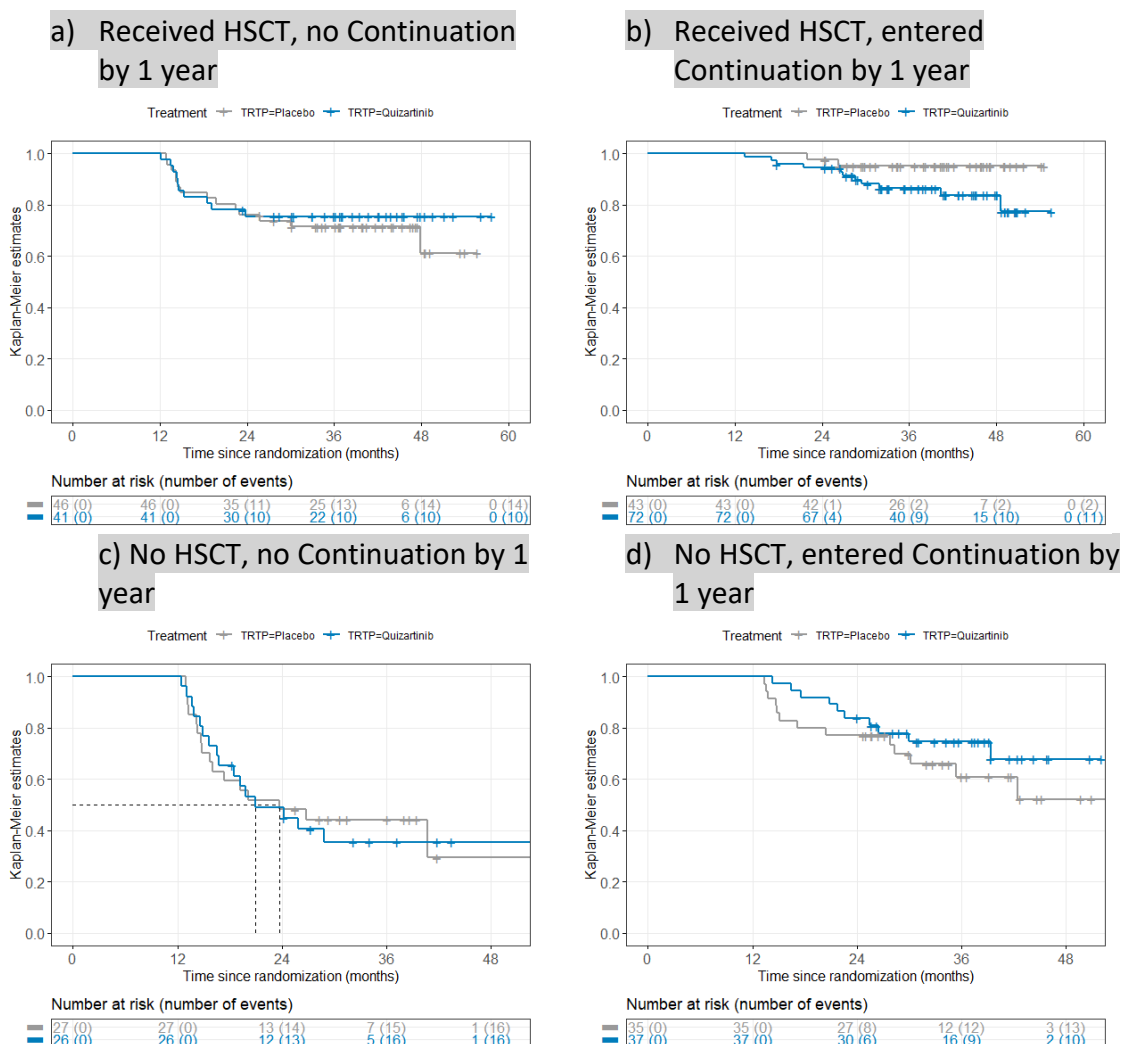
Source: Applicant's information response dated 9 January 2023

Additional FDA Analyses

Landmark analyses are survival analyses which consider only a subset of patients who have lived at least a specified amount of time. These analyses help to address immortal time bias and allow for comparisons to patients who did not experience the post-randomization event of

interest. FDA conducted a landmark analysis in which only patients who survived at least 1 year after randomization are included. The choice of 1 year as the landmark time is due to (1) most patients in Continuation Analysis Set entered Continuation within 1 year after randomization, and (2) most patients with HSCT received it within 1 year after randomization. Figure 41 shows the comparison of OS between treatment arms for the subgroup of patients who entered continuation by 1 year versus not and those who received HSCT by 1 year versus not. Figure 41(d) suggests the quizartinib treatment improves OS for patients who receive continuation therapy without HSCT; in contrast, in Figure 41(b) the placebo curve stays on top of the quizartinib curve, making it unclear if patients derive benefit from continuation after HSCT.

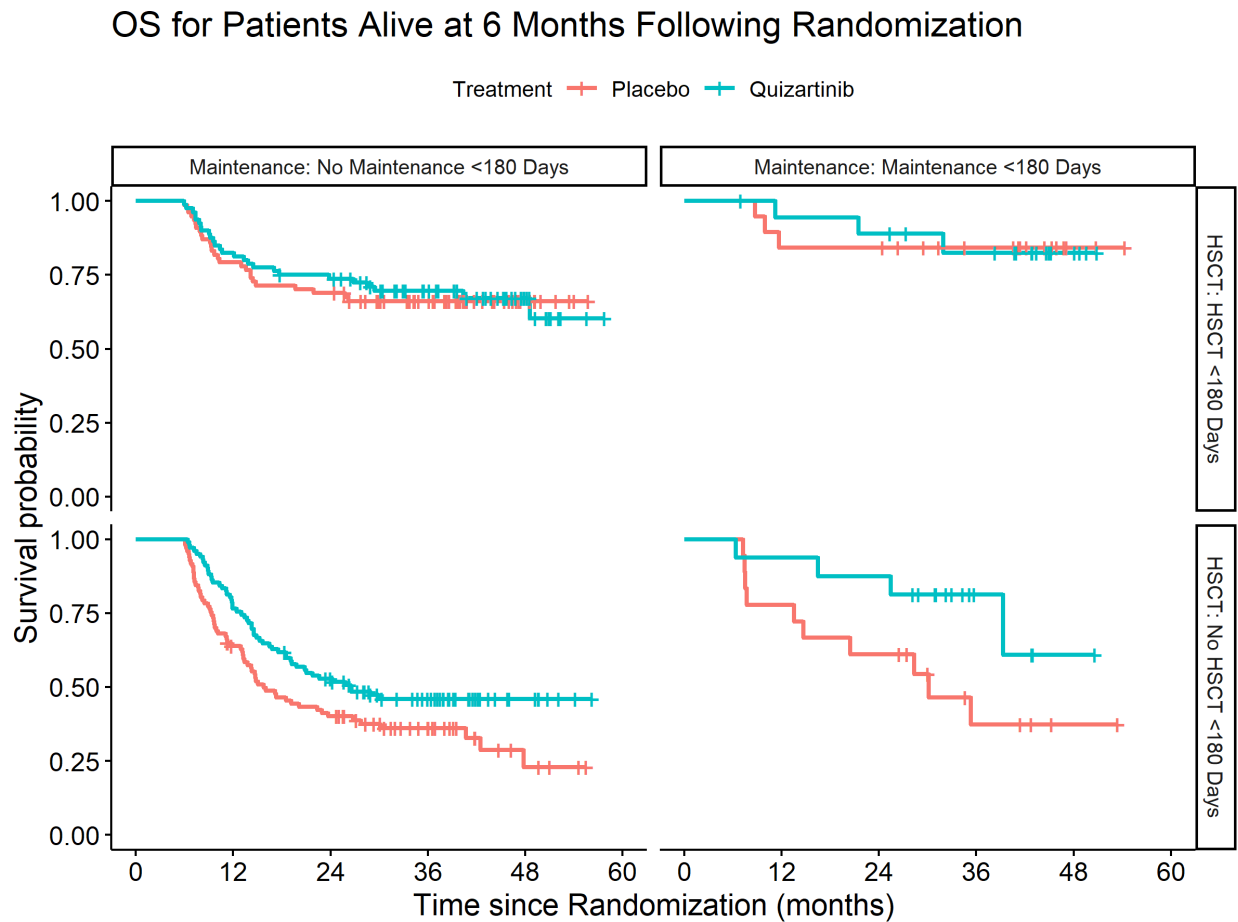
Figure 41: Landmark OS for patients alive at 1 year following randomization



Source: FDA analysis

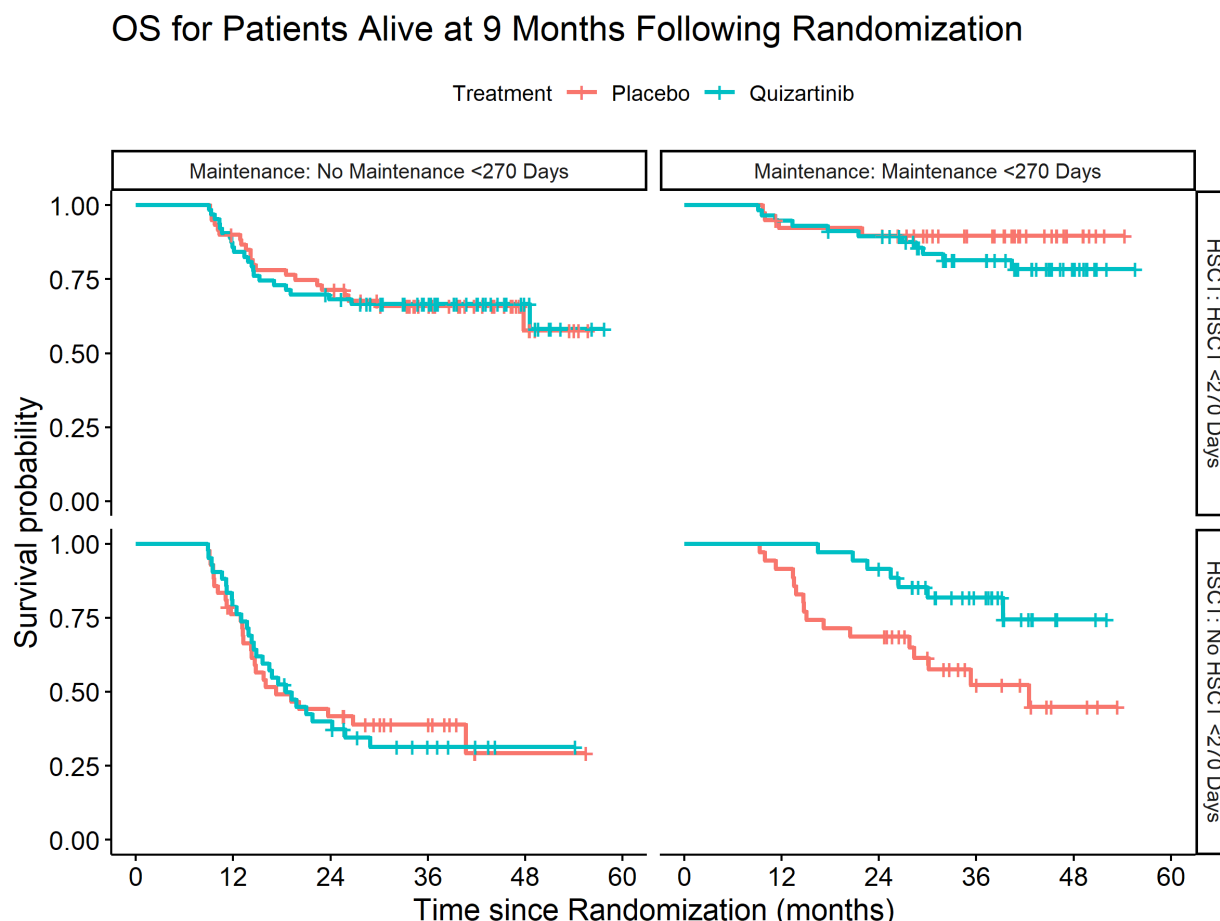
Figure 42 and Figure 43 show these results using 6- and 9-month landmarks.

Figure 42: Landmark OS for patients alive at 6 months following randomization



Source: FDA analysis.

Figure 43: Landmark OS for patients alive at 9 months following randomization



Source: FDA analysis.

While the above analyses correct for immortal time bias by removing patients who did not live long enough to reach HSCT or continuation therapy, they do not account for granular differences in times to these events. To address these limitations, an expanded Cox model was implemented. The expanded model includes a time-dependent indicator for HSCT and another time-dependent indicator for initiation of continuation therapy. Results from the expanded model are presented in Table 135, where the treatment effect of quizartinib during Continuation in terms of HR is estimated to 1.67 (95% CI: 0.64, 4.33) in favor of placebo among patients who received HSCT and continuation, and 0.42 (0.20, 0.88) in favor of quizartinib among patients who did not receive HSCT and continuation. These results are similar to the unadjusted results.

Table 135: Estimation of treatment effect of quizartinib on OS in the continuation phase based on the expanded Cox model (Continuation Analysis Set)

Continuation	HSCT	HR (95% CI)
No	No	0.87 (0.66, 1.15)
No	Yes	0.68 (0.36, 1.28)
Yes	No	0.42 (0.20, 0.88)
Yes	Yes	1.67 (0.64, 4.33)

Source: FDA analysis

Similar analyses were conducted on RFS. As for the adjusted OS analyses, the adjusted analyses of RFS were similar to the unadjusted RFS analyses.

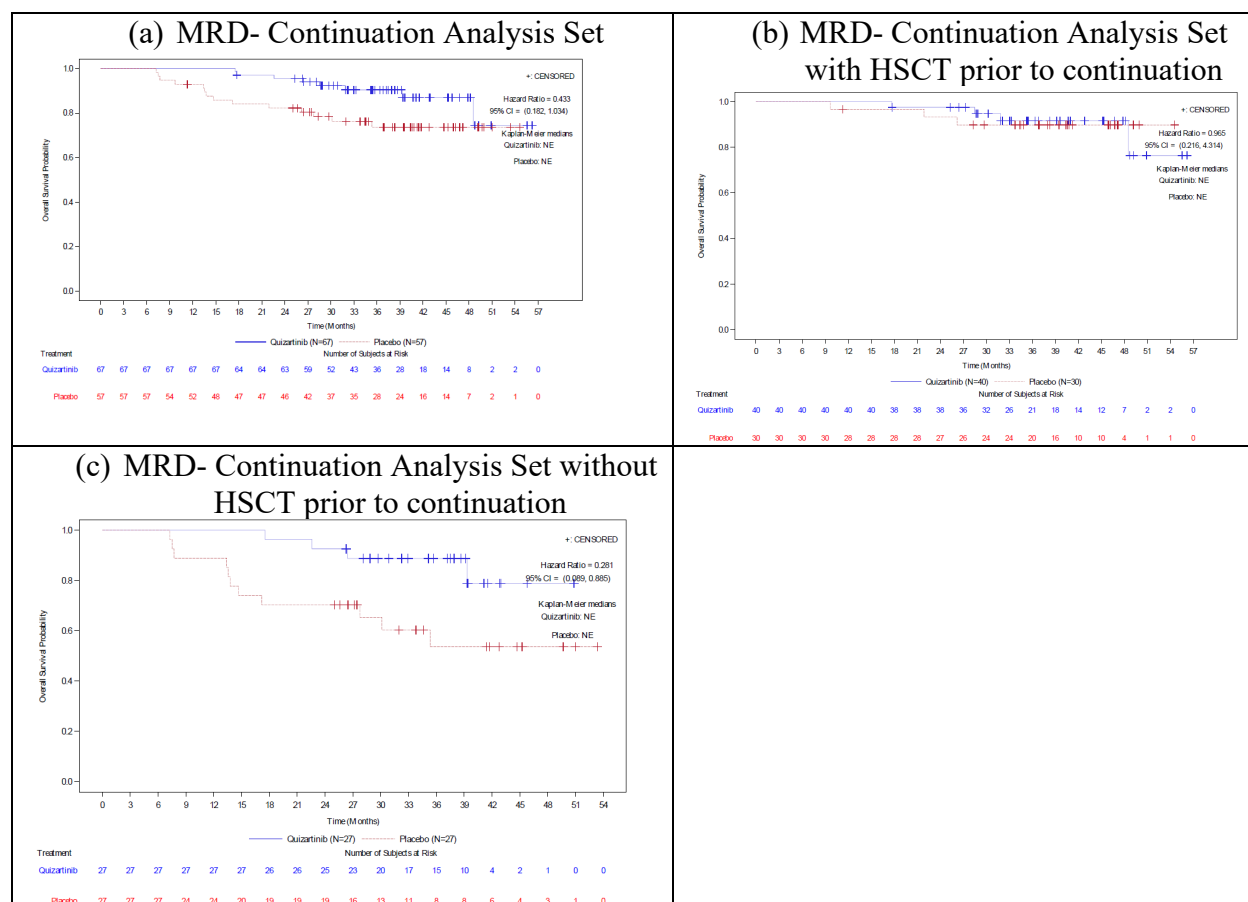
As documented above, FDA requested the Applicant to conduct their own independent analysis of the effect of quizartinib 1) in the continuation setting and 2) with emphasis on possible differential effects for HSCT vs. non-HSCT patients. The results are similar to those presented above. These analyses defined the HSCT subgroup as patients who received protocol-specified HSCT rather than any HSCT.

While the analysis above suggests benefit for patients who receive quizartinib continuation without HSCT, this analysis is speculative and makes various untestable, strong assumptions. One such assumption is that the treatment effect (i.e., HR) due to any treatment period (induction/consolidation, continuation) is constant. For instance, the above analysis estimates the effect of induction/consolidation quizartinib therapy on OS to be 0.87 (95% CI: 0.66, 1.15). Though it is possible that continued quizartinib continuation increases this treatment effect for patients who do not receive HSCT, it is also possible that this treatment effect would increase on its own over time without further treatment. Similar logic applies to patients who receive HSCT and subsequent quizartinib continuation therapy. Because QuANTUM-First was not re-randomized during the continuation phase, more rigorous comparisons cannot be made.

19.5.3. Effect of MRD in Continuation

Among 124 patients in MRD- Continuation Analysis Set, 70 (56%) and 54 (44%) started the continuation therapy with and without HSCT respectively. The OS analysis results among these patients and a breakdown by the HSCT status are provided in Figure 44. There is a separation of Kaplan-Meier curves in favor of quizartinib (HR = 0.43 [95% CI: 0.18, 1.03]), although such an effect is mostly driven by the patients without HSCT prior to continuation (HR = 0.28 [95% CI: 0.09, 0.89]). Whereas among the patients with HSCT prior to continuation, the survival curves overlap for most of the time, which suggests lack of benefit of the quizartinib treatment as continuation therapy in this subgroup.

Figure 44 Kaplan-Meier plot of OS in Continuation Analysis Set (overall and by HSCT status, MRD- only)



Source: Applicant's information response dated 9 January 2023

19.6. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Grouped preferred terms are displayed in the Table below.

Grouped Term	Preferred Terms
Abdominal pain	Abdominal discomfort
	Abdominal pain
	Abdominal pain lower
	Abdominal pain upper
	Abdominal tenderness
	Epigastric discomfort
Acute febrile neutrophilic dermatosis	Gastrointestinal pain
	Acute febrile neutrophilic dermatosis

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	Neutrophilic dermatosis
Anemia	Anaemia
	Haematocrit decreased
	Haemoglobin decreased
	Red blood cell count decreased
Arrhythmia	Arrhythmia
	Arrhythmia supraventricular
	Atrial fibrillation
	Atrial flutter
	Atrial tachycardia
	Bradycardia
	Extrasystoles
	Sinus arrhythmia
	Sinus bradycardia
	Sinus tachycardia
	Supraventricular extrasystoles
	Supraventricular tachycardia
	Tachyarrhythmia
	Tachycardia
	Torsade de pointes
	Ventricular arrhythmia
	Ventricular extrasystoles
	Ventricular fibrillation
	Ventricular tachycardia
Cardiac failure	Cardiac failure
	Cardiac failure congestive
	Cardiomyopathy
	Cardiotoxicity
	Ejection fraction decreased
	Hypertensive cardiomyopathy
	Left ventricular dysfunction
	Right ventricular dysfunction
	Stress cardiomyopathy
	Ventricular dysfunction
Cellulitis	Anorectal cellulitis
	Breast cellulitis
	Catheter site cellulitis
	Cellulitis
	Cellulitis of male external genital organ
	Cellulitis orbital
	Erysipelas
	External ear cellulitis
	Periorbital cellulitis
	Vulval cellulitis
Chest pain	Angina pectoris
	Chest discomfort
	Chest pain
Clostridial infection	Clostridial infection

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	Clostridium colitis
	Clostridium difficile colitis
	Clostridium difficile infection
Conduction disorder	Atrioventricular block complete
	Bundle branch block left
	Bundle branch block right
	Conduction disorder
Cough	Cough
	Productive cough
Diarrhea	Colitis
	Diarrhoea
	Diarrhoea infectious
	Enteritis
	Enterocolitis
	Gastroenteritis
	Neutropenic colitis
Dyspnea	Acute respiratory failure
	Bronchospasm
	Dyspnoea
	Dyspnoea at rest
	Dyspnoea exertional
	Respiratory distress
	Respiratory failure
	Respiratory rate increased
	Tachypnoea
Edema	Eyelid oedema
	Face oedema
	Fluid overload
	Fluid retention
	Generalised oedema
	Gravitational oedema
	Lip oedema
	Localised oedema
	Oedema
	Oedema genital
	Oedema peripheral
	Orbital oedema
	Periorbital oedema
	Peripheral swelling
	Scrotal swelling
	Swelling
	Swelling face
Eye irritation	Dry eye
	Eye inflammation
	Eye irritation
	Eye pain
	Eye pruritus
	Foreign body sensation in eyes

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	Keratitis
	Ulcerative keratitis
Fatigue	Asthenia
	Fatigue
Fungal infection	Aspergillosis oral
	Aspergillus infection
	Bronchitis fungal
	Bronchopulmonary aspergillosis
	Candida infection
	Candida sepsis
	Fungal infection
	Fungal sepsis
	Fungal skin infection
	Fusarium infection
	Gastrointestinal candidiasis
	Gastrointestinal fungal infection
	Genital infection fungal
	Hepatic infection fungal
	Hepatosplenic candidiasis
	Lower respiratory tract infection fungal
	Mucormycosis
	Oral candidiasis
	Oral fungal infection
	Oropharyngeal candidiasis
	Respiratory tract infection fungal
	Sinusitis aspergillus
	Sinusitis fungal
	Skin candida
	Systemic candida
	Systemic mycosis
	Tinea cruris
	Tinea infection
	Vulvovaginal candidiasis
	Vulvovaginal mycotic infection
Gastrointestinal hemorrhage	Anal haemorrhage
	Diarrhoea haemorrhagic
	Gastric haemorrhage
	Gastric ulcer haemorrhage
	Gastritis haemorrhagic
	Gastrointestinal haemorrhage
	Haematemesis
	Haematochezia
	Haemorrhoidal haemorrhage
	Intestinal haemorrhage
	Lip haemorrhage
	Lower gastrointestinal haemorrhage
	Mouth haemorrhage
	Mucosal haemorrhage

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	Rectal haemorrhage
	Tongue haemorrhage
	Tonsillar haemorrhage
	Ulcer haemorrhage
	Upper gastrointestinal haemorrhage
Hemorrhage intracranial	Cerebral haematoma
	Cerebral haemorrhage
	Haemorrhage intracranial
	Haemorrhagic stroke
	Intraventricular haemorrhage
	Subarachnoid haemorrhage
	Subdural haematoma
	Subdural haemorrhage
Herpesvirus infection	Disseminated varicella zoster virus infection
	Genital herpes
	Herpes ophthalmic
	Herpes simplex
	Herpes virus infection
	Herpes zoster
	Ophthalmic herpes simplex
	Oral herpes
	Varicella zoster virus infection
Hyperbilirubinemia	Bilirubin conjugated increased
	Blood bilirubin increased
	Blood bilirubin unconjugated increased
	Hyperbilirubinaemia
	Jaundice
	Jaundice cholestatic
Hyperglycaemia	Blood glucose increased
	Diabetes mellitus
	Diabetes mellitus inadequate control
	Diabetic ketoacidosis
	Hyperglycaemia
	Steroid diabetes
	Type 1 diabetes mellitus
	Type 2 diabetes mellitus
Hypersensitivity	Anaphylactic reaction
	Drug eruption
	Drug hypersensitivity
	Erythema multiforme
	Hypersensitivity
	Urticaria
Hypertransaminasemia	Alanine aminotransferase increased
	Aspartate aminotransferase increased
	Hepatic enzyme increased
	Hypertransaminasaemia
	Transaminases increased
Hypoalbuminemia	Blood albumin decreased

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	Hypoalbuminaemia
Injection site reaction	Injection site erythema
	Injection site haematoma
	Injection site induration
	Injection site inflammation
	Injection site reaction
Mucositis	Anal inflammation
	Anal ulcer
	Anorectal discomfort
	Anorectal disorder
	Aphthous ulcer
	Erosive oesophagitis
	Laryngeal inflammation
	Laryngeal pain
	Mucosal inflammation
	Mucosal ulceration
	Oedema mucosal
	Oesophageal pain
	Oesophageal ulcer
	Oesophagitis
	Oral blood blister
	Oral disorder
	Oral mucosa erosion
	Oral mucosal blistering
	Oral mucosal erythema
	Oral pain
	Oropharyngeal pain
	Pharyngeal erythema
	Pharyngeal inflammation
	Pharyngeal ulceration
	Proctalgia
	Proctitis
	Stomatitis
	Tongue ulceration
	Vaginal ulceration
	Vulvovaginal inflammation
Musculoskeletal pain	Axillary pain
	Back pain
	Bone pain
	Flank pain
	Fracture pain
	Musculoskeletal chest pain
	Musculoskeletal discomfort
	Musculoskeletal pain
	Myalgia
	Neck pain
	Non-cardiac chest pain
	Pain

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	Pain in extremity
	Spinal pain
	Tendon pain
Myelosuppression	Myelosuppression
	Pancytopenia
Myocardial ischemia	Acute coronary syndrome
	Acute myocardial infarction
	Myocardial infarction
	Myocardial ischaemia
	Troponin I increased
	Troponin increased
	Troponin T increased
Neutropenia	Neutropenia
	Neutrophil count decreased
Phlebitis	Catheter site phlebitis
	Infusion site phlebitis
	Injection site phlebitis
	Phlebitis
	Phlebitis infective
	Phlebitis superficial
	Thrombophlebitis
	Thrombophlebitis superficial
Pneumonia	Atypical pneumonia
	Lung abscess
	Metapneumovirus pneumonia
	Pneumonia
	Pneumonia aspiration
	Pneumonia bacterial
	Pneumonia fungal
	Pneumonia influenzal
	Pneumonia klebsiella
	Pneumonia parainfluenzae viral
	Pneumonia pneumococcal
	Pneumonia pseudomonal
	Pneumonia respiratory syncytial viral
	Pneumonia staphylococcal
	Pneumonia streptococcal
	Pneumonia viral
	Respiratory tract infection bacterial
Pneumonitis	Acute respiratory distress syndrome
	Interstitial lung disease
	Organising pneumonia
	Pneumonitis
Rash	Butterfly rash
	Dermatitis
	Dermatitis acneiform
	Dermatitis allergic
	Dermatitis atopic

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	Dermatitis bullous
	Dermatitis contact
	Dermatitis exfoliative
	Dermatitis exfoliative generalised
	Dermo-hypodermatitis
	Exfoliative rash
	Hand dermatitis
	Herpes dermatitis
	Perivascular dermatitis
	Rash
	Rash erythematous
	Rash follicular
	Rash macular
	Rash maculo-papular
	Rash papular
	Rash pruritic
	Rash pustular
	Toxic skin eruption
Renal insufficiency	Acute kidney injury
	Blood creatinine increased
	Creatinine renal clearance decreased
	Glomerular filtration rate decreased
	Renal disorder
	Renal failure
	Renal function test abnormal
	Renal impairment
Sepsis	Acinetobacter bacteraemia
	Acinetobacter infection
	Bacteraemia
	Bacterial sepsis
	Clostridial sepsis
	Corynebacterium bacteraemia
	Device related bacteraemia
	Device related sepsis
	Enterobacter bacteraemia
	Enterobacter sepsis
	Enterococcal bacteraemia
	Enterococcal sepsis
	Escherichia bacteraemia
	Escherichia sepsis
	Klebsiella bacteraemia
	Klebsiella sepsis
	Meningitis bacterial
	Neutropenic infection
	Neutropenic sepsis
	Pneumococcal sepsis
	Pseudomonal bacteraemia
	Pseudomonal sepsis

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	Pulmonary sepsis
	Sepsis
	Sepsis syndrome
	Septic shock
	Serratia bacteraemia
	Staphylococcal bacteraemia
	Staphylococcal infection
	Staphylococcal sepsis
	Stenotrophomonas sepsis
	Streptococcal bacteraemia
	Streptococcal sepsis
	Urosepsis
Thrombosis	Aortic thrombosis
	Brachiocephalic vein thrombosis
	Catheter site thrombosis
	Deep vein thrombosis
	Device related thrombosis
	Jugular vein thrombosis
	Peripheral artery thrombosis
	Pulmonary embolism
	Subclavian vein thrombosis
	Thrombosis
	Thrombosis in device
	Venous thrombosis
	Venous thrombosis limb
Transfusion reaction	Allergic transfusion reaction
	Anaphylactic transfusion reaction
	Transfusion reaction
	Transfusion related complication
Upper respiratory tract infection	Acute sinusitis
	Chronic sinusitis
	Laryngitis
	Laryngopharyngitis
	Nasopharyngitis
	Peritonsillar abscess
	Pharyngitis
	Pharyngitis bacterial
	Pharyngotonsillitis
	Rhinitis
	Sinus congestion
	Sinusitis
	Tonsillitis
	Tonsillitis bacterial
	Upper respiratory tract infection
	Viral pharyngitis
	Viral upper respiratory tract infection
Urinary tract infection	Bacterial pyelonephritis
	Cystitis

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	Cystitis escherichia
	Escherichia urinary tract infection
	Genitourinary tract infection
	Pyelonephritis
	Pyelonephritis acute
	Urinary tract infection
	Urinary tract infection bacterial
	Urinary tract infection enterococcal
	Urinary tract infection fungal
Visual impairment	Diplopia
	Vision blurred
	Visual acuity reduced
	Visual field defect
	Visual impairment

[NDA 216993]				
Signatures				
DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2023.06.27 17:06:58 -04'00'			
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Clinical Team Leader	Kelly Norsworthy, MD	OOD/DHM1	Sections: 2, 3, 7, 8, 9, 10, 11, 12, and 13	Select one: ☐ Authored ☒ Approved
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Statistical Team Leader	Jonathon Vallejo, PhD	OB/DBIX	Sections: 7 and 8	Select one: ☐ Authored ☒ Approved
	Signature: Jonathon J. Vallejo -S Digitally signed by Jonathon J. Vallejo -S Date: 2023.06.29 13:18:25 -04'00'			
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Division Director (Clinical)	R. Angelo de Claro, MD	OOD/DHM1	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: Romeo De Claro -S Digitally signed by Romeo De Claro -S Date: 2023.07.05 12:56:05 -04'00'			
Division Director (OB) (NMF only)	Yuan-Li Shen, PhD	OB/DBIX	Sections: 7 and 8	Select one: ☐ Authored ☒ Approved

(NME Only)	Signature: Yuan-li Shen -S			Digitally signed by Yuan-li Shen -S Date: 2023.06.29 14:53:11 -04'00'
Office Director or signatory (NME only)	Marc Theoret, MD	Oncology Center of Excellence (OCE)	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature:			
OOD: Office of Oncologic Diseases				
DHOT: Division of Hematology, Oncology, Toxicology				
OCP: Office of Clinical Pharmacology				
DPM: Division of Pharmacometrics				
DTPM: Division of Translational and Precision Medicine (DTPM)				
DCPI: Division of Cancer Pharmacology I				
OB: Office of Biostatistics				
DBIX: Division of Biometrics IX				
DHM1: Division of Hematologic Malignancies 1				

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/s/

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07/19/2023 05:18:51 PM

ROMEO A DE CLARO
07/20/2023 08:23:23 AM

MARC R THEORET
07/20/2023 10:30:03 AM

My signature indicates that I have considered the assessments of the data in this application and FDA recommendations included in this Review in determining the regulatory action.