European Union Risk Management Plan for VANFLYTA (quizartinib)

RMP version to be assessed as part of this application:

Data lock point for this RMP	13 Aug 2021	RMP Version number	1.0
Date of final sign off	08 Sep 2023		

Qualified Person Responsible for Pharmacovigilance (QPPV) name: Dr. Stefan Freudenthaler

QPPV Oversight Declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

TABLE OF CONTENTS

LIST OF TABLES

PART I PRODUCT OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name):	Quizartinib
Pharmacotherapeutic group(s) (ATC Code):	L01XE11
Name of Marketing Authorisation Applicant:	Daiichi Sankyo Europe GmbH
Medicinal products to which this RMP refers:	1
Invented name in the EEA:	VANFLYTA
Marketing authorisation procedure:	Centralised
Brief description of the product:	Chemical class: Second-generation, Class III RTK inhibitor
	Summary of mode of action: Quizartinib is a small-molecule inhibitor of the RTK FLT3. Quizartinib and its active metabolite AC886 competitively bind to the adenosine triphosphate binding pocket of FLT3 with high affinity (Kd = 1.3 and 0.54 nM, respectively). Quizartinib and AC886 inhibit FLT3 kinase activity, preventing autophosphorylation of the receptor, thereby inhibiting further downstream FLT3 receptor signalling and FLT3-ITD-dependent cell proliferation.
	Important information about its composition: Quizartinib is available as 17.7- and 26.5-mg film-coated tablets. Each 17.7-mg film-coated tablet contains 17.7 mg quizartinib (as dihydrochloride). Each 26.5-mg film-coated tablet contains 26.5 mg quizartinib (as dihydrochloride).
Hyperlink to the Product Information:	VANFLYTA (quizartinib) Summary of Product Characteristics (SmPC)
Indication(s) in the EEA:	VANFLYTA is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by VANFLYTA single agent maintenance therapy for adult patients with newly diagnosed AML that is *FLT3*-ITD positive.

Dosage in the EEA:	VANFLYTA should be administered in combination with standard chemotherapy at a dose of 35.4 mg QD for 2 weeks in each cycle of induction. For patients who achieve CR or CRi, VANFLYTA should be administered at 35.4 mg QD for 2 weeks in each cycle of consolidation chemotherapy followed by VANFLYTA continuation monotherapy initiated at 26.5 mg QD. After 2 weeks the continuation dose should be increased to 53 mg QD if QTcF is ≤450 ms (see SmPC Section 4.4). Continuation therapy may be continued for up to 36 cycles (SmPC Table 1). For patients taking strong CYP3A inhibitors concomitantly, the dose should be reduced. See SmPC Table 3 for dosing recommendations.
Pharmaceutical form(s) and strengths:	Film-coated tablets 17.7 mg and 26.5 mg
Is/will the product be subject to additional monitoring in the EU?	Yes

AML = acute myeloid leukaemia; ATC = Anatomical Therapeutic Chemical; CR = complete remission; CRi = complete remission with incomplete haematologic recovery; CYP = cytochrome P450; EAA = European Economic Area; EU = European Union; FLT3 = Feline McDonough sarcoma-like tyrosine kinase 3; Kd = dissociation constant; INN = International Nonproprietary Name; ITD = internal tandem duplication; QD = once daily; QTcF = QT interval corrected by Fridericia's formula; RMP = Risk Management Plan; RTK = receptor tyrosine kinase

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Acute Myeloid Leukaemia

The epidemiology of acute myeloid leukaemia (AML) is summarised below. Given that the quizartinib development programme included studies in subjects with relapsed/refractory (R/R) AML and that data presented in the Risk Management Plan (RMP) include both subjects with newly diagnosed (ND) and R/R AML (see Section Part II: Module SIII), epidemiology data on R/R AML are presented for completeness.

Incidence and Prevalence

AML is the most common acute leukaemia in adults; according to the United States (US) Surveillance, Epidemiology, and End Results (SEER) data (2020), 33% of all leukaemia cases are AML. GLOBOCAN estimates the worldwide total leukaemia incidence of AML for 2020 to

be 474,519, with an age-standardised rate of 6.3 and 4.5 per 100,000 for males and females, respectively.

Europe: In Europe, an estimated 22,250 new cases of AML are diagnosed each year, consisting of approximately 0.6% of all cancers and representing 30% of all leukaemia cases in adults. The annual incidence rate of AML is between 3 and 4 per 100,000 in Europe. For the European Union (EU) 28, the estimated number of new AML cases in 2013 was 19,819, and the crude annual incidence rate was 3.5 per 100,000 (based on 2000 to 2007 data). In a recent study involving the Global Health Data Exchange database, the estimated annual incidence rates of AML across Europe were lower than older estimates. The age-adjusted AML incidence rates for Central, Eastern, and Western Europe were 1.56, 1.39, and 2.5 per 100,000, respectively (2017 data). Based on 2008 data, there were an estimated 53,486 persons living with AML in the EU, and the 5-year prevalence estimate was 4.10 per 100,000.

According to NORDCAN the overall crude incidence of AML in Scandinavia from 2012 to 2016 was 2.9 and 2.6 per 100,000 for males and females, respectively. In Burgundy, France, the overall crude incidence was reported to be 2.5 per 100,000 (2.8 in males vs. 2.2 in females) whereas in Switzerland, the overall crude incidence was 3.8 per 100,000 (4.1 in males vs. 3.4 in females). In Sweden, the reported crude incidence increased from 4.7 (1997 to 1996) to 5.3 (2007 to 2015) per 100,000, resulting in an annual increase of 1.2%. Based on 2008 data, there were an estimated 53,486 persons living with AML in the EU, and the 5-year prevalence estimate was 4.10 per 100,000. In Scandinavia alone, the overall prevalence of AML in 2014 was estimated to 13.9 per 100,000 from Swedish registry data (1997 to 2013).

United Kingdom: There were 3164 new AML cases reported in the United Kingdom (UK) in 2017. Of these, approximately 1700 were in males, and 1300 were in females. AML accounts for <1% of all new cancers in the UK. Since the early 1990s, AML incidence rates have increased by 20% in the UK. The increase is similar in males (19%) and females (16%). The lifetime risk of AML diagnosis is 1 in 200 in men and 1 in 255 in women. An estimated 6100 people who had previously been diagnosed with AML were alive in the UK at the end of 2010. Age-adjusted incidence rates of AML by sex in the UK are presented in Table Part II: Module SI.1. The 5- and 10-year prevalence estimates are not readily available for the UK.

Table Part II: Module SI.1: Age-adjusted Incidence Rate per 100,000 Persons by Sex in Acute Myeloid Leukaemia in the United Kingdom (2017)

Sex		Country			
	UK	England	Scotland	Wales	Northern Ireland
All Sexes	5.1	5.2	3.7	4.8	4.4
Male	6.3	6.4	4.3	6.6	5.7
Female	4.1	4.2	3.3	3.4	3.6

UK = United Kingdom
Source: Cancer Research UK

Spain: AML incidence estimates were not available for Spain. In Spain, an analysis of the Ministry of Health records via the Spanish claims database reported a total of 39,568 cases of

AML diagnosed between 1997 and 2015. Of these, female patients with AML accounted for 44.7% of all cases whereas male patients accounted for 55.3%.

United States: US SEER estimates the number of new AML cases for 2020 to be 19,940, which represents 1.1% of all new cancer cases in the US. The 5-year prevalence of AML in the US is 25,363, and the 10-year prevalence is 11,650. The lifetime risk of developing AML in the US is approximately 0.5%. As of 2018, there was an estimated 66,988 people living with AML in the US.

The distribution of AML incidence rates by age group, race/ethnicity, and sex is presented in Table Part II: Module SI.2.

Table Part II: Module SI.2: Age-Adjusted Incidence Rate per 100,000 Persons by Age Group, Race/Ethnicity, and Sex in Acute Myeloid Leukaemia (2013 to 2017)

Sex and Race		Age Groups (years)					
		Overall	<15	15-39	40-64	65-74	75+
Male	All races	5.2	0.8	1.2	4.1	19.1	35.2
	White	5.4	0.8	1.2	4.1	20.1	37.2
	Black	4.4	0.7	1.2	3.9	15.4	26.1
	Asian/Pacific Islander	4.1	1.2	1.2	3.4	13.9	25.1
	American Indian/Alaska Native	2.9	-	-	3.0	-	-
	Hispanic	4.2	0.8	1.3	3.5	12.6	28.0
	Non-Hispanic	5.4	0.7	1.2	4.2	21.0	38.1
Female	All races	3.6	0.7	1.3	3.4	11.6	19.1
	White	3.7	0.7	1.2	3.5	12.2	20.1
	Black	3.3	0.7	1.4	3.5	9.8	15.1
	Asian/Pacific Islander	2.9	0.8	1.2	3.0	8.6	14.4
	American Indian/Alaska Native	1.9	-	-	-	-	-
	Hispanic	3.2	0.7	1.2	3.3	10.7	15.0
	Non-Hispanic	3.6	0.7	1.2	3.5	12.4	20.7

SEER = Surveillance, Epidemiology, and End Results
Source: SEER

Japan: The incidence of AML has been increasing in Japan since 1993 (Monitoring of Cancer Incidence in Japan project). In 2008, there were 1477 new AML cases reported from 16 prefectures. The age-adjusted overall incidence rate was 1.9 per 100,000 (2.99 per 100,000 among males and 1.87 per 100,000 among females).

Feline McDonough sarcoma-like tyrosine kinase 3 (*FLT3*)-internal tandem duplication (ITD) mutations: Mutation of *FLT3* can be found in up to 30% of patients with AML (*FLT3*- ITD accounts for approximately 20% and *FLT3*-tyrosine kinase domain [TKD] mutations in up to 10% of AML). In cytogenetically normal AML, this proportion can be as high as 42%

(31% *FLT3*-ITD and 11% *FLT3*-TKD mutations). *FLT3*-ITD is associated with poorer prognosis and survival, especially in normal karyotype AML (hazard ratio [HR] = 3.1; 95% confidence interval [CI] = 1.1 to 8.8; $P = 0.03$). *FLT3*-ITD is less common in children than in adults (13% to 16%). In a pooled analysis of 1722 subjects aged 0 to 60 years, *FLT3*-ITD mutations were found among 13% of subjects with AML <15 years, 19% in subjects 15 to 39 years, 23% in subjects >40 years, and 27% in subjects >65 years.

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 >60 years. In a retrospective pooled analysis of 1321 adult subjects treated by the German AML Cooperative Group and 148 paediatric subjects treated by the AML-Berlin/Frankfurt/Muenster study group, the median age of *FLT3*-ITD positive subjects was significantly lower compared with subjects with wild-type *FLT3* (55 vs. 61 years; $P < 0.001$).

The incidence of R/R AML is defined on the basis of the number of subjects whose AML has relapsed following initial remission (relapsed AML) or on the number of subjects who do not achieve an initial remission following induction therapy (refractory AML). These numbers vary depending on the type of induction therapy regimen used to achieve the initial remission. Broad estimates on the incidence of R/R AML based on the available data are provided below.

Overall, 10% to 40% of patients with ND AML do not achieve complete remission (CR) after induction therapy and are defined as primary refractory or resistant cases. With induction chemotherapy consisting of 3 days of anthracycline and 7 days of cytarabine (commonly referred to as “7 + 3” regimen), CR is achieved in 60% to 80% of younger adults and in 40% to 60% of older adults (60 years or older). With high-dose cytarabine (HiDAC)-containing induction regimens, 894 subjects with AML (61%) achieved CR, and 285 subjects with AML (19%) were refractory to the first cycle of induction. Among the 285 subjects who were refractory to initial induction therapy, 197 received salvage therapy, and only 35 (18%) achieved CR after salvage therapy. Other induction regimens (cytarabine, daunorubicin, and etoposide and fludarabine, cytarabine, granulocyte colony-stimulating factor [G-CSF], and idarubicin [FLAG-Ida]) have been associated with lower rates of primary refractory disease, with 82% and 84% of subjects achieving CR, compared with 76% of subjects receiving cytarabine and daunorubicin.

Relapse can be expected in nearly all patients with AML who initially achieve CR, unless postremission therapy is given. The goal of postremission therapy is to eliminate any residual, undetectable disease and achieve a cure. Consolidation chemotherapy and haematopoietic stem cell transplantation (HSCT) are the 2 options for postremission therapy. Even with postremission therapy, patients with AML experience relapse. In prospective studies, subjects <55 years of age who were in the first CR received consolidation therapy with allogeneic stem cell transplantation (alloSCT), autologous stem cell transplantation (autoSCT), or chemotherapy, with 4-year event-free survival (EFS) rates of 43% to 55% for alloSCT, 35% to 54% for autoSCT, and only 30% to 40% for chemotherapy. For patients with very poor prognostic factors, the risk of relapse following consolidation by chemotherapy or by autoSCT or alloSCT ranges from 90% for chemotherapy and 40% to 50% for autoSCT or alloSCT. For patients with favourable prognostic factors, the risk of relapse following consolidation by chemotherapy, or by autoSCT or alloSCT, ranges from 35% to 40% for chemotherapy and 15% to 20% for autoSCT or alloSCT.

Demographics of the Target Population

AML is more common in older adults and among men compared with women. In both Europe and the US, AML incidence rates increase with age, with the highest incidence among those ≥65 years of age. Among children, the highest incidence rate is observed among infants <1 year of age. Each year, 42% of all new AML cases in the UK are diagnosed in people ≥75 years old. Additionally, incidence rates for AML in the UK are highest in patients aged 85 to 89 years. In a report of incidence rates of leukaemia by ethnic group in England during 2002 to 2006, the Black ethnic group had statistically significantly higher incidence rates across all age groups.

In the US, the median age at diagnosis is 68 years, and the majority (58.9%) of all AML patients are diagnosed at age ≥65 years. Based on 2013 to 2017 data, incidence rates of AML vary across race/ethnic groups, with White patients having the highest rate, followed by Black, Hispanic, Asian/Pacific Islander, and American Indian/Alaska Native patients. That pattern holds regardless of sex. The percentage of new cases by age group based on SEER data from 2013 to 2017 is presented in Table Part II: Module SI.3.

Table Part II: Module SI.3: Percentage of New Cases by Age Group for Acute Myeloid Leukaemia (SEER 21, 2013 to 2017)

Age Groups (years)	Percentage of New Cases
<20	4.5%
20-34	5.6%
35-44	5.1%
45-54	9.2%
55-64	16.7%
65-74	25.5%
75-84	22.5%
>84	10.9%

SEER = Surveillance, Epidemiology, and End Results
Source: SEER.

Risk Factors

Risk factors for developing AML can be broadly described in 2 categories: non-patient-related risk factors and patient-related risk factors.

Non-patient-related Risk Factors

Physical and chemical exposures: Certain solvents, such as benzene, used in the rubber industry, oil refineries, chemical plants, and other industries and found in cigarette smoke, gasoline, combustion and cleaning products, and paints are identified as risk factors for developing AML. Other chemicals that can increase the risk of AML include herbicides, pesticides, or embalming fluids. Cigarette smoking is a risk factor for developing AML among adults. Parental smoking has also been found to be a risk factor for childhood leukaemia. In 2011, 14.6% of 9047 deaths among patients with AML were attributed to cigarette smoking (23% deaths among males and

3% among females). In a pooled analysis of 9 cohort studies in Japan, cigarette smoking was found to increase risk for AML among the Asian population. For both sexes combined, current smokers had a marginally significant increased risk of AML compared to never smokers (HR = 1.44; 95% CI = 0.97, 2.14). Ever smokers with more than 30 pack-years had a statistically significant increased risk of AML compared with never smokers among both sexes combined (HR = 1.66; 95% CI = 1.06, 2.63).

Radiation exposure: High-dose radiation exposure (eg, nuclear plant accident) increases the chance of developing AML. Therapeutic radiation for cancer treatment has also been reported to increase the risk of developing secondary AML.

Therapy-related or previous haematologic disease-related AML (secondary AML): Approximately 5% of AML cases are therapy related. Alkylating agents (cyclophosphamide and mechlorethamine), platinum agents (cisplatin and carboplatin), and topoisomerase II inhibitors (etoposide or doxorubicin) have been linked to increased risk of AML developing following treatment of a primary malignancy. Latency varies with AML therapy, developing as early as 2 years after treatment with topoisomerase II inhibitors and up to 5 to 8 years after therapy with alkylating agents. There is a female predominance of therapy-related AML, primarily because of chemotherapy for female cancers. The proportion of secondary AML due to cytotoxic therapy and secondary myelodysplasia increases with age.

Patient-related Risk Factors

Age: Leukaemia occurs mostly in adults, and the risk of AML diagnosis increases with age, with the highest rates occurring among those ≥65 years of age. The progression of myelodysplastic syndromes (MDS) to AML in older people might explain the increased incidence of AML and poor survival among the elderly, as AML in this age group shares characteristic risk factors for MDS in terms of abnormal cytogenetics, Fanconi anaemia, or alkylating agent therapy.

Sex and race/ethnicity: The incidence of AML differs by sex and ethnicity. Slight male predominance can be found for AML in adults for most countries, including the US and Europe. Similarly, White subjects seem to have higher rates of AML when compared with other races.

Blood disorders/MDS: Blood disorders such as myeloproliferative disorders (eg, polycythaemia vera) or essential thrombocythaemia and idiopathic myelofibrosis have increased risk of AML. People with MDS may also develop AML. In a retrospective analysis of the SEER database, Ye et al found that the rate of secondary AML from MDS was 3.7% among patients ≤40 years and 2.5% among those >40 years old ($P = 0.039$).

Genetic disorders: Children with Down syndrome have a 10- to 20-fold increased likelihood of developing acute leukaemia. Other inherited diseases associated with AML include Klinefelter syndrome, Li-Fraumeni syndrome, Fanconi anaemia, Patau syndrome, Ataxia telangiectasia, Shwachman syndrome, Kostman syndrome, and neurofibromatosis.

Genes: There are several genes and associated genetic syndromes that predisposes the carrier to developing AML. Recently identified genes include *CEBPA*, *RUNX1*, *GATA2*, *ETV6*, *DDX41*, *ANKRD26*, *SAMD9*, and *SAMD9L*. In some conditions (eg, familial AML with *CEBPA* mutation), AML is the primary manifestation. In other conditions (eg, thrombocytopenia 5), AML occurs secondary to thrombocytopenia. In Emberger and MIRAGE syndrome, MDS occurs prior to AML.

Risk stratification: A number of genetic factors that predict the EFS and overall survival (OS) in AML have been identified (Table Part II: Module SI.4). These genetic factors are important prognostic factors for AML as treatment is often dictated by the risk categories that genetic factors fall under.

Table Part II: Module SI.4: 2017 European LeukemiaNet Risk Stratification by Genetics

Risk Category[a]	Genetic Abnormality
Favourable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low b] Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD[high b] Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low b] (without adverse risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[c] Cytogenetic abnormalities not classified as favourable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11)(q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); *GATA2*,*MECOM*(*EVI1*) -5 or del(5q); -7; -17/abn(17p) Complex karyotype,[d] monosomal karyotype[e] Wild-type *NPM1* and *FLT3*-ITD[high b] Mutated *RUNX1*[f] Mutated *ASXL1*[f] Mutated *TP53*[g]

AML = acute myeloid leukaemia; *ASXL1* = additional sex comblike 1; DNA = deoxyribonucleic acid; *FLT3*-ITD = Feline McDonough sarcoma-like tyrosine kinase 3-internal tandem duplication; HCT = haematopoietic cell transplantation; *NPM1* = nucleophosmin member 1; *RUNX1* = runt-related transcription factor 1; WHO = World Health Organisation

[a] The prognostic impact of a marker is treatment dependent and may change with new therapies.

[b] Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as the ratio of the area under the curve "*FLT3*-ITD" divided by the area under the curve "*FLT3*-wild type." Recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favourable prognosis and patients should not routinely be assigned to allogeneic HCT.

[c] The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse risk gene mutations.

[d] Three or more unrelated chromosome abnormalities in the absence of one of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3), or t(3;3); AML with *BCR-ABL1*.

[e] Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).

[f] These markers should not be used as an adverse prognostic marker if they co-occur with favourable-risk AML subtypes.

[g] *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

Source: Döhner et al, Table 5

A number of risk factors have been established to predict the development of R/R disease as well as EFS and OS in AML patients. These include patient-related factors such as age, performance status, general health, specific comorbidities that modulate the effect of age on tolerance of chemotherapy, and AML-related factors (white cell count, prior MDS or cytotoxic therapy for another disorder, and leukaemic cell genetic changes including alterations in *FLT3*) that predict resistance to current standard therapy.

- Age: Older age seems to act as an adverse prognostic marker even in younger AML patients. A population-based retrospective study from the UK including 11,303 subjects with AML diagnosed from 2001 to 2006 reported an estimated 5-year OS rate of 15%, which varied according to the age at diagnosis; OS (%) by age group (years): 15 to 24: 53%; 25 to 39: 49%; 40 to 59: 33%; 60 to 69: 13%; 70 to 79: 3%; >80 years: 0%.
- Intensity of conditioning regimen: Many AML patients are not considered candidates for conventional myeloablative conditioning procedures before transplant because of advanced age, previous therapies, or comorbidities. Reduced intensity conditioning (RIC) was adopted to reduce early nonrelapse mortality in AML patients. However, this is associated with a higher rate of relapse. A retrospective study by the European Group for Blood and Marrow Transplantation found that the cumulative incidence of relapse was 23% for subjects receiving myeloablative conditioning versus 39% for subjects receiving RIC during 7-year follow-up.
- *FLT3*-ITD mutation status: Among disease-specific risk factors, the presence of *FLT3*-ITD has been proposed as one of the most important prognostic factors in AML for the duration of CR and relapse-free survival. A retrospective cohort study involving 171 subjects with AML who underwent *FLT3*-ITD mutation testing reported that *FLT3*-mutated AML was associated with nearly twice the risk of relapse compared with those without *FLT3* mutation 3 years after HSCT (63% vs. 37%, respectively). Consistent with the role of *FLT3*-ITD as a driver mutation, outcomes for these patients seem to be correlated with the *FLT3*-ITD allelic burden, expressed as *FLT3* mutant to wild-type ratio or as the percentage of total alleles. Accordingly, a high allelic burden is the best predictor of FLT3 inhibition (and, correspondingly, prognosis after FLT3 targeted therapy), and a low allelic burden has a similar prognosis to *FLT3* wild type. *FLT3*-ITD presents with high leukaemic burden (ie, leukocytosis, with high infiltration of the bone marrow), has poor prognosis, and has a significant negative impact on the management of patients with AML. Of the AML patients with *FLT3*-ITD mutations, only approximately 26% are expected to be alive after 5 years, and their condition is 3 times more likely to relapse within 2 years after transplant. Among molecular abnormalities, *FLT3* mutations are the most common. They are well characterised and were the first, and they are still one of the very few “actionable” mutations in AML.
- Minimal residual disease: Patients in morphological remission may have varying, sometimes high, levels of minimal residual disease (MRD). Several studies in subjects undergoing myeloablative and nonmyeloablative conditioning show that the presence of MRD has a negative impact on post-transplant relapse risk.

- Hyperleukocytosis: Up to 20% of AML patients present initially with hyperleukocytosis. In a registry-based retrospective study in the EU, hyperleukocytosis was independently associated with increased relapse incidence.

Main Existing Treatment Options

Treatment for ND AML

Treatment for AML in general is split into 3 phases: induction, consolidation, and maintenance. The goal of treatment is to achieve CR or complete response. CR is achieved if there is no sign of leukaemia after treatment, blood counts are back to normal levels, and the patient has <5% myeloblasts (blasts) in the bone marrow. CR is defined on the basis of the methodology used for assessment (eg, morphologic, cytogenetic, and molecular). There are a few treatment categories that may be utilised either alone or in conjunction when treating AML. Chemotherapy, targeted therapy, clinical studies, and stem cell transplant are the core treatment options for AML. Treatment schemes are divided into 2 groups: for patients <60 years old and for patients ≥60 years old.

Induction: Induction is the first treatment phase. The goal is to achieve CR by reducing the number of myeloblasts in the bone marrow. Induction treatment is selected on the basis of several factors, including age and cytogenetic risk. Patients may undergo more than 1 round of induction based on response. If patients achieve CR, then they can move onto consolidation treatment. If the initial induction therapy and reinduction fail, then the AML is considered refractory. Induction treatment schemes for patients <60 years are described in the National Comprehension Cancer Network (NCCN) AML Guidelines, Version 3.2020.

Induction treatment for patients ≥60 years old follows the same principles as those for patients <60 years, but additional factors need to be considered. Factors such as age, performance status, functional status, and comorbid conditions are considered when evaluating a patient for intensive induction chemotherapy. Induction treatment schemes for patients ≥60 years are described in NCCN AML Guidelines, Version 3.2020. For patients ≥75 years old with ND AML who are candidates for nonintensive therapy, glasdegib with low-dose cytarabine (LDAC) is an induction option. The other would be ventetoclax alone or with azacitidine, decitabine, or LDAC.

Consolidation: Consolidation is the second treatment phase with the goal to prevent the cancer from returning by killing any cancer cells left in the body after induction. Only a patient who achieves CR during induction/reinduction therapy will continue to consolidation. Consolidation therapy is selected on the basis of age, cytogenetics, and molecular test results. Consolidation treatment schemes are detailed in NCCN AML Guidelines, Version 3.2020.

Maintenance: Maintenance therapy is to prevent AML from relapsing. Not all AML patients will receive maintenance therapy as it is highly dependent on the type of disease, consolidation, and risk of relapse. Treatment may include drugs, vaccines, or antibodies that kill cancer cells and may be given over months/years.

The NCCN guideline provides a list of several commonly used regimens for AML that are grouped according to age, intensity, or specific mutation.

Induction treatment strategies for AML patients <60 years:

- Standard-dose cytarabine with idarubicin or daunorubicin/cladribine

- HiDAC with idarubicin or daunorubicin
- Fludarabine with HiDAC, idarubicin, and G-CSF

Intensive induction treatment strategies for AML patients ≥60 years:

- Cluster of Differentiation 33 (CD33)-positive AML: Standard-dose cytarabine with daunorubicin and gemtuzumab
- Standard-dose cytarabine with 1 of the following: idarubicin, daunorubicin, or mitoxantrone
- *FLT3*-mutated (ITD or TKD) AML: Standard-dose cytarabine with daunorubicin and midostaurin
- Venetoclax with 1 of the following: decitabine, azacitidine, or LDAC
- Low-intensity therapy of azacitidine or decitabine

Low- and nonintensive induction treatment strategies for AML patients ≥60 years:

- Venetoclax with 1 of the following: decitabine, azacitidine, or LDAC
- Glasdegib and LDAC
- Gemtuzumab for CD33-positive
- Best supportive care
- AML with *IDH1* mutation: ivosidenib
- AML with *IDH2* mutation: enasidenib
- AML with *FLT3* mutation: Low-intensity therapy (of azacitidine or decitabine) with sorafenib or venetoclax-based therapy in combination with (azacitidine, decitabine, or LDAC)

Consolidation postremission treatment strategies for AML patients <60 years:

- HiDAC with or without gemtuzumab
- Matched sibling or other donor haematopoietic cell transplantation (HCT)
- HiDAC with oral midostaurin for *FLT3*-mutated AML

Consolidation postremission treatment strategies and other options for AML patients ≥60 years:

- Allogeneic HCT
- Cytarabine options
- Maintenance therapy with hypomethylating regimens (of azacitidine or decitabine) every 4 to 6 weeks until progression
- Observation

According to the European Society for Medical Oncology (ESMO) Clinical Practice guideline for the treatment of AML, based on eligibility criteria and patient preference, all ND AML patients must be assigned to either standard induction and consolidation chemotherapy or

nonintensive treatment. Patients should be encouraged to participate in clinical studies whenever possible.

The recommended treatment regimens for patients with ND AML include the following:

- Adult patients eligible for standard chemotherapy:
  - 1 to 2 cycles of induction with
    - "7 + 3" with or without gemtuzumab ozogamicin
    - "7 + 3" with midostaurin for *FLT3*-mutated disease
    - Liposomal daunorubicin and cytarabine
    - "7 + 3" with cladribine or fludarabine
  - 1 to 2 cycles of consolidation and/or HSCT
    - Intermediate-dose cytarabine with or without gemtuzumab ozogamicin
    - Liposomal daunorubicin and cytarabine
    - Intermediate-dose cytarabine with midostaurin for *FLT3*-mutated disease
  - Maintenance with midostaurin for *FLT3*-mutated disease
- Adult patients not eligible for standard chemotherapy:
  - 4 cycles of induction
    - Hypomethylating agents + venetoclax; LDAC, 6-mercaptopurine, melphalan, or hydroxycarbamide
    - Hypomethylating agents or LDAC with or without venetoclax
  - Consolidation: Continue induction and re-evaluate eligibility for transplant

Treatment for R/R AML

According to the ESMO guideline, the prognosis of primary R/R AML patients remains poor, and treatment is challenging. A primary consideration in the therapeutic approach of R/R AML patients should be their suitability for intensive chemotherapy and allogeneic HCT. Mutation analysis for *FLT3* should be repeated in relapsed patients.

The recommended treatment regimens for patients with R/R AML include the following:

- Enrolment in a clinical study
- Primary refractory patients fit for chemotherapy: first or second allogeneic HSCT, or donor lymphocyte infusion
- Patients with relapse, fit for chemotherapy: cytarabine/anthracycline reinduction, followed by first or second allogeneic HSCT or by donor lymphocyte infusion
- All other patients:
  - Hypomethylating agents or LDAC with or without venetoclax
  - Gilteritinib for FLT-mutated AML

- Melphalan
- Best supportive care

According to the NCCN AML Guidelines, Version 3.2020, it is strongly preferred for patients <60 years and patients ≥60 years old who are physically fit and whose cancers have relapsed to be enrolled in clinical studies. The guidelines also provide a list of several commonly used regimens for R/R disease that are grouped as aggressive, less aggressive, or mutation specific. The therapy options are listed in the NCCN AML Guidelines, Version 3.2020.

- Clinical study is strongly preferred
- AML with *FLT3*-ITD mutation: Gilteritinib or hypomethylating agents with sorafenib
- Ivosidenib/enasidenib for *IDH1/2* mutation
- Gemtuzumab for CD33-positive AML
- Aggressive chemotherapy for appropriate patients

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

AML is an aggressive cancer that rapidly progresses. In some cases, AML can spread to other organs, including the brain, spinal cord, liver, and spleen. If untreated, AML is uniformly and rapidly fatal because of infectious and/or haemorrhagic complications associated with severe neutropenia and thrombocytopenia; survival is counted in days and weeks. The prognosis of a person diagnosed with AML is dependent on genetic prognostic factors, age, and overall fitness. Treatment selection is also determined by those prognostic factors. With supportive care, it is possible for patients to survive for a period of time (median survival: 11 to 20 weeks).[1] However, patients ultimately die of complications associated with bone marrow failure, such as infection and haemorrhage. If treated, survival can be extended, and remission is possible; despite treatment, long-term prognosis is generally unfavourable, especially in the elderly and R/R populations. Survival estimates in AML patients are presented below.

Europe: In EU28, 5-year relative survival among patients with AML was estimated to be 15 to 17.5% (2000 to 2007 data). The EU average survival rates were similar among males and females at 14.8% and 18.3%, respectively. Sex-specific 5-year relative survival (in percentages) varies by country: 8.5% in Malta to 20.2% in Belgium for males and 7.4% in Estonia to 23.1% in Belgium for females. Survival rates of AML patients differ by age and sex, with females having slightly better survival rates, but that difference fades as age increases. At age 75+ years, survival rates are similarly poor between males and females. Age-specific 5-year relative survival (in percentage) among AML patients in Europe is presented in Table Part II: Module SI.5. The mortality rate of AML in Europe was estimated to be between 4 and 6 per 100,000 in 2013. Estimates from more recent studies suggest that the mortality rate may be lower.

Table Part II: Module SI.5: Age-specific 5-year Relative Survival Among Acute Myeloid Leukaemia Patients in Europe

Sex	Age Groups (years)				
	15-44	45-54	55-64	65-74	75+
Male	46.9%	34.4%	21.7%	7.5%	3.7%
Female	52.0%	38.5%	25.6%	9.8%	3.8%

ECIS = European Cancer Information System
Source: ECIS

United Kingdom: There are no UK-wide statistics available for AML survival. Based on 2000 to 2007 data, the 5-year relative survival for male AML patients in England, Wales, and Scotland are 14%, 12%, and 13%, respectively. For females, the 5-year relative survival (in percentage) in England and Scotland are 16% and 18%, respectively. Based on 2008 to 2010 data from England, the estimated 5-year survival was approximately 20%. Consistent with findings from other countries, survival among younger patients was much higher than that in the elderly population; 5-year relative survival for age groups (years) was 65% for patients aged <15 years, 60% for patients aged 15 to 24 years, 40% for patients aged 35 to 64 years, and 5% for patients aged >65 years. The annual mortality rate of AML in the UK was estimated to 4.3 cases per 100,000 in 2017. The rates differ slightly by sex and by region.

United States: The 5-year relative survival (in percentage) for all patients with AML in the US is 28.7% (2010 to 2016 data). Survival rates differ by age, sex, and race/ethnicity, with female patients and White patients having slightly better survival rates at a younger age. However, these differences become less pronounced with increasing age, and at age ≥75 years, survival rates are similarly poor across the board. Overall, the 5-year relative survival for AML has been increasing, from 6.2% in 1975 to 28.7% in 2016.

SEER estimates 11,180 deaths among AML patients in 2020 in the US. The overall age-adjusted AML mortality rate was 2.8 per 100,000 per year based on 2014 to 2018 data. The median age at death was 73 years, with most deaths occurring among those ≥65 years old. Sex- and race/ethnicity-specific age-adjusted AML mortality rates in the US are described in Table Part II: Module SI.6.

Table Part II: Module SI.6: Age-adjusted Mortality Rate per 100,000 Persons by Race/Ethnicity and Sex in Acute Myeloid Leukaemia in the United States (2014 to 2018)

Sex	All Races	White	Black	Asian/Pacific Islander	American Indian/Alaska Native	Hispanic	Non-Hispanic
Male	3.6	3.7	2.7	2.6	2.2	2.4	3.7
Female	2.2	2.2	1.9	1.5	1.3	1.6	2.2

SEER = Surveillance, Epidemiology, and End Results
Source: SEER

Although incidence rates and death rates have remained somewhat stable in the last few decades, there has been a significant increase in 5-year relative survival. However, this increase in 5-year

relative survival can be attributed to better survival of younger AML patients because the survival among those ≥75 years of age has not increased (Table Part II: Module SI.7).

Table Part II: Module SI.7: Five-year Relative Survival for Patients With Acute Myeloid Leukaemia by Age Group, Sex, and Race in the United States (2010 to 2016 SEER 18 Program Data)

Sex and Race		Age Groups (years)					
		Overall	**<45**	**45-54**	**55-64**	**65-74**	**75+**
All Sexes	All Races	28.7%	61.5%	45.3%	30.4%	14.8%	3.2%
	Caucasian	28.3%	63.2%	46.6%	31.5%	15.5%	3.2%
	African American	28.6%	53.8%	36.4%	19.1%	9.5%	2.6%
Male	All Races	27.7%	60.4%	44.4%	28.1%	14.5%	3.8%
	Caucasian	27.2%	61.8%	45.5%	28.5%	15.5%	3.8%
	African American	27.7%	51.1%	35.8%	21.2%	4.5%	5.5%
Female	All Races	29.9%	62.7%	46.4%	33.5%	15.3%	2.4%
	Caucasian	29.6%	64.6%	47.9%	35.6%	15.5%	2.5%
	African American	29.5%	56.1%	37.2%	16.2%	14.1%	0.9%

Sex and Race		**<50 years**	**50-64 years**	**65+ years**
All Sexes	American Indian/Alaska Native	59.8%	-	-
All Sexes	Hispanic (any race)	61.7%	32.7%	6.5%
All Sexes	Asian/Pacific Islander	54.2%	35.1%	6.8%

SEER = Surveillance, Epidemiology, and End Results
Source: SEER*Stat

Adverse Events Anticipated to Occur in the Targeted Population

Adverse events (AEs) that occur frequently in AML patients are described below. These include AEs associated with the disease or with AML therapies. These events are expected to occur in the proposed patient population independent of the effect of quizartinib and are included here as a reference for the assessment of the safety profile of quizartinib.

Cytopenia: Most patients with AML will present with anaemia of varying severity simply because of the nature of the disease. Patients may also present with thrombocytopenia, neutropenia, or even pancytopenia. In patients with MDS, which has a high risk of transforming into AML, the prevalence of thrombocytopenia (platelets $<100 \times 10^9$/L) is estimated to range from 40% to 65%. For those patients who undergo induction chemotherapy, their anaemia and

other cytopenias will worsen, which may lead to further complications. Chemotherapy used for the treatment of AML is highly toxic to developing cells and thus worsens the myelosuppression already occurring in AML. Majority of AML patients suffer from prolonged Grade 4 neutropenia (according to the Common Terminology Criteria for Adverse Events [CTCAE]) during induction and intensive consolidation chemotherapy. Failure to achieve neutrophil and platelet regrowth following chemotherapy has been reported in up to 26% of subjects with R/R AML receiving FLAG-Ida.

Infection: AML patients have an increased risk of developing infections because of the myelosuppression occurring at baseline. If patients undergo induction chemotherapy or consolidation therapy, then that risk increases because of the myelosuppression that accompanies most chemotherapeutic agents. Those who receive stem cell transplantation (SCT) are at high risk of developing infections due to the significant depth and duration of neutropenia that occurs in SCT recipients. Risk factors for increased susceptibility to infections in AML patients are profound neutropenia, impaired immunity, haemorrhage, and multiple skin-penetrating catheters. In a study by the Polish Adult Leukemia Group, 91% of subjects with AML had infection after induction chemotherapy, and 43% had a major infection. Invasive fungal infection (IFI) is also very common in AML patients. Along with other haematologic malignancies, 2% to 49% of AML patients suffer from IFI. In an Italian study of subjects with R/R AML, infections occurred in 44% of subjects treated with fludarabine, cytarabine, and G-CSF.

Neutropenic fevers are exceedingly common among HSCT recipients and AML patients. The incidence of neutropenic fever ranges between 50% and 90%, depending on the phase of the disease and the intensity of chemotherapy. A common cause of neutropenic fevers is mucositis, a side effect of several chemotherapeutic agents. Mucositis can be present along the entire gastrointestinal (GI) tract, and with mucosal barrier injury, bacterial organisms present in the GI tract can translocate into the systemic system, leading to neutropenic fever.

Bleeding: Patients with AML have thrombocytopenia as a result of underlying disease, as well as cytotoxic therapy. Thrombocytopenia can cause haemorrhages in AML patients. Haemorrhage can also occur in AML patients with a normal platelet count due to vascular defects, fibrinolysis, and platelet function abnormalities. Approximately 20% to 32% of thrombocytopenic AML patients as well as 34% to 58% of AML patients undergoing alloSCT demonstrate clinically significant bleeding. Platelet transfusion reduces the risk of bleeding in patients with AML undergoing induction therapy or SCT; however, in 1 study, 11% of patients with AML undergoing induction chemotherapy had a fatal haemorrhage even after they received platelet transfusion. Aside from thrombocytopenia and associated haemorrhages, AML patients can have coagulative disorders. Leukemic cells can cause an inappropriate release of procoagulants directly into the bloodstream, initiating the clotting cascade and causing simultaneous clot formation and haemorrhage leading to disseminated intravascular coagulation (DIC). Rapid DIC causes bleeding into the organs, as well as microvascular thromboses, which in turn cause dysfunction and failure of multiple organs.

Hyperleukocytosis and leukostasis: AML patients have elevated counts of leukaemic cells. The elevation of leukaemic cells is called hyperleukocytosis. Leukostasis, or symptomatic hyperleukocytosis, is characterised by extreme elevations of leukaemic cells, causing white cell plugs in the microvasculature. This can lead to respiratory failure and intraparenchymal brain

haemorrhages. The frequency of hyperleukocytosis ranges from 5% to 13% in adult AML patients.

Tumour lysis syndrome (TLS): Clinical TLS occurs in AML patients spontaneously or as a result of induction chemotherapy. TLS is characterised by hyperphosphatemia, hyperkalaemia, hyperuricemia, hypocalcaemia, and renal insufficiency. Approximately 5% of AML patients develop clinical TLS after induction chemotherapy. TLS was the major cause of death in 2% of AML patients who underwent induction therapy mainly due to renal failure. In a Spanish study of 772 adult subjects with AML receiving induction chemotherapy between 1980 and 2002, 17% developed TLS (5% clinical TLS and 12% laboratory TLS).

Acute febrile neutrophilic dermatosis: Acute febrile neutrophilic dermatosis, also known as Sweet's syndrome, is characterised by fever, multiple tender skin rashes, and neutrophilic infiltrate in the skin. Sweet's syndrome may occur in association with a malignancy in approximately 15% to 20% of cases. In a study of subjects with AML diagnosed, treated, and followed up at the MD Anderson Cancer Center between 2000 and 2011, Sweet's syndrome developed in 1% of subjects with AML. *FLT3* mutations were common in AML patients with Sweet's syndrome. Treatment with FLT3 inhibitors may induce terminal differentiation of myeloid blasts to mature neutrophils and may contribute to Sweet's syndrome-like clinical entity in AML patients.

Electrolyte abnormalities: Hypokalaemia is very common in AML patients, with an estimated incidence of 43% to 64%. The main etiological factor for hypokalaemia is increased serum lysozyme level in AML patients, which induces renal tubular injury and eventual kaliuresis. Other etiological factors of hypokalaemia in patients with AML include lysozyme independent tubular dysfunction, hypomagnesemia, potassium entry into cells, and antibiotic therapy. AML is also reported to be associated with hypomagnesemia (32%), hypophosphatemia (35%), hyponatremia (9%), and hypocalcaemia (52%). In addition, GI side effects of cytarabine chemotherapy comprise oral and anal inflammation or ulceration, anorexia, nausea, vomiting, and diarrhoea, which can contribute to electrolyte abnormalities via GI tract loss.

Extramedullary involvement: AML may be associated with extramedullary infiltrates (EMI) of blast cells, which include myeloid sarcoma, leukaemia cutis, meningeal and gingival infiltrates, and hepatosplenomegaly. EMI have been reported in 2% to 9% of ND AML patients. This is considered to be an underestimate, because at diagnosis, AML patients are not routinely checked for EMI. In childhood AML, EMI at diagnosis is reported in 7% to 49% of patients. The overall frequency of EMI in AML patients is reported to be 20% to 40%. The most common locations for EMI include soft tissue, bones, central nervous system (CNS), and lymph nodes. Specific cutaneous infiltrates or leukaemia cutis are reported in 3% of AML patients. CNS involvement is seen in up to 5% of AML patients. CNS involvement was found in 1% of AML patients with *FLT3*-ITD mutation at initial diagnosis. Younger AML patients have a higher proportion of CNS involvement. Myeloid sarcoma can be found in 2% to 8% of AML patients.

Acute pulmonary failure: Acute pulmonary failure (APF) is a serious complication of induction chemotherapy in AML patients. It may result from pulmonary haemorrhage, capillary leak as a result of tumour lysis and/or fluid overload, infections, or sepsis. In a retrospective study, 8% of AML/MDS patients developed APF as a complication of induction therapy. Elevated creatinine or bilirubin, poor performance status, and lung infiltrates at diagnosis were identified as adverse

prognostic factors for APF in these patients. In a study conducted by Al Ameri et al among 1541 subjects referred for remission induction chemotherapy for AML or high-risk myelodysplasia, 8% developed APF requiring ventilatory support within 2 weeks of the initiation of chemotherapy. The mortality rate during induction therapy for these subjects was 73%.

Pericardial effusion: Pericardial effusion (PEf) occurs in up to 21% of AML patients. Most of these PEfs are small in size and have no apparent effect on patient survival. Three-fourths of these PEfs are therapy related.

Neutropenic enterocolitis: An estimated 4.3% of AML patients undergoing induction therapy develop neutropenic enterocolitis.

Venous thromboembolism: In the first 3 months of treatment, AML patients have an increased risk of developing venous thromboembolism (VTE). Approximately 2.5% of patients without M3-AML present with VTE at baseline. Ku et al found that among 5394 cases of AML, the 2-year cumulative incidence of VTE was 5.2%; 64% of the VTE events occurred within 3 months of AML diagnosis.

Complications related to HSCT: AML patients undergoing HSCT must contend with a host of complications that follow HSCT. Pulmonary complications, occurring in 30% to 60% of recipients, are the most common life-threatening conditions that develop following HSCT. In addition, patients can develop graft-versus-host disease (GVHD). In allotransplantation, the 100-day mortality rate is 10% to 40%, and the main causes of death are GVHD, interstitial pneumonitis, and multiple organ failure. In a retrospective, observational study of subjects with leukaemia (acute lymphocytic leukaemia [ALL], AML, or chronic myeloid leukaemia [CML]) following allo-HSCT or auto-HSCT between 1980 and 2015, mortality from GVHD was reported to be 15.9% of all leukaemia patients and more specifically 19.0% of patients who received allo-HSCT. After allo-HSCT, mortality from GVHD decreased in the very early (30-day time period, 0.20 [0.17 to 0.24]), early (100-day time period, 2.49 [2.37 to 2.61]), and intermediate phases (1-year time period, 4.28 [4.10 to 4.46]), but increased in the late phase (5-year time period, 3.85 [3.62 to 4.08]). In 646 subjects with leukaemia (AML, ALL, MDS, or CML) who underwent haplo-HSCT, Grade 2 to Grade 4 acute GVHD at 6 months post-transplant was reported by 46% (95% CI, 39% to 54%) of subjects receiving myeloablative conditioning/peripheral blood (MAC-PB) transplant, and by 36% (95% CI, 29% to 43%) of subjects receiving reduced intensity conditioning/peripheral blood (RIC-PB). A similar pattern was observed for chronic GVHD, where the incidence at 1 year was highest in MAC-PB at 40% (95% CI: 32%, 47%), followed by RIC-PB at 34% (95% CI: 27%, 41%).

Important Comorbidities

With age, there are marked physiologic declines in most bodily systems: cardiovascular, GI, pulmonary, and renal. Hence, comorbidities occur more frequently among older adults and with greater severity. In a nationwide cohort study of subjects with AML aged ≥15 years (n = 3055) during 2000 to 2013 in Denmark, 42% of subjects with AML had at least 1 comorbidity listed in the Charlson Comorbidity Index (CCI); 32% had ≥2 comorbidities. Similarly, in a nationally representative (95% coverage) cancer registry in Sweden including adult AML patients (n = 2550) during 2002 to 2009, 44% of patients had at least 1 comorbid condition prior to AML diagnosis. Additionally, in a large cohort study conducted by using the National Cancer Database

(in the US and Puerto Rico) during 2004 to 2014, 50,688 subjects with AML ≥60 years old were assessed for comorbidities: 24% had a CCI of 1, and 11% had a CCI ≥2. The 1-month mortality rate for patients in the study was 13%, 19%, and 26% for patients with CCI of 0, 1, and ≥2, respectively ($P < 0.001$). The likelihood of poor survival and adverse outcomes increased as the number of comorbidities increased.' In addition, patients with elevated CCI scores are less likely to receive chemotherapy, whether single or multiagent. The important comorbidities listed below are expected to occur in the proposed patient population independently of the effect of quizartinib and are included here as a reference for the assessment of the safety profile of quizartinib.

Cardiovascular disease: The reported baseline prevalence of cardiovascular disease among adult subjects with AML ranges from 8.7% to 14% in large observational studies conducted in the US and Sweden. Major et al characterised the incidence of new cardiovascular comorbidities in adults >18 years old with AML who achieved and maintained CR for at least 3 years after the initial therapy. The incidence of cardiovascular disease 3 years after the initial therapy was 34 of 453 (7.5%). In addition, Dhopeshwarkar et al found that the incidence rate of new-onset ischaemic heart disease/coronary artery disease was 20.8 vs. 6.2 per 100 person-years (PY) in overall AML vs. noncancer controls ($P < 0.01$).

Peripheral vascular disease: The reported baseline prevalence of peripheral vascular disease among subjects with AML (≥15 to ≥65 years old) ranges from 3% to 19.4% in large observational studies conducted in the US, Denmark, and Sweden.

Congestive heart failure: The reported baseline prevalence of congestive heart failure among subjects with AML (≥15 to ≥65 years old) ranges from 2% to 21.5% in large observational studies conducted in the US and Denmark. Dhopeshwarkar et al found that the incidence rate of new-onset heart failure was 31.8 vs. 4.7 per 100 PY in overall AML vs. noncancer controls ($P < 0.01$).

Cerebrovascular disease: The reported baseline prevalence of cerebrovascular disease among subjects with AML (≥15 to ≥65 years old) ranges from 7% to 18.2% in large observational studies conducted in the US, Denmark, and Sweden. An unweighted analysis of the 2012 US National Inpatient Sample, a representative sample of all US hospitalisations, found a total of 10,984 admissions with active AML (9384 admissions for AML yet to achieve remission and 1600 for relapsed AML). Concomitant stroke, either ischaemic or haemorrhagic, was found among 0.59% of the patients with active AML. There was a 50-fold increase in the risk of stroke in active AML patients compared with all admissions. Dhopeshwarkar et al found that the incidence rate of stroke (ischaemic, haemorrhagic, or transient ischaemic attack) was 17.0 vs. 5.7 per 100 PY in overall AML vs. noncancer controls ($P < 0.01$).

Myocardial infarction: The reported baseline prevalence of myocardial infarction among subjects with AML (≥15 to ≥65 years old) ranges from 4% to 10.5% in large observational studies conducted in the US and Denmark. Dhopeshwarkar et al found that the incidence rate of myocardial infarction was 9.4 vs. 2.1 per 100 PY in overall AML vs. noncancer controls ($P < 0.01$).

Hypertension: The reported baseline prevalence of hypertension among subjects with AML (all ages) ranges from 8.7% to 35% in large observational studies conducted in the US and Brazil. Major et al characterised the incidence of new-onset hypertension in adults >18 years old with

AML who achieved and maintained CR for at least 3 years after the initial therapy. The incidence of hypertension 3 years after initial therapy was 15%.

Dyslipidaemia: The reported baseline prevalence of dyslipidaemia among subjects with AML (>18 years old) ranges from 8.7% to 35% in large observational studies conducted in the US. Major et al characterised the incidence of new-onset dyslipidaemia in adults >18 years old with AML who achieved and maintained CR for at least 3 years after initial therapy. The incidence of dyslipidaemia 3 years after initial therapy was 9%.

Diabetes: The reported baseline prevalence of diabetes among subjects with AML (all ages) ranges from 4.2% to 41.3% in large observational studies conducted in the US, Denmark, Sweden, and Brazil. Major et al characterised the incidence of new-onset diabetes in adults >18 years old with AML who achieved and maintained CR for at least 3 years after initial therapy. The incidence of diabetes 3 years after initial therapy was 6%.

Obesity: The reported baseline prevalence of obesity among subjects with AML (>18 years old) ranges from 11% to 38% in large observational studies conducted in the US. In a hospital-based retrospective study, obesity was found to confer worse prognosis in overweight compared with normal-weight AML subjects (HR = 0.6; 95% CI = 0.4, 0.9; $P = 0.03$). There was also a statistically significant difference in the obese group in having coronary artery disease and hypertension as comorbid conditions compared with the overweight and normal weight groups (coronary artery disease: 13.2% vs. 8.5% vs. 3.4%, $P = 0.04$; hypertension: 51.2% vs. 31.1% vs. 17.2%, $P < 0.0001$).

Pulmonary disease: The reported baseline prevalence of pulmonary disease among subjects with AML (≥15 to ≥65 years old) ranges from 5.8% to 28.2% in large observational studies conducted in the US, Denmark, and Sweden. Major et al characterised the incidence of new-onset pulmonary disease in adults >18 years old with AML who achieved and maintained CR for at least 3 years after initial therapy. The incidence of pulmonary disease 3 years after initial therapy was 11%.

Renal disease: The reported baseline prevalence of renal disease among subjects with AML (≥15 to ≥65 years old) ranges from 0.9% to 10.7% in large observational studies conducted in the US, Denmark, and Sweden. Major et al characterised the incidence of new-onset renal disease in adults >18 years old with AML who achieved and maintained CR for at least 3 years after initial therapy. The incidence of renal disease 3 years after initial therapy was 14%. In addition, Dhopeshwarkar et al found that the incidence rate of renal failure (acute/chronic) was 28.7 vs. 4.8 per 100 PY in overall AML vs. noncancer controls ($P < 0.01$).

Malignancies: The reported baseline prevalence of malignancies among subjects with AML (>18 years old) ranges from 14% to 15% in large observational studies conducted in the US and Sweden. Major et al characterised the incidence of new comorbid malignancies in adults >18 years old with AML who achieved and maintained CR for at least 3 years after initial therapy. The incidence of new malignancies 3 years after initial therapy was 12%. In addition, Dhopeshwarkar et al found that the incidence rate of neoplasms was 61.3 vs. 4.4 per 100 PY in overall AML vs. noncancer controls ($P < 0.01$).

Comorbidities in R/R AML: In a retrospective cohort study including subjects with AML (N = 3911) ≥65 years old using the SEER-Medicare database, a subset of the AML population

was identified as R/R AML (N = 1881). Subjects with R/R AML were younger, had lower National Cancer Institute comorbidity scores, lower incidence of events of interest, and a longer follow-up time compared with non-R/R AML subjects. Specific comorbidities and their baseline prevalence in the R/R AML population are listed in Table Part II: Module SI.8.

Table Part II: Module SI.8: Prevalence of Comorbid Conditions in Relapsed/Refractory Acute Myeloid Leukaemia Patients in the United States

Author, Study (sample size)	**Study Type and Population**	**Treatment N = 1881 n (%)**	**Comorbidities**	**Baseline Prevalence N = 1881 n (%)**
Dhopeshwarkar et al, 2019 SEER-Medicare Study (2000 to 2013) (N=1881)	Retrospective cohort study of adults ≥65 years old with first primary diagnosis of AML; R/R AML included	**Chemotherapy** 1842 (97.9%) **BMT** 187 (9.9%) **Stem cell transplantation** 174 (9.3%)	Congestive heart failure	296 (15.7)
			Peripheral vascular disease	284 (15.1)
			Cerebrovascular Disease	292 (15.5)
			Myocardial Infarctions	170 (9.0)
			Diabetes	745 (39.6)
			COPD	446 (23.7)
			Renal Disease	175 (9.3)

AML = acute myeloid leukaemia; BMT = bone marrow transplant; COPD = chronic obstructive pulmonary disease; N = total number of subjects; n = number of subjects in each category; R/R = relapsed/refractory; SEER = Surveillance, Epidemiology, and End Results.

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

The nonclinical safety profile of quizartinib (including its active metabolite, AC886) has been characterised in the drug safety programme using both in vitro and in vivo pharmacological, pharmacokinetic (PK), and toxicological studies in mice, rats, rabbits, guinea pigs, dogs, and monkeys. The toxicity profile of quizartinib has been well characterised in a comprehensive battery of in vitro and in vivo nonclinical studies. Safety concerns identified in the nonclinical studies include corrected QT interval (QTc) prolongation on electrocardiogram (ECG), myelosuppression, lymphoid depletion, drug-drug interaction (DDI) with strong cytochrome P450 (CYP) 3A inhibitors and strong and moderate CYP3A inducers, GI toxicity, and liver function test (LFT) abnormalities. Other potential safety concerns not refuted by clinical data include embryo-foetal and reproductive toxicity.

Information on key safety findings from nonclinical studies and their relevance to human usage is presented in Table Part II: Module SII.1.

Table Part II: Module SII.1: Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Toxicity	
Single- and repeat-dose toxicity: Rats: Single-dose quizartinib at ≥150 mg/kg and repeated doses at ≥60/30 mg/kg for 28 days resulted in adverse clinical signs (including blood in urine, liquid faeces, decreased physical activity, and pale skin) and mortality. No mortality or treatment-related abnormal clinical signs were observed in the 13-week rat study at doses up to 10 mg/kg. Dogs: Single doses of quizartinib up to 200 mg/kg were well tolerated; however, multiple doses of 200/250 mg/kg for 7 days or 150/40 mg/kg for 28 days resulted in either mortality or moribund sacrifice. Clinical signs in moribund dogs included weight loss, decreased food consumption, decreased activity, few or no faeces, and hunched back or lying on cage floor. In the 13-week dog study, the only observation was skin pallor in both sexes at 15 mg/kg. Monkeys: No mortality was observed in the single-dose study at up to 400 mg/kg or in the 5- or 14-day study at 200 mg/kg. In the 13-week study, reduced appetite, decreased activity, severe dehydration, moderate to severe uncoordination, soft and/or liquid faeces, severe emesis, hunched posture, prominent backbone, and partly closed eyes were observed at ≥10/6 mg/kg.	Nonclinical studies demonstrated the potential for GI effects including decreased appetite, emesis, and liquid faeces; similar GI toxicity has been observed in humans. GI toxicity is not considered an important risk for quizartinib (Section Part II: Module SVII).

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Reproductive and developmental toxicity: Reversible testicular seminiferous tubular degeneration and failure of sperm release were evident in rats at 10 mg/kg in the 13-week study. Female rats at 10 mg/kg in the 13-week study had toxicologically significant ovarian cysts and nonreversible vaginal mucosal mucification. In the 13-week monkey study, minimal to severe germ cell depletion in the testes and atrophy of the uterus, ovary, and vagina were noted at ≥10/6 mg/kg. These changes were reversible following a 4-week recovery period. In the 13-week dog study, no toxicological significant findings were noted at up to 15 mg/kg. In the rat embryo-foetal development study, foetotoxicity was evident at 6 mg/kg, primarily consisting of lower foetal weights and effects on skeletal ossification. Teratogenicity was also observed at 6 mg/kg as evidenced by a high incidence of foetal malformations (anasarca).	Reproductive studies in animals indicate reversible and irreversible changes to the reproductive organs of males and females. These changes are relevant to humans. Reproductive toxicity is included as an important potential risk for quizartinib (Section Part II: Module SVII). Embryo-foetal development studies in animals indicate embryo-foetal defects. These changes are relevant to humans. To date, there have been no pregnancies in female patients or partners of male subjects receiving quizartinib to evaluate this risk in human subjects. Embryo-foetal toxicity is included as an important potential risk for quizartinib (Section Part II: Module SVII).
Nephrotoxicity: Dose-dependent kidney changes (renal tubular birefringent crystal deposition, which was reversible, and tubular basophilia) were most prevalent in male rats at ≥10 mg. No abnormal serum chemistry (BUN and creatinine) or urinalysis parameters correlating with renal microscopic changes were noted, suggesting that renal function was not compromised. In dogs, renal tubular basophilia was evident at ≥1 mg/kg without any serum chemistry correlates. In addition, nonbirefringent renal tubular pigment was evident in male dogs at 15 mg/kg in the 13-week study. In monkeys, slight increases in urea and creatinine were observed, but renal tubular basophilia was not observed at up to 30/12 mg/kg.	Toxicity studies in animals indicate reversible dose-dependent kidney changes with no compromise of renal function. Quizartinib is eliminated through the liver with little renal elimination (<2%). Subjects with mild or moderately impaired renal function were eligible for treatment in the clinical development programme. No safety concern of nephrotoxicity has been identified.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Hepatotoxicity: Quizartinib mediated liver toxicity is dependent on dose level, treatment duration, and species. In rats, doses of quizartinib for 28 days resulted in slightly elevated liver enzymes (ALT, AST, and ALP) at ≥5 mg/kg. Liver histological changes (single-cell necrosis) were evident in found dead rats at 60/30 mg/kg, but were not observed in any per-schedule sacrificed animals. In the 13-week rat study, only slight increases in liver enzymes were evident at ≥3 mg/kg, and no histological liver changes were evident. In monkeys, a moderate increase in ALT, but no elevation of bilirubin or histopathological hepatic changes, was noted at up to 100/60 mg/kg. However, slight increases in AST, ALT, and TBIL and minimal histologic changes (single-cell necrosis, centrilobular necrosis, or hepatocellular vacuolation) were observed at ≥10/6 mg/kg in the 13-week study. The dog appeared to be more sensitive to hepatotoxic effects of quizartinib (increased AST, ALT, ALP, and bilirubin) and more likely to show histologic changes (birefringent crystal deposition, sinusoidal cell activation, and hepatocellular vacuolation). Liver crystal deposition occurred with dose-dependent severity and incidence in dogs and was not observed in rats or monkeys. In the 13-week dog study the NOAEL for crystal deposition in the liver without inflammation and liver enzyme elevation was considered to be 5 mg/kg/day.	Toxicity studies in animals indicate minor to moderate reversible increases in AST, ALT, ALP, or TBIL in rats, monkeys, and dogs. Dogs appeared to be more sensitive to these effects, and hepatic crystal deposition occurred only in dogs. Nonclinical studies have shown that there are inherent differences in the hepatic metabolism (parent and metabolites) involving hepatocellular transport across species. In addition, there are differences in the xenobiotic transport within the hepatocytes and in transport into bile, which leads to dogs being more susceptible to the accumulation of quizartinib and metabolites in an intrahepatic crystalline form. Although not definitively implicated in crystal pathogenesis, a unique quizartinib metabolite (morpholino oxidation product) has been observed only in the dog and not in the human, rat, or monkey species. As a result, crystal deposition in dog liver is not considered relevant to humans. Elevations of AST, ALT, ALP, or TBIL have also been observed in human studies; however, these have been mild and transient in general. LFT abnormalities are not considered an important risk for quizartinib (Section Part II: Module SVII).
Genotoxicity: Quizartinib showed potential for mutagenicity in a bacterial reverse mutation assay but was negative in a mammalian cell mutation (mouse lymphoma thymidine kinase) assay and in a 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.	Based on the available data the genotoxic potential of quizartinib is considered to be low. Quizartinib is proposed for the treatment of an acute malignant condition, and the potential for genotoxicity is not considered a safety risk for quizartinib.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Carcinogenicity: No carcinogenicity studies were conducted.	Quizartinib is indicated for the treatment of an acute malignant condition. De novo carcinogenicity is not considered a safety risk for the proposed patient population consisting of adults with ND AML.
Haematological/haematopoietic toxicity: In all species, the principal target organs affected were the bone marrow and lymphoid organs. Nonclinical studies demonstrated the potential for bone marrow suppression resulting in haematopoietic toxicity. Decreased WBC and/or red blood cell indices correlating with bone marrow hypocellularity were observed in rats, dogs, and monkeys. The NOAELs for severe haematopoietic inhibition and resultant bone marrow hypocellularity in 13-week studies were 3 mg/kg/day in rats, 5 mg/kg/day in dogs, and 3 mg/kg/day in monkeys.	Infiltration of the bone marrow by leukaemic blasts is a major cause of morbidity and mortality in patients with AML owing to neutropenia, anaemia, thrombocytopenia, and lymphopenia. Chemotherapy used for the treatment of AML is highly toxic to developing cells and thus worsens myelosuppression already occurring in AML. Almost all patients with AML suffer from prolonged Grade 4 neutropenia during induction and intensive consolidation chemotherapy, and the incidence of neutropenic fever ranges between 50% and 90%, depending on the phase of the disease and the intensity of chemotherapy. Haematological abnormalities, including anaemia, neutropenia, and thrombocytopenia, have been observed in human studies with quizartinib. Myelosuppression can be associated with the development of infections and haemorrhage in treated subjects. The incidence of these disorders in the quizartinib studies is not markedly higher than that seen in the general AML population owing to AML itself and/or to chemotherapeutic regimens. Management of haematological abnormalities constitutes part of the routine clinical care of subjects with AML. Myelosuppression is an identified risk for quizartinib; however, it is not considered to have an impact on the benefit-risk balance of quizartinib in the treatment of patients with ND AML and is not included as an important safety risk (Section Part II: Module SVII).

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Lymphoid organ toxicity: In all species, the principal target organs affected were the bone marrow and lymphoid organs. Nonclinical studies demonstrated the potential for reversible lymphoid organ toxicity. Decreased thymic organ weights and thymic lymphoid necrosis/atrophy were observed in rats, dogs, and monkeys in a dose- and treatment duration-dependent manner. Thymic atrophy/necrosis was evident in rats at ≥1 mg/kg, in dogs at ≥1 mg/kg, and in monkeys at ≥10/6 mg/kg. Splenic atrophy was observed in rats at ≥60/30 mg/kg, in dogs at 50/25 mg/kg, and in monkeys at ≥3 mg/kg. Lymphoid organ changes were reversible in rats, dogs, and monkeys following a 4-week recovery period.	Infiltration of the bone marrow by leukaemic blasts is a major cause of morbidity and mortality in patients with AML owing to neutropenia, anaemia, thrombocytopenia, and lymphopenia. Chemotherapy used for the treatment of AML is highly toxic to developing cells and thus worsens myelosuppression already occurring in AML. Lymphopenia has been observed in clinical studies to date. Lymphoid depletion is likely to be associated with the development of infections, including opportunistic infections in the treated subjects. Patients with AML are at a high risk of developing infections, regardless of any additional risk conferred from AML therapy. Risk factors contributing to the increased susceptibility of patients with AML to infections are profound neutropenia, impaired immunity, haemorrhage, and multiple skin-penetrating catheters. Infections have been observed in human studies with quizartinib. The incidence of infections in the quizartinib studies is not markedly higher than that seen in the general AML population owing to AML itself and/or to chemotherapeutic regimens. Management of infections constitutes part of the routine clinical care of subjects with AML. Myelosuppression is an identified risk for quizartinib; however, it is not considered to have an impact on the benefit-risk balance of quizartinib in the treatment of patients with ND AML, and is not included as an important safety risk (Section Part II: Module SVII).

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Cardiotoxicity: Studies in animals demonstrated a potential for QTc prolongation in a dose-dependent manner. No other significant effects on the cardiovascular system were identified in those studies. Quizartinib and its metabolite AC886 at 3 µM showed statistically significant inhibition of hERG channel currents by 16.4% and 12.0%, respectively. Quizartinib inhibited slowly activating delayed I_{Ks} more strongly with the maximum inhibition of 67.5% at 2.9 µM. The maximum inhibition of I_{Ks} by AC886 was 26.9% at 2.9 µM. Neither quizartinib nor AC886 showed toxicologically significant inhibition on I_{Ca-L}, I_{Na}, and I_{Na-L}, at up to 3 µM, the highest concentration tested. Therefore, it is suggested that quizartinib and AC886 induced blockade of hERG and I_{Ks} currents and, therefore, caused prolongation of the QTc interval on ECG by a decrease in the net repolarisation currents. The effect on I_{Ks} was more dominant than that on hERG. No treatment-related changes in ECGs were observed in dogs at 150/40 mg/kg in the 28-day study and at 15 mg/kg in the 13-week study and in monkeys at 100/60 mg/kg in the 28-day study and at 10/6 mg/kg in the 13-week study. Furthermore, no toxicologically significant morphological changes in the heart occurred in rats, dogs, or monkeys following single and repeated oral administration of up to 13 weeks.	Dose-dependent QTc interval prolongation has been observed in human studies with quizartinib. QTc interval prolongation is considered a potential risk factor for the development of ventricular arrhythmias, including torsade de pointes. QTc interval prolongation and torsade de pointes are considered an important identified risk for quizartinib (see Section Part II: Module SVII).

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
General Safety Pharmacology	
CNS and respiratory system: Rat CNS and respiratory system safety pharmacology studies were not conducted because there was no indication of CNS or pulmonary effects in the rat, dog, or monkey in general toxicology studies of up to 13-week duration.	No safety concern identified.
Contact sensitisation/phototoxicity: Quizartinib was not considered to be a contact sensitiser in guinea pigs. In addition, quizartinib was not phototoxic in the in vitro neutral red uptake phototoxicity test with Balb/c 3T3 mouse fibroblasts.	No safety concern identified.
Drug-drug interactions: Role of CYP enzymes in quizartinib metabolism: CYP3A4/5 is the primary isoform responsible for the metabolism of quizartinib in vitro. AC886 is both formed and further metabolised by CYP3A4/5. P-gp-mediated transport of quizartinib: Quizartinib is a P-gp substrate. In vitro studies (MDCK cell lines) showed reduced transport of digoxin in the presence of quizartinib. In vitro studies using MDCKII-MDR1 cells showed that IC_{50} of quizartinib and AC886 for P-gp transport was 9.55 and >30 µM, respectively. Quizartinib has weak potential to inhibit P-gp, primarily on P-gp-mediated GI transport (I_{gut}/IC_{50} >10).	In vitro findings in CYP3A4/5 metabolic studies and P-gp-mediated transport are relevant to humans. In vitro metabolism and clinical drug interaction studies indicate that there is a potential for other medications to alter the PK of quizartinib. For quizartinib, both the parent and the active metabolite (AC886) are metabolised by CYP3A4/5. Therefore, strong CYP3A inhibitors, such as azole antifungals, increase quizartinib plasma exposure. Increased exposure of quizartinib may result in an increase in the adverse effects of quizartinib. DDIs with strong CYP3A inhibitors are included as an important identified risk for quizartinib (see Section Part II: Module SVII). Clinical PK data showed that quizartinib C_{max} and AUC_{inf} decreased by approximately 45% and 90%, respectively, when coadministered with efavirenz, a moderate CYP3A inducer. Induction of CYP3A metabolism is expected to result in decreased efficacy of quizartinib. DDIs with strong or moderate CYP3A inducers are included as an important identified risk for quizartinib (see Section Part II: Module SVII).

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
	In vitro studies assessing the effect of the efflux transporter, P-gp, suggest that quizartinib is both a substrate and an inhibitor of P-gp. Although quizartinib is a P-gp substrate based on in vitro data, clinical data suggest that P-gp plays a minimal role in the absorption or clearance of quizartinib. Additionally, as dose adjustment is required for concomitant strong CYP3A inhibitors, many of which also inhibit P-gp, no specific dose adjustment is required for P-gp inhibitors. DDI with P-gp inhibitors or P-gp inducers is not considered a safety risk for quizartinib. In vitro studies showed that quizartinib is a potential intestinal P-gp inhibitor. Clinical PK data showed that coadministration of quizartinib and dabigatran etexilate (a P-gp substrate) increased total and free dabigatran C_{max} by 12% and 13%, respectively, and increased total and free dabigatran AUC_{inf} by 13% and 11%, respectively. P-gp transport inhibition due to quizartinib is not considered a safety risk. Quizartinib demonstrates a concentration-dependent QTc interval-prolonging effect, which increases the risk of interactions with drugs known to prolong the QT interval. DDI interaction with QT interval-prolonging drugs is not considered an additional important risk for quizartinib (Section Part II: Module SVII).

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AML = acute myeloid leukaemia; AST = aspartate aminotransferase; AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity; BUN = blood urea nitrogen; C_{max} = maximum plasma concentration; CNS = central nervous system; CYP = cytochrome P450; DDI = drug-drug interaction; ECG = electrocardiogram; GI = gastrointestinal; hERG = human ether-a-go-go-related gene; IC_{50} = half maximal inhibitory concentration; I_{Ca-L} = L-type calcium current; I_{gut} = unbound maximum plasma liver inlet concentration; I_{Ks} = inward rectifier potassium channel; LFT = liver function test; I_{Na} = sodium current; I_{Na-L} = late sodium current; MDCK = Madin-Darby Canine Kidney; MDR1 = multidrug resistance protein 1; ND = newly diagnosed; NOAEL = no-observed-adverse-effect-level; P-gp = P-glycoprotein; PK = pharmacokinetic(s); QT = interval between the start of the Q wave and the end of the T wave; QTc = corrected QT interval; TBIL = total bilirubin; WBC = white blood cell

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

The quizartinib clinical programme consists of 26 studies conducted by the Sponsor, including 13 studies in either ND or R/R AML, 1 study in solid tumours, and 12 single-dose studies in healthy subjects and subjects with hepatic impairment. Of the 13 studies in AML, 10 are completed. Across the completed studies, quizartinib has been administered to 1081 subjects with AML (hereafter referred to as All AML Pool) up to the data cut-off date (ie, 13 Aug 2021).

Throughout the development of quizartinib, the expression of strength of quizartinib doses was conveyed in protocols, manuscripts, and clinical study reports as the dihydrochloride salt and not the active moiety (freebase). The milligram dose for the dihydrochloride salt is slightly larger than that of the freebase for equivalent strengths, as shown in Table Part II: Module SIII.1. The doses cited throughout this submission are for the dihydrochloride salt; however, the doses used in the packaging and labelling are for the freebase in order to comply with the US Food and Drug Administration and EU policy.

Table Part II: Module SIII.1: Equivalent Doses of Quizartinib Freebase and Dihydrochloride Salt

Freebase (Active Moiety)	Dihydrochloride Salt
17.7 mg	20 mg
26.5 mg	30 mg
35.4 mg	40 mg
53 mg	60 mg

As of the data cut-off date (ie, 13 Aug 2021), quizartinib monotherapy has been administered to 1081 subjects with AML (Table Part II: Module SIII.2).

The 1081 subjects in the All AML Pool received at least 1 dose of quizartinib in Studies AC220-A-U302 (n = 265), 2689-CL-0005 (n = 18), AC220-A-J102 (n = 7), AC220-007 (n = 241), AC220-002 (n = 333), 2689-CL-2004 (n = 74), CP0001 (n = 76), AC220-A-J101 (n = 16), AC220-A-J201 (n = 38), and 2689-CL-0011 (n = 13) (Module 2.7.4 Section 1.1.1). Among these 1081 subjects, 535 (49.5%) were male, 546 (50.5%) were female, 577 (53.4%) were <60 years old, 140 (13.0%) were 60 to <65 years old, 304 (28.1%) were 65 to <75 years old, and 60 (5.6%) were ≥75 years old. Most subjects were White (72.2%).

The majority of exposure data in subjects with ND AML come from the pivotal study AC220-A-U302. Therefore, the tables below present pooled AML exposure data rather than exposure data by indication.

Exposure to quizartinib was generally similar in males and females, although more females than males were exposed for ≥731 days (Table Part II: Module SIII.3).

Exposure to quizartinib slightly varied by age group (Table Part II: Module SIII.4), and the lowest exposures were observed in subjects aged ≥75 years.

Exposure to quizartinib is shown by race and sex in Table Part II: Module SIII.5 and in special populations by sex in Table Part II: Module SIII.6.

The majority of subjects (669/1081) received quizartinib at doses of 30 to 60 mg (Table Part II: Module SIII.7). Exposure by dose group and sex is shown in Table Part II: Module SIII.8.

Table Part II: Module SIII.2: Duration of Exposure to Quizartinib in Subjects with Acute Myeloid Leukaemia

Duration of Quizartinib Exposure (days)	n (%)	Person-Time (years)[a]
All AML Pool	**N = 1081**	
0 to 30	208 (19.2)	9.2
31 to 90	407 (37.7)	65.9
91 to 180	239 (22.1)	81.7
181 to 365	94 (8.7)	62.0
366 to 730	70 (6.5)	101.4
≥731	63 (5.8)	179.3
Total person-time (years)[a]	1081 (100.0)	499.5

AML = acute myeloid leukaemia; EU = European Union; N = total number of subjects; n = number of subjects in each category; RMP = Risk Management Plan

[a] Person-time is the total time in years on study drug.

Source: Module 5.3.5.3 EU RMP Table 1

Table Part II: Module SIII.3: Duration of Quizartinib Exposure by Sex

Duration of Quizartinib Exposure (days) All AML Pool	Sex	Subjects	Person-Time (years)[a]
0 to 30	Male	99	4.4
	Female	109	4.8
	Total	208	9.2
31 to 90	Male	194	30.8
	Female	213	35.1
	Total	407	65.9
91 to 180	Male	131	44.5
	Female	108	37.2
	Total	239	81.7
181 to 365	Male	48	32.1
	Female	46	29.9
	Total	94	62.0
366 to 730	Male	37	53.4
	Female	33	48.0
	Total	70	101.4
≥731	Male	26	73.0
	Female	37	106.3
	Total	63	179.3

AML = acute myeloid leukaemia; EU = European Union; RMP = Risk Management Plan

[a] Person time is the total time in years on study drug.

Source: Module 5.3.5.3 EU RMP Table 2

Table Part II: Module SIII.4: Exposure to Quizartinib by Age Group and Sex

Age Group (years) All AML Pool	Sex	Subjects	Person-Time (years)[a]
<45	Male	120	73.1
	Female	132	59.0
	Total	252	132.1
45 to <55	Male	108	45.2
	Female	98	46.0
	Total	206	91.2
55 to <65	Male	113	49.0
	Female	146	78.6
	Total	259	127.6
65 to <75	Male	163	56.5
	Female	141	67.7
	Total	304	124.2
≥75	Male	31	14.4
	Female	29	10.0
	Total	60	24.4

AML = acute myeloid leukaemia; EU = European Union; RMP = Risk Management Plan
[a] Person-time is the total time in years on study drug.
Source: Module 5.3.5.3 EU RMP Table 3

Table Part II: Module SIII.5: Exposure to Quizartinib by Race and Sex

Race All AML Pool	Sex	Subjects	Person-Time (years)[a]
White	Male	399	179.0
	Female	381	167.2
	Total	780	346.3
Black or African American	Male	10	6.7
	Female	22	9.3
	Total	32	16.0
Asian	Male	85	36.6
	Female	91	57.1
	Total	176	93.7
Other	Male	20	11.3
	Female	25	15.5
	Total	45	26.8

AML = acute myeloid leukaemia; EU = European Union; RMP = Risk Management Plan
[a] Person-time is the total time in years on study drug.
Source: Module 5.3.5.3 EU RMP Table 4

Table Part II: Module SIII.6: Exposure to Quizartinib in Special Populations by Sex

Special Population All AML Pool	Sex	Subjects	Person-Time (years)[a]
Pregnant women	Female	0	0
Lactating women	Female	0	0
Renal impairment (creatinine clearance <30 mL/minute)	Male	2	0.5
	Female	3	1.2
	Total	5	1.7
Renal impairment (creatinine clearance 30 to <60 mL/minute)	Male	35	14.1
	Female	54	26.8
	Total	89	40.9
Renal impairment (creatinine clearance 60 to <90 mL/minute)	Male	132	56.6
	Female	173	70.2
	Total	305	126.8
Hepatic impairment (yes)	Male	174	77.7
	Female	163	72.1
	Total	337	149.8
Hepatic impairment (no)	Male	336	156.5
	Female	365	184.7
	Total	701	341.1

AML = acute myeloid leukaemia; EU = European Union; RMP = Risk Management Plan
[a] Person-time is the total time in years on study drug.
Notes: Renal impairment is defined as creatinine clearance <90 mL/min at baseline. Hepatic impairment is defined as any of alanine aminotransferase, aspartate aminotransferase, and total bilirubin greater than the upper limit of normal at baseline.
Source: Module 5.3.5.3 EU RMP Table 5

Table Part II: Module SIII.7: Doses of Quizartinib Used to Treat Subjects With Acute Myeloid Leukaemia

Dose of Quizartinib All AML Pool	Subjects	Person-Time (years)[a]
<30 mg	30	6.7
30 to 60 mg	669	384.1
>60 mg	382	108.7
Total	1081	499.5

AML = acute myeloid leukaemia; EU = European Union; RMP = Risk Management Plan
[a] Person-time is the total time in years on study drug.
Source: Module 5.3.5.3 EU RMP Table 6

Table Part II: Module SIII.8: Exposure to Quizartinib by Dose Group and Sex

Quizartinib Dose Group (mg) All AML Pool	Sex	Subjects	Person-Time (years)[a]
<30	Male	14	2.8
	Female	16	3.9
	Total	30	6.7
30 to 60	Male	319	174.3
	Female	350	209.8
	Total	669	384.1
>60	Male	202	61.2
	Female	180	47.6
	Total	382	108.7

AML = acute myeloid leukaemia; EU = European Union; RMP = Risk Management Plan
[a] Person-time is the total time in years on study drug.
Source: Module 5.3.5.3 EU RMP Table 7

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

The quizartinib clinical development programme includes 1 pivotal clinical study (Study AC220-A-U302) in subjects with ND AML. Enrolment of subjects in the study was based on the inclusion and exclusion criteria to allow for the evaluation of safety and efficacy for the specific indication while minimising risk for subjects.

The following populations were excluded from the pivotal study:

- **Age <18 years**

  Reason for exclusion: The safety and efficacy of quizartinib in children and adolescents younger than 18 years have not been established.

  Is it considered to be included as missing information? No

  Rationale: The safety and efficacy of quizartinib in children and adolescents younger than 18 years are being investigated in a specific paediatric development programme. The subject population consisting of children younger than 18 years is not relevant for the pursued indication of treatment of adults with ND AML, which is *FLT3*-ITD positive.

- **Absence of FLT3-ITD-activating mutation in bone marrow (allelic ratio of ≤ 3% *FLT3*-ITD/total *FLT3*)**

  Reason for exclusion: Quizartinib is a highly potent intracellular inhibitor of FLT3-ITD catalytic activity but has little activity against other kinases. Because of the highly specific activity of quizartinib, it is intended for the treatment of AML where *FLT3*-ITD is the main driver mutation (allelic ratio of ≥3% *FLT3* ITD/total *FLT3*).

  Is it considered to be included as missing information? No

  Rationale: Quizartinib is not intended for the treatment of subjects with AML where *FLT3*-ITD is not the main driver mutation.

- **Women who were pregnant or women of childbearing potential at risk of becoming pregnant**

  Reason for exclusion: Potential risks to unborn baby due to quizartinib.

  Is it considered to be included as missing information? No

  Rationale: Embryo-foetal and reproductive toxicity is included as an important potential risk in the RMP.

- **Women who are lactating**

  Reason for exclusion: No data on quizartinib secretion in breast milk.

  Is it considered to be included as missing information? No

  Rationale: Use of quizartinib in women who are breastfeeding is not recommended (see Summary of Product Characteristics [SmPC] Section 4.6). Alternatives to breast milk are readily available and the likelihood of breastfed infants to be exposed to quizartinib is considered to be very small.

- **Pre-existing severe renal impairment**

  Reason for exclusion: Potential effect of impaired renal function on quizartinib elimination and exposure.

  Is it considered to be included as missing information? No

  Rationale: Because quizartinib has minimal renal excretion (<2%), it is not expected that pre-existing renal impairment will increase exposure to quizartinib or its metabolites. Subjects with mild or moderately impaired renal function were eligible for treatment in the clinical development programme. Safety in subjects with severe renal impairment is unknown; however, subjects with severe renal impairment who also have AML are considered to have poor prognosis and to be unfit for intensive chemotherapy, and no significant use of quizartinib in this patient population is anticipated.

- **Pre-existing severe hepatic impairment**

  Reason for exclusion: Potential effect of impaired hepatic function on quizartinib elimination and exposure.

  Is it considered to be included as missing information? No

Rationale: Quizartinib is primarily eliminated by hepatic metabolism and biliary excretion. In 2 dedicated hepatic impairment studies (one based on Child-Pugh criteria in subjects with mild and moderate hepatic impairment and the other based on National Cancer Institute Organ-Dysfunction Working Group criteria in subjects with moderate hepatic impairment), no clinically meaningful changes in quizartinib and its active metabolite AC886 were observed. Quizartinib after a single administration of a 30-mg dose was found to be well tolerated in subjects with mild or moderate pre-existing hepatic impairment and no safety concern was identified. No dose adjustment is required for subjects with mild or moderate hepatic impairment.

Safety in subjects with severe hepatic impairment is unknown; however, subjects with severe hepatic impairment who also have AML are considered to have extremely poor prognosis and to be unfit for intensive chemotherapy, and no significant use of quizartinib in this patient population is anticipated.

- **Subjects with pre-existing QT interval prolongation, diagnosis or suspicion of long QT syndrome**

  Reason for exclusion: Quizartinib has been associated with QTc interval prolongation on ECG.

  Is it considered to be included as missing information? No

  Rationale: QTc interval prolongation is included as an important identified risk for quizartinib. The risk of QT prolongation and associated arrhythmias in subjects with a pre-existing QT interval prolongation will be monitored and evaluated as part of the evaluation of the risk of serious adverse drug reactions (ADRs) related to QTc interval prolongation in the general quizartinib patient population. Congenital long QT syndrome is a contraindication for the use of quizartinib.

- **Subjects with serum electrolytes outside the institution's normal limits: potassium, calcium, and magnesium**

  Reason for exclusion: Serum electrolyte abnormalities are an independent risk factor for QT interval prolongation on ECG and for the development of cardiac arrythmias.

  Is it considered to be included as missing information? No

  Rationale: QTc interval prolongation is included as an important identified risk for quizartinib. Correction of electrolyte abnormalities before and during treatment with quizartinib is required by the proposed product label. The risk of QTc prolongation and associated arrhythmias in subjects with any serum electrolyte abnormalities will be monitored and evaluated as part of the assessment of the risk of QTc interval prolongation/torsade the pointes in the general quizartinib patient population.

- **Patients with uncontrolled or significant cardiovascular disease (including arrhythmias and cardiac conduction abnormalities, ischaemic heart disease, and congestive heart failure)**

  Reason for exclusion: Subjects with significant cardiovascular disease are at an increased risk of developing QTc interval prolongation and cardiac arrhythmias.

  Is it considered to be included as missing information? No

  Rationale: Serious ADRs related to QTc interval prolongation is an important identified risk for quizartinib. The risk of QTc prolongation and associated arrhythmias in subjects with a history of cardiovascular disease will be monitored and evaluated as part of the evaluation of the risk of serious ADRs related to QTc interval prolongation in the general quizartinib patient population.

- **Severe medical conditions (including unresolved toxicity from previous treatment, another malignancy, infection, and medical conditions considered by the investigator to put the subjects at risk from participation in the study)**

  Reason for exclusion: To ensure that subjects with relatively preserved functional capacity are included in the study population, to mitigate potential confounders in the assessment of the safety profile, and to exclude conditions that may preclude adherence to study protocol schedules.

  Is it considered to be included as missing information? No

  Rationale: The safety profile of quizartinib in the population of adults with AML, which is *FLT3*-ITD positive, is well described in the clinical development programme, which has included older subjects (aged up to 75 years), and those with concurrent severe medical conditions, including infections and bleeding. Chemotherapy regimens, which form the standard of care for the treatment of ND AML, are associated with significant and severe toxicities. Quizartinib has demonstrated an acceptable benefit-risk profile in this patient population, with manageable toxicities. The safety profile of quizartinib in patients with pre-existing severe medical conditions, who are judged by the treating physicians to be able to tolerate treatment with quizartinib, is expected to be the same as that of the general quizartinib patient population.

  Acute promyelocytic leukaemia (AML subtype M3)

  Reason for exclusion: Acute promyelocytic leukaemia (APL [AML subtype M3]) was excluded because effective treatment for this subtype of AML exists.

  Is it considered to be included as missing information? No

  Rationale: Quizartinib is not indicated for this subtype of AML. The treatment of APL differs from usual AML treatment. Initial treatment of APL includes the non-chemotherapy drug all-trans-retinoic acid, which is most often combined with an anthracycline (daunorubicin or idarubicin), sometimes also with cytarabine. Use of quizartinib in subjects with APL is not anticipated.

- **AML secondary to prior chemotherapy for other neoplasms, except secondary to prior MDS**

  Reason for exclusion: AML secondary to prior chemotherapy for other neoplasms is a distinct clinical entity, with poor prognosis.

  Is it considered to be included as missing information? No

  Rationale: The safety and efficacy profile of quizartinib in subjects with *FLT3*-ITD positive AML has been thoroughly evaluated during the clinical programme. No additional safety concerns are anticipated in subjects with *FLT3*-ITD positive AML secondary to prior chemotherapy for other neoplasms and who are judged by the treating physician to be able to benefit from treatment with quizartinib.

- **History of or current CNS involvement with AML**

  Reason for exclusion: CNS involvement from AML is a serious complication requiring treatment with intrathecal chemotherapy or cranial radiation. Quizartinib is not expected to be effective for the treatment of CNS involvement from AML.

  Is it considered to be included as missing information? No

  Rationale: Use of quizartinib is not anticipated in subjects with CNS involvement from AML not managed by standard-of-care therapy.

- **Prior treatment with quizartinib**

  Reason for exclusion: To adequately assess the efficacy and safety profile of quizartinib in treatment-naïve subjects.

  Is it considered to be included as missing information? No

  Rationale: The safety of quizartinib has been assessed in the clinical development programme, and no additional safety concerns are expected in subjects with prior exposure to quizartinib.

- **Prior treatment with a FLT3 targeted therapy**

  Reason for exclusion: To adequately assess the efficacy and safety profile of quizartinib in subjects naïve to previous FLT3 targeted therapy

  Is it considered to be included as missing information? No

  Rationale: The safety and efficacy profile of quizartinib in subjects with *FLT3*-ITD positive AML has been thoroughly evaluated during the clinical programme. No additional safety concerns are anticipated in subjects with *FLT3*-ITD positive AML who have previously been treated with FLT3-targeted therapy and who are judged by the treating physicians to be able to benefit from treatment with quizartinib.

- **Prior treatment for AML (except for leukapheresis, hydroxyurea, cranial radiotherapy, intrathecal chemotherapy, and growth factor/cytokine support)**

  Reason for exclusion: To adequately assess the efficacy and safety profile of quizartinib in subjects naïve to previous AML therapy.

Is it considered to be included as missing information? No

Rationale: The safety and efficacy profile of quizartinib in subjects with *FLT3*-ITD positive AML has been thoroughly evaluated during the clinical programme. No additional safety concerns are anticipated in subjects with *FLT3*-ITD positive AML who have previously been treated for AML therapy and who are judged by the treating physicians to be able to benefit from treatment with quizartinib.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development programme for quizartinib is unlikely to detect certain types of adverse reactions such as rare adverse reactions and those occurring as part of the underlying disease being treated. The quizartinib clinical development programme included 133 (12%) subjects treated for >12 months, which is considered sufficient to detect adverse reactions from prolonged and cumulative quizartinib exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programs

The number of subjects from under-represented populations that were exposed to quizartinib in the clinical development programme is presented in Table Part II: Module SIV.1.

Table Part II: Module SIV.1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Number of Subjects (Person-Years) All AML Pool
Pregnant women	Not included in the clinical development programme
Breastfeeding women	
Elderly	
≥65 to <75 years	304 (124.2)
≥75 years	60 (24.4)
Patients with relevant comorbidities	
Patients with hepatic impairment (abnormal hepatic function defined as any ALT, AST, or TBIL >ULN)	337 (149.8)
Patients with renal impairment	
Severe impairment (CrCL <30 mL/min)	5 (1.7)
Moderate impairment (CrCL ≥30 to <60 mL/min)	89 (40.9)
Mild impairment (CrCL ≥60 to <90 mL/min)	305 (126.8)
Immunocompromised patients	Patients with ND and R/R AML have compromised immune systems due to clonal malignancy itself and antileukaemic therapies.
Patients with a disease severity different from inclusion criteria in clinical studies	No data available
Population with relevant different racial and/or ethnic origin	
White	780 (346.3)
Asian	176 (93.7)
Black or African American	32 (16.0)
Other	45 (26.8)

ALT = alanine aminotransferase; AML = acute myeloid leukaemia; AST = aspartate aminotransferase; CrCL = creatinine clearance; EU = European Union; ND = newly diagnosed; R/R = relapsed/refractory; RMP = Risk Management Plan; TBIL = total bilirubin; ULN = upper limit of normal
Source: Module 5.3.5.3 EU RMP Table 3, Table 4, and Table 5

PART II: MODULE SV POSTAUTHORISATION EXPERIENCE

SV.1 Postauthorisation Exposure

Marketing authorisation of VANFLYTA was first granted by the Ministry of Health, Labour and Welfare of Japan for the treatment of adult subjects with *FLT3*-ITD positive R/R AML on 18 Jun 2019. The approved dose regimen is 26.5 to 53 mg once daily (QD). Currently, quizartinib is not approved for marketing in any other country other than Japan.

Cumulatively, from 18 Jun 2019 to 28 Oct 2021, 228 patients are estimated to have received quizartinib in the postmarketing setting [redacted].

Marketing exposure data from subjects with R/R AML have been obtained at similar doses to the dose regimen for the proposed indication; therefore, data obtained in this setting are relevant for the overall assessment of the safety of quizartinib.

SV.1.1 Method Used to Calculate Exposure

Following marketing authorisation, quizartinib was subject to all-case safety surveillance. Data collected have been used to calculate exposure.

SV.1.2 Exposure

Exposure data available for 201 of the 228 patients exposed to quizartinib (oral formulation) [redacted] are presented in Table Part II: Module SV.1.

Table Part II: Module SV.1: Postmarketing Exposure by Indication, Sex, Age Group, and Maximum Dose

Indication	Sex n (%)		Age (years)			Maximum Dose (mg)				
	Male	Female	<60	60≤ <65	≥65	≤17.7	>17.7 ≤26.5	>26.5 ≤53	>53	Unknown /missing
FLT3-ITD positive R/R AML	112 (55.7)	89 (44.3)	81 (40.3)	13 (6.5)	107 (53.2)	29 (14.4)	87 (43.3)	84 (41.8)	0	1 (0.5)

AML = acute myeloid leukaemia; EU = European Union; *FLT3*-ITD = feline McDonough sarcoma-like tyrosine kinase 3-internal tandem duplication; R/R = relapsed/refractory; RMP = Risk Management Plan
Source: Module 5.3.5.3 EU RMP Table 8

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

There is no evidence of potential for misuse of quizartinib for illegal purposes. Quizartinib is prescription-only medication, prescribed in an oncology setting, which minimises possible misuse. In addition, given its mode of action and no evidence of CNS activity or withdrawal symptoms associated with quizartinib treatment, the potential for misuse is considered negligible. The pharmaceutical characteristics and PK/pharmacodynamic characteristics of quizartinib are not characteristic of drugs with high dependence potential (eg, rapid-onset/short-acting active substances).

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

The pivotal Phase 3 study, Study AC220-A-U302, is the main source of safety information for the target indication of ND *FLT3*-ITD (+) AML. As the majority of subjects with ND AML in the quizartinib clinical development programme were from the pivotal study, no integrated analyses for the ND population were performed. Instead, data from Study AC220-A-U302 were pooled with those of 8 other completed clinical studies in AML, including both subjects with ND AML and subjects with R/R AML treated with quizartinib monotherapy or in combination with chemotherapy, to provide an integrated safety profile of quizartinib (All AML Pool; see Section Part II: Module SIII).

Integrated safety analyses of the All AML Pool were used to provide supportive data with quizartinib at all dose ranges and, in particular, to assess the safety profile of quizartinib at the target dose (30 to 60 mg). The sections below focus on safety data from the overall study period in Study AC220-A-U302 and the 30 to 60 mg group of the All AML Pool (N = 669; hereafter referred to as 30 to 60 mg group of the All AML Pool). This dose group includes quizartinib-treated subjects from the pivotal Study AC220-A-U302 and from Studies AC220-007, 2689-CL-0011, AC220-A-J201, 2689-CL-2004, and 2689-CL-0005, and subjects who were assigned to a dose of 30 to 60 mg QD from the remaining studies (CP0001, AC220-A-J101, AC220-A-J102).

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The reasons for not including identified or potential risks in the list of safety concerns are presented in the following sections.

SVII.1.1.1. Risks with Minimal Clinical Impact on Patients (in Relation to the Severity of the Indication Treated)

SVII.1.1.1.1. Gastrointestinal Symptoms and Appetite Disorders

Abdominal pain, nausea, vomiting, diarrhoea, dyspepsia, and decreased appetite are recognised ADRs for quizartinib. Although frequent, these ADRs were generally nonserious, rarely led to discontinuation of quizartinib therapy, and are considered to have minimal clinical impact on patients with ND AML.

The incidence of these ADRs (including associated preferred terms [PTs]) is presented in Table Part II: Module SVII.1 for Study AC220-A-U302 and in Table Part II: Module SVII.2 for the 30 to 60 mg group of the All AML Pool (N = 699).

Table Part II: Module SVII.1: Overall Summary of Adverse Drug Reactions of Gastrointestinal Symptoms and Appetite Disorders in Study AC220-A-U302 (Safety Analysis Set)

Preferred Term	Overall		Grade ≥3		Serious		Study Drug Discontinuation	
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)
Diarrhoea	98 (37.0)	94 (35.1)	10 (3.8)	10 (3.7)	1 (0.4)	0	1 (0.4)	0
Nausea	90 (34.0)	84 (31.3)	4 (1.5)	5 (1.9)	0	0	2 (0.8)	0
Vomiting	65 (24.5)	53 (19.8)	0	4 (1.5)	2 (0.8)	2 (0.7)	1 (0.4)	0
Abdominal pain	46 (17.4)	38 (14.2)	3 (1.1)	3 (1.1)	0	0	0	0
Decreased appetite	46 (17.4)	36 (13.4)	13 (4.9)	5 (1.9)	0	0	2 (0.8)	0
Dyspepsia	30 (11.3)	23 (8.6)	1 (0.4)	2 (0.7)	1 (0.4)	1 (0.4)	0	0
Abdominal pain upper	29 (10.9)	25 (9.3)	3 (1.1)	2 (0.7)	0	0	0	0
Abdominal discomfort	8 (3.0)	4 (1.5)	5 (3.1)	2 (1.3)	0	0	0	0
Abdominal pain lower	4 (1.5)	2 (0.7)	0	0	0	0	0	0
Gastrointestinal pain	2 (0.8)	1 (0.4)	0	0	0	0	0	0
Diarrhoea haemorrhagic	1 (0.4)	0	0	0	0	0	0	0

AML = acute myeloid leukaemia; N = total number of subjects; n = number of subjects; SCS = Summary of Clinical Safety
Source: Module 5.3.5.3 SCS Tables 4.1.3, 4.1.5, 4.1.11, and 4.1.13

Table Part II: Module SVII.2: Overall Summary of Adverse Drug Reactions of Gastrointestinal Symptoms and Appetite Disorders in the 30 to 60 mg Group of the All Acute Myeloid Leukaemia Pool (Safety Analysis Set)

	All AML Pool Quizartinib 30 to 60 mg (N = 669)			
Preferred Term	**Overall n (%)**	**Grade ≥3 n (%)**	**Serious n (%)**	**Study Drug Discontinuation n (%)**
Nausea	272 (40.7)	17 (2.5)	10 (1.5)	3 (0.4)
Diarrhoea	220 (32.9)	19 (2.8)	5 (0.7)	2 (0.3)
Vomiting	195 (29.1)	16 (2.4)	12 (1.8)	1 (0.1)
Decreased appetite	122 (18.2)	25 (3.7)	1 (0.1)	2 (0.3)
Abdominal pain	104 (15.5)	10 (1.5)	2 (0.3)	1 (0.1)
Dyspepsia	65 (9.7)	2 (0.3)	1 (0.1)	0
Abdominal pain upper	57 (8.5)	3 (0.4)	0	0
Abdominal discomfort	19 (2.8)	0	0	0
Abdominal pain lower	7 (1.0)	0	0	0
Gastrointestinal pain	4 (0.6)	0	0	0
Diarrhoea haemorrhagic	1 (0.1)	0	0	0

AML = acute myeloid leukaemia; N = total number of subjects; n = number of subjects; SCS = Summary of Clinical Safety
Source: Module 5.3.5.3 SCS Tables 4.1.3, 4.1.5, 4.1.11, and 4.1.13

SVII.1.1.1.2. Oedema

Oedema is recognised as an ADR for quizartinib. These events were generally nonserious, did not lead to discontinuation of quizartinib therapy, and are considered to have minimal clinical impact on patients with ND AML. The incidence of oedema ADRs (including associated PTs) is presented in Table Part II: Module SVII.3 for Study AC220-A-U302 and in Table Part II: Module SVII.4 for the 30 to 60 mg group of the All AML Pool (N = 699).

Table Part II: Module SVII.3: Overall Summary of Adverse Drug Reactions of Oedema in Study AC220-A-U302 (Safety Analysis Set)

Preferred Term	Overall		Grade ≥3		Serious		Study Drug Discontinuation	
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)
Oedema peripheral	30 (11.3)	37 (13.8)	1 (0.4)	3 (1.1)	0	0	0	0
Face oedema	7 (2.6)	1 (0.4)	0	0	0	0	0	0
Fluid overload	5 (1.9)	4 (1.5)	0	0	0	0	0	
Generalised oedema	5 (1.9)	0	0	0	1 (0.4)	0	0	0
Oedema	5 (1.9)	8 (3.0)	0	0	0	0	0	0
Peripheral swelling	4 (1.5)	2 (0.7)	0	0	0	0	0	0
Localised oedema	2 (0.8)	2 (0.7)	0	0	0	0	0	0
Swelling face	1 (0.4)	1 (0.4)	0	1 (0.4)	0	0	0	0

AML = acute myeloid leukaemia; N = total number of subjects; n = number of subjects; SCS = Summary of Clinical Safety
Source: Module 5.3.5.3 SCS Tables 4.1.3, 4.1.5, 4.1.11, and 4.1.13

Table Part II: Module SVII.4: Overall Summary of Adverse Drug Reactions of Oedema in the 30 to 60 mg Group of the All Acute Myeloid Leukaemia Pool (Safety Analysis Set)

	All AML Pool Quizartinib 30 to 60 mg (N = 669)			
Preferred Term	**Overall n (%)**	**Grade ≥3 n (%)**	**Serious n (%)**	**Study Drug Discontinuation n (%)**
Oedema peripheral	105 (15.7)	4 (0.6)	2 (0.3)	0
Oedema	19 (2.8)	0	0	0
Face oedema	17 (2.5)	0	0	0
Peripheral swelling	14 (2.1)	0	0	0
Fluid overload	11 (1.6)	1 (0.1)	0	0
Generalised oedema	8 (1.2)	0	1 (0.1)	0
Swelling face	8 (1.2)	0	0	0
Localised oedema	4 (0.6)	0	0	0

AML = acute myeloid leukaemia; N = total number of subjects; n = number of subjects; SCS = Summary of Clinical Safety
Source: Module 5.3.5.3 SCS Tables 4.1.3, 4.1.5, 4.1.11, and 4.1.13

SVII.1.1.1.3. Nervous System Disorders

Headache is recognised as an ADR for quizartinib. The events of headache were generally nonserious, did not lead to discontinuation of quizartinib therapy, and are considered to have minimal clinical impact on patients with AML. The incidence of headache ADRs (including associated PTs) is presented in Table Part II: Module SVII.5 for Study AC220-A-U302 and in Table Part II: Module SVII.6 for the 30 to 60 mg group of the All AML Pool (N = 699).

Table Part II: Module SVII.5: Overall Summary of Adverse Drug Reactions of Nervous System Disorders in Study AC220-A-U302 (Safety Analysis Set)

Preferred Term	Overall		Grade ≥3		Serious		Study Drug Discontinuation	
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)
Headache	73 (27.5)	53 (19.8)	0	2 (0.7)	0	0	0	0
Tension headache	1 (0.4)	0	0	0	0	0	0	0
Migraine	0	1 (0.4)	0	0	0	0	0	0

AML = acute myeloid leukaemia; N = total number of subjects; n = number of subjects; SCS = Summary of Clinical Safety
Source: Module 5.3.5.3 SCS Tables 4.1.3, 4.1.5, 4.1.11, and 4.1.13

Table Part II: Module SVII.6: Overall Summary of Adverse Drug Reactions of Nervous System Disorders in the 30 to 60 mg Group of the All Acute Myeloid Leukaemia Pool (Safety Analysis Set)

	All AML Pool Quizartinib 30 to 60 mg (N = 669)			
Preferred Term	**Overall n (%)**	**Grade ≥3 n (%)**	**Serious n (%)**	**Study Drug Discontinuation n (%)**
Headache	157 (23.5)	3 (0.4)	2 (0.3)	0
Migraine	1 (0.1)	0	0	0
Tension headache	1 (0.1)	0	0	0

AML = acute myeloid leukaemia; N = total number of subjects; n = number of subjects; SCS = Summary of Clinical Safety
Source: Module 5.3.5.3 SCS Tables 4.1.3, 4.1.5, 4.1.11, and 4.1.13

SVII.1.1.1.4. Liver Function Test Abnormalities

Adverse Events

LFT abnormalities occur frequently in subjects with AML due to various factors, including AML therapy, concomitant medications, and AML disease process. The LFT abnormalities that occurred in the quizartinib programme were generally mild, transient, and manageable by dose interruption and/or reduction. None of the cases of LFT abnormalities were considered indicative of drug-induced liver injury due to quizartinib, and they are not considered to have a significant impact on the risk-benefit balance of the product.

Increased alanine aminotransferase (ALT) is recognised as an ADR for quizartinib. In Study AC220-A-U302, events of ALT increased were reported in 42 (15.8%) subjects in the quizartinib group and 27 (10.1%) subjects in the placebo group, and were of Grade ≥3 in 2 (0.8%) and 2 (0.7%) subjects, respectively (Module 5.3.5.3 SCS Tables 4.1.3 and 4.1.5). Serious events were reported only in 2 (0.7%) subjects in the placebo group, while events leading to study drug discontinuation were reported only in 1 (0.1%) subject in the quizartinib group (Module 5.3.5.3 SCS Tables 4.1.11 and 4.1.13).

In the 30 to 60 mg group of the All AML Pool, events of ALT increased were reported in 92 (13.8%) subjects and were of Grade ≥3 in 28 (4.2%) subjects (Module 5.3.5.3 SCS Tables 4.1.3 and 4.1.5). Few of the subjects had events that were serious (2 [0.3%] subjects) or that led to study drug discontinuation (2 [0.3%] subjects) (Module 5.3.5.3 SCS Tables 4.1.11 and 4.1.13).

Laboratory Data

In Study AC220-A-U302, ALT levels ≥3 × upper limit of normal were reported in 75 (28.3%) subjects in the quizartinib group and 56 (20.9%) subjects in the placebo group (Module 5.3.5.3 SCS Table 5.1.2). In the 30 to 60 mg group of All AML Pool, a total of 140 (20.9%) subjects had ALT levels ≥3 × upper limit of normal.

SVII.1.1.2. Known Risks that Do Not Impact the Risk-Benefit Balance

SVII.1.1.2.1. Risks Associated with Myelosuppression

Cytopenias (anaemia, thrombocytopenia, neutropenia, and pancytopenia) and associated disorders of infection (upper respiratory tract infections, herpes infections, fungal infections, and bacteraemia), and bleeding (epistaxis) are recognised ADRs for quizartinib.

Cytopenias, infection, and bleeding occur frequently in subjects with AML, irrespective of quizartinib treatment (Section Part II: Module SI). Management of cytopenias, infection, and bleeding is part of the routine clinical care of subjects with ND AML. The incidences of these disorders in the quizartinib studies is not markedly higher than that seen in the general AML population owing to AML itself and/or to chemotherapeutic regimens, and they are not considered to have a significant impact on the risk-benefit balance of the product. The risk of cytopenias and the associated risks of infection and bleeding are well described in the proposed label, and no additional pharmacovigilance activities or risk minimisation measures are proposed. The events of cytopenias, infections, and epistaxis in Study AC220-A-U302 and in the 30 to 60 mg group of the All AML Pool are described below. The occurrence of events of cytopenias (including associated PTs) is presented in Table Part II: Module SVII.7 for Study AC220-A-U302 and in Table Part II: Module SVII.8 for the 30 to 60 mg group of the All AML Pool. The occurrence of events of infections (including associated PTs) is presented in Table Part II: Module SVII.9 for Study AC220-A-U302 and in Table Part II: Module SVII.10 for the 30 to 60 mg group of the All AML Pool.

SVII.1.1.2.1.1. Cytopenias

Adverse Events

Study AC220-A-U302

Overall, in Study AC220-A-U302, the most frequent cytopenia events were neutropenia (54 [20.4%] and 27 [10.1%] subjects in the quizartinib and placebo groups, respectively), thrombocytopenia (30 [11.3%] and 30 [11.2%] subjects in the quizartinib and placebo groups, respectively), and anaemia (29 [10.9%] and 19 [7.1%] subjects in the quizartinib and placebo groups, respectively) (Table Part II: Module SVII.7).

Events of neutropenia were reported in 54 (20.4%) subjects in the quizartinib group and 27 (10.1%) subjects in the placebo group, and were mostly of Grade ≥3. Four (1.5%) subjects in the quizartinib group and 5 (1.9%) subjects in the placebo group had serious events of neutropenia, and 2 (0.8%) subjects in the quizartinib group had events associated with study drug discontinuation. Events of neutrophil count decreased were reported in 27 (10.2%) subjects in the quizartinib group and 12 (4.5%) subjects in the placebo group, were mostly of Grade ≥3, and were serious in 4 (1.5%) subjects in the quizartinib group. There were no events of neutrophil count decreased associated with study drug discontinuation. None of the subjects had an event of neutropenia or neutrophil count decreased with a fatal outcome.

Events of thrombocytopenia were reported in 30 (11.3%) subjects in the quizartinib group and 30 (11. 2%) subjects in the placebo group, and were mostly of Grade ≥3. Two (0.8%) subjects in the quizartinib group and 8 (3.0%) in the placebo group had serious events of thrombocytopenia, and 3 (1.1%) subjects in the quizartinib group had events associated with study drug

discontinuation. Events of platelet count decreased were reported in 18 (6.8%) subjects in the quizartinib group and 8 (3.0%) subjects in the placebo group, and were mostly of Grade ≥3. One (0.4%) subject in each treatment group has a serious event of platelet count decreased, and none had events associated with study drug discontinuation. None of the subjects had an event of thrombocytopenia or platelet count decreased associated with a fatal outcome.

Events of anaemia were reported in 29 (10.9%) subjects in the quizartinib group and 19 (7.1%) subjects in the placebo group, and were of Grade ≥3 in 15 (5.7%) and 14 (5.2%) subjects, respectively. Two (0.8%) subjects in the quizartinib group and 2 (0.7%) subjects in the placebo group had serious events of anaemia, and 1 (0.7%) subject in the quizartinib group had an event associated with study drug discontinuation. None of the events of anaemia were associated with a fatal outcome.

Events of pancytopenia were reported in 7 (2.6%) subjects in the quizartinib group and 1 (0.4%) subject in the placebo group, and were mostly of Grade ≥3. Pancytopenia was serious in 1 (0.4%) subject in the placebo group, and was associated with study drug discontinuation in 1 (0.4%) subject in the quizartinib group. None of the subjects had an event of pancytopenia associated with a fatal outcome.

30 to 60 mg Group of the All AML Pool

Overall, in the 30 to 60 mg group of the All AML Pool, the most frequent cytopenia events were anaemia (165 [24.7%] subjects), neutropenia (128 [19.1%] subjects), and thrombocytopenia (125 [18.7%] subjects) (Table Part II: Module SVII.8).

A total of 165 (24.7%) subjects had treatment-emergent adverse events (TEAEs) of anaemia. Most were Grade ≥3; 11 (1.6%) subjects had serious events, and 1 (0.1%) subject had an event associated with study drug discontinuation. None of the events of anaemia were associated with a fatal outcome.

A total of 128 (19.1%) subjects had TEAEs of neutropenia and 70 (10.5%) had TEAEs of neutrophil count decreased, most of whom had Grade ≥3 events. Serious events of neutropenia and neutrophil count decreased were reported in 10 (1.5%) subjects and 6 (0.9%) subjects, respectively. A total of 4 (0.6%) subjects had neutropenia that was associated with study drug discontinuation, while none of the neutrophil count decreased events were associated with study drug discontinuation. None of the subjects had an event of neutropenia or neutrophil count decreased with a fatal outcome.

A total of 125 (18.7%) subjects had TEAEs of thrombocytopenia and 74 (11.1%) subjects had TEAEs of platelet count decreased, most of whom had Grade ≥3 events . Serious events of thrombocytopenia and platelet count decreased were reported in 7 (1.0%) subject and 3 (0.4%) subjects, respectively. A total of 4 (0.6%) subjects had thrombocytopenia that was associated with the study drug discontinuation and 1 (0.1%) subject had an event of thrombocytopenia with fatal outcome. None of the events of platelet count decreased was associated with study drug discontinuation or with a fatal outcome.

Pancytopenia was reported in 17 (2.5%) of subjects, most of whom had Grade ≥3 events. Four (0.6%) subjects had events of pancytopenia that were serious, and 2 (0.3%) subjects had events that were associated with study drug discontinuation. None of the events of pancytopenia was associated with a fatal outcome.

Table Part II: Module SVII.7: Overall Summary of Adverse Drug Reactions of Cytopenia in Study AC220-A-U302 (Safety Analysis Set)

Preferred Term	Overall		Grade ≥3		Serious		Study Drug Discontinuation		Death	
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)
Neutropenia	54 (20.4)	27 (10.1)	48 (18.1)	23 (8.6)	4 (1.5)	5 (1.9)	2 (0.8)	0	0	0
Thrombocytopenia	30 (11.3)	30 (11.2)	21 (7.9)	26 (9.7)	2 (0.8)	8 (3.0)	3 (1.1)	0	0	0
Anaemia	29 (10.9)	19 (7.1)	15 (5.7)	14 (5.2)	2 (0.8)	2 (0.7)	1 (0.4)	0	0	0
Neutrophil count decreased	27 (10.2)	12 (4.5)	23 (8.7)	9 (3.4)	4 (1.5)	0	0	0	0	0
Platelet count decreased	18 (6.8)	8 (3.0)	14 (5.3)	7 (2.6)	1 (0.4)	1 (0.4)	0	0	0	0
Pancytopenia	7 (2.6)	1 (0.4)	6 (2.3)	1 (0.4)	0	1 (0.4)	1 (0.4)	0	0	0

AML = acute myeloid leukaemia; N = total number of subjects; n = number of subjects; SCS = Summary of Clinical Safety
Source: Module 5.3.5.3 SCS Tables 4.1.3, 4.1.5, 4.1.9, 4.1.11, and 4.1.13

Table Part II: Module SVII.8: Overall Summary of Adverse Drug Reactions of Cytopenia in the 30 to 60 mg Group of the All Acute Myeloid Leukaemia Pool (Safety Analysis Set)

Preferred Term	All AML Pool Quizartinib 30 to 60 mg (N = 669)				
	Overall n (%)	Grade ≥3 n (%)	Serious n (%)	Study Drug Discontinuation n (%)	Death n (%)
Anaemia	165 (24.7)	128 (19.1)	11 (1.6)	1 (0.1)	0
Neutropenia	128 (19.1)	118 (17.6)	10 (1.5)	4 (0.6)	0
Thrombocytopenia	125 (18.7)	109 (16.3)	7 (1.0)	4 (0.6)	1 (0.1)
Platelet count decreased	74 (11.1)	61 (9.1)	3 (0.4)	0	0
Neutrophil count decreased	70 (10.5)	63 (9.4)	6 (0.9)	0	0
Pancytopenia	17 (2.5)	16 (2.4)	4 (0.6)	2 (0.3)	0

AML = acute myeloid leukaemia; N = total number of subjects; n = number of subjects; SCS = Summary of Clinical Safety
Source: Module 5.3.5.3 SCS Tables 4.1.3, 4.1.5, 4.1.9, 4.1.11, and 4.1.13

Laboratory Data

In addition to the reported TEAE of cytopenias, laboratory data for the respective haematological parameters are included below for Study AC220-A-U302 and for the 30 to 60 mg group of the All AML Pool.

Study AC220-A-U302

Shifts to Grade 3 anaemia were mostly observed in subjects with Grade 2 values at Baseline (87 [33.7%] and 106 [39.7%] subjects in the quizartinib and placebo groups, respectively) followed by subjects with Grade 1 values at Baseline (6 [2.3%] and 8 [3.0%] subjects in the quizartinib and placebo groups, respectively), and subjects with normal values at Baseline (only 1 [0.4%] subject in the quizartinib group) (Module 5.3.5.3 SCS Table 5.1.1). There were no subjects with shifts to Grade 4 anaemia on treatment.

More than 70% of subjects in both treatment groups had Grade 4 neutrophil count decreased at Baseline that persisted during treatment (181 [74.8%] and 196 [76.3%] subjects in the quizartinib and placebo groups, respectively; Module 5.3.5.3 SCS Table 5.1.1). Shifts to Grade 3 neutrophil count decreased were observed in 1 (0.4%) subject with normal value at Baseline and in 1 (0.4%) subject with Grade 2 at Baseline in the quizartinib group, and in no subjects in the placebo group. Shifts to Grade 4 neutrophil count decreased were observed in: subjects with normal values at Baseline (21 [8.7%] and 10 [3.9%] subjects in the quizartinib and placebo groups, respectively), subjects with Grade 1 values (3 [1.2%] and 5 [1.9%] subjects, respectively),

subjects with Grade 2 values (4 [1.7%] and 8 [3.1%] subjects, respectively), and subjects with Grade 3 values (20 [8.3%] and 26 [10.1%] subjects, respectively).

Approximately half of subjects had Grade 4 platelet count decreased at Baseline that persisted during treatment (138 [53.5%] and 128 [47.9%] subjects in the quizartinib and placebo groups, respectively; Module 5.3.5.3 SCS Table 5.1.1). Shifts to Grade 3 platelet count decreased were observed in only 1 (0.4%) subject in the placebo group with Grade 1 values at Baseline, and in subjects with Grade 2 values (3 [1.2%] and 3 [1.1%] subjects in the quizartinib and placebo groups, respectively). Shifts to Grade 4 platelet count decreased were observed in subjects with normal values at Baseline (1 [0.4%] and 5 [1.9%] subjects in the quizartinib and placebo groups, respectively), subjects with Grade 1 values (9 [3.5%] and 9 [3.4%] subjects, respectively), subjects with Grade 2 values (21 [8.1%] and 14 [5.2%] subjects, respectively), and subjects with Grade 3 values (72 [27.9%] and 86 [32.2%] subjects, respectively).

30 to 60 mg group of the All AML Pool

Shifts to Grade 3 anaemia were mostly observed in subjects with Grade 2 values at Baseline (235 [35.8%]), followed by subjects with Grade 1 and normal values at Baseline (53 [8.1%] and 14 [2.1%], respectively) (Module 5.3.5.3 SCS Table 5.1.1). There were no subjects with shifts to Grade 4 anaemia on treatment.

Approximately half of the subjects had Grade 4 neutrophil count decreased at Baseline that persisted during treatment (Module 5.3.5.3 SCS Table 5.1.1). Shifts to Grade 3 neutrophil count decreased were observed in 12 (1.9%) subjects with normal values at Baseline, in 5 (0.8%) subjects with Grade 1 values, and in 6 (1.0%) subjects with Grade 2 values. Shifts to Grade 4 neutrophil count decreased were observed in 100 (16.2%) subjects with normal values at Baseline, 25 (4.1%) subjects with Grade 1 values, 27 (4.4%) subjects with Grade 2 values, and 75 (12.2%) subjects with Grade 3 values.

Approximately 40% of subjects had Grade 4 platelet count decreased at Baseline that persisted during treatment (Module 5.3.5.3 SCS Table 5.1.1). Shifts to Grade 3 platelet count decreased were observed in 4 (0.6%) subjects with normal values at Baseline, in 9 (1.4%) subjects with Grade 1 values, and in 10 (1.5%) subjects with Grade 2 values. Shifts to Grade 4 neutrophil count decreased were observed in 18 (2.7%) subjects with normal values at Baseline, 45 (6.9%) subjects with Grade 1 values, 56 (8.5%) subjects with Grade 2 values, and 184 (28.0%) subjects with Grade 3 values.

SVII.1.1.2.1.2. Infections

Study AC220-A-U302

Overall, in Study AC220-A-U302, infections ADRs were reported in <10% of subjects (Table Part II: Module SVII.9). The most frequently reported events were upper respiratory tract infection (21 [7.9%] subjects in the quizartinib group and 15 [5.6%] subjects in the placebo group), oral herpes (18 [6.8%] subjects in the quizartinib group and 12 [4.5%] subjects in the placebo group), and bacteraemia (16 [6.0%] subjects in the quizartinib group and 6 [2.2%] subjects in the placebo group). Grade ≥3 events were reported in ≤3.8% of subjects. Generally, events were nonserious and not associated with study drug discontinuation. Mucormycosis was the only event associated with a fatal outcome in 2 (0.3%) subjects in the quizartinib group.

30 to 60 mg group of the All AML Pool

Overall, in the 30 to 60 mg group of the All AML Pool, infections ADRs were reported in <10% of subjects (Table Part II: Module SVII.10). The most frequently reported events were upper respiratory tract infection (in 52 [7.8%] subjects) and oral herpes (in 34 [5.1%] subjects). Grade ≥3 events were reported in ≤3.1% of subjects. Generally, events were nonserious and not associated with study drug discontinuation. Events associated with a fatal outcome were: mucormycosis (in 2 [0.3%] subjects), sinusitis and bronchopulmonary aspergillosis (each in 1 [0.1]% subject).

Table Part II: Module SVII.9: Overall Summary of Adverse Drug Reactions of Infections in Study AC220-A-U302 (Safety Analysis Set)

Preferred Term	Overall		Grade ≥3		Serious		Study Drug Discontinuation		Death	
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)
Upper respiratory tract infections										
Upper respiratory tract infection	21 (7.9)	15 (5.6)	1 (0.4)	4 (1.5)	2 (0.8)	0	0	0	0	0
Nasopharyngitis	12 (4.5)	7 (2.6)	0	0	0	0	0	0	0	0
Sinusitis	11 (4.2)	6 (2.2)	1 (0.4)	2 (0.7)	0	0	0	0	0	0
Rhinitis	5 (1.9)	3 (1.1)	0	0	0	0	0	0	0	0
Tonsillitis	5 (1.9)	0	1 (0.4)	0	0	0	0	0	0	0
Laryngopharyngitis	1 (0.4)	0	1 (0.4)	0	0	0	0	0	0	0
Pharyngitis bacterial	1 (0.4)	0	1 (0.4)	0	0	0	0	0	0	0
Pharyngotonsillitis	1 (0.4)	0	0	0	0	0	0	0	0	0
Viral pharyngitis	1 (0.4)	0	0	0	0	0	0	0	0	0
Herpes infections										
Oral herpes	18 (6.8)	12 (4.5)	2 (0.8)	2 (0.7)	1 (0.4)	1 (0.4)	0	0	0	0
Herpes zoster	10 (3.8)	4 (1.5)	5 (1.9)	1 (0.4)	5 (1.9)	1 (0.4)	0	0	0	0
Herpes virus infection	5 (1.9)	2 (0.7)	1 (0.4)	0	0	0	0	0	0	0
Herpes simplex	3 (1.1)	4 (1.5)	0	0	0	0	0	0	0	0
Human herpesvirus 6 infection	1 (0.4)	0	0	0	0	0	0	0	0	0
Genital herpes	0	2 (0.7)	0	1 (0.4)	0	1 (0.4)	0	0	0	0

Preferred Term	Overall		Grade ≥3		Serious		Study Drug Discontinuation		Death	
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)
Fungal infections										
Oral candidiasis	11 (4.2)	9 (3.4)	1 (0.4)	1 (0.4)	0	0	0	0	0	0
Bronchopulmonary aspergillosis	8 (3.0)	2 (0.7)	4 (1.5)	1 (0.4)	1 (0.4)	0	0	0	0	0
Fungal infection	3 (1.1)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	0	0	0	0
Vulvovaginal candidiasis	3 (1.1)	1 (0.4)	1 (0.4)	0	0	0	0	0	0	0
Aspergillus infection	2 (0.8)	2 (0.7)	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	0	0
Candida infection	2 (0.8)	1 (0.4)	0	0	0	0	0	0	0	0
Fungal skin infection	2 (0.8)	0	0	0	0	0	0	0	0	0
Lower respiratory tract infection fungal	2 (0.8)	2 (0.7)	1 (0.4)	2 (0.7)	1 (0.4)	0	0	0	0	0
Mucormycosis	2 (0.8)	0	2 (0.8)	0	2 (0.8)	0	2 (0.8)	0	2 (0.8)	0
Oral fungal infection	2 (0.8)	2 (0.7)	0	0	0	0	0	0	0	0
Oropharyngeal candidiasis	2 (0.8)	0	0	0	0	0	0	0	0	0
Aspergillosis oral	1 (0.4)	0	1 (0.4)	0	0	0	0	0	0	0
Hepatic infection fungal	1 (0.4)	0	1 (0.4)	0	0	0	0	0	0	0
Hepatosplenic candidiasis	1 (0.4)	0	1 (0.4)	0	1 (0.4)	0	0	0	0	0

Preferred Term	Overall		Grade ≥3		Serious		Study Drug Discontinuation		Death	
	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)	Quizartinib N = 265 n (%)	Placebo N = 268 n (%)
Bacteraemia										
Bacteraemia	16 (6.0)	6 (2.2)	10 (3.8)	6 (2.2)	2 (0.8)	1 (0.4)	0	0	0	0
Klebsiella bacteraemia	5 (1.9)	2 (0.7)	4 (1.5)	1 (0.4)	2 (0.8)	0	0	0	0	0
Staphylococcal bacteraemia	5 (1.9)	1 (0.4)	3 (1.1)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	0	0
Enterococcal bacteraemia	3 (1.1)	2 (0.7)	2 (0.8)	2 (0.7)	0	1 (0.4)	0	0	0	0
Streptococcal bacteraemia	3 (1.1)	0	2 (0.8)	0	0	0	0	0	0	0
Device related bacteraemia	2 (0.8)	1 (0.4)	0	1 (0.4)	0	0	0	0	0	0
Escherichia bacteraemia	2 (0.8)	1 (0.4)	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	0	0
Corynebacterium bacteraemia	1 (0.4)	0	1 (0.4)	0	0	0	0	0	0	0
Pseudomonal bacteraemia	1 (0.4)	0	1 (0.4)	0	1 (0.4)	0	0	0	0	0

AML = acute myeloid leukaemia; N = total number of subjects; n = number of subjects; SCS = Summary of Clinical Safety
Source: Module 5.3.5.3 SCS Tables 4.1.3, 4.1.5, 4.1.9, 4.1.11, and 4.1.13

Table Part II: Module SVII.10: Overall Summary of Adverse Drug Reactions of Infections in the 30 to 60 mg Group of the All Acute Myeloid Leukaemia Pool (Safety Analysis Set)

Preferred Term	All AML Pool Quizartinib 30 to 60 mg (N = 669)				
	Overall n (%)	Grade ≥3 n (%)	Serious n (%)	Study Drug Discontinuation n (%)	Death n (%)
Upper respiratory tract infections					
Upper respiratory tract infection	52 (7.8)	7 (1.0)	8 (1.2)	0	0
Sinusitis	26 (3.9)	6 (0.9)	3 (0.4)	1 (0.1)	1 (0.1)
Nasopharyngitis	23 (3.4)	0	0	0	0
Rhinitis	16 (2.4)	0	0	0	0
Tonsillitis	9 (1.3)	2 (0.3)	0	0	0
Laryngopharyngitis	1 (0.1)	1 (0.1)	0	0	0
Pharyngitis bacterial	1 (0.1)	1 (0.1)	0	0	0
Pharyngotonsillitis	1 (0.1)	0	0	0	0
Viral pharyngitis	1 (0.1)	0	0	0	0
Herpes infections					
Oral herpes	34 (5.1)	3 (0.4)	1 (0.1)	0	0
Herpes zoster	19 (2.8)	7 (1.0)	6 (0.9)	1 (0.1)	0
Herpes simplex	9 (1.3)	1 (0.1)	0	0	0
Herpes virus infection	5 (0.7)	1 (0.1)	0	0	0
Human herpesvirus 6 infection	2 (0.3)	0	0	0	0
Genital herpes	1 (0.1)	0	0	0	0
Fungal infections					
Oral candidiasis	24 (3.6)	1 (0.1)	0	0	0
Bronchopulmonary aspergillosis	10 (1.5)	6 (0.9)	3 (0.4)	0	1 (0.1)

Preferred Term	All AML Pool Quizartinib 30 to 60 mg (N = 669)				
	Overall n (%)	Grade ≥3 n (%)	Serious n (%)	Study Drug Discontinuation n (%)	Death n (%)
Candida infection	10 (1.5)	1 (0.1)	2 (0.3)	0	0
Fungal infection	7 (1.0)	4 (0.6)	0	0	0
Oral fungal infection	4 (0.6)	0	0	0	0
Aspergillus infection	3 (0.4)	3 (0.4)	2 (0.3)	0	0
Fungal skin infection	3 (0.4)	0	0	0	0
Vulvovaginal candidiasis	3 (0.4)	1 (0.1)	0	0	0
Hepatic infection fungal	2 (0.3)	2 (0.3)	1 (0.1)	0	0
Lower respiratory tract infection fungal	2 (0.3)	1 (0.1)	1 (0.1)	0	0
Mucormycosis	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Oropharyngeal candidiasis	2 (0.3)	0	0	0	0
Aspergillosis oral	1 (0.1)	1 (0.1)	0	0	0
Hepatosplenic candidiasis	1 (0.1)	1 (0.1)	1 (0.1)	0	
Bacteraemia					
Bacteraemia	28 (4.2)	21 (3.1)	10 (1.5)	0	0
Klebsiella bacteraemia	7 (1.0)	6 (0.9)	3 (0.4)	0	0
Staphylococcal bacteraemia	9 (1.3)	7 (1.0)	4 (0.6)	1 (0.1)	0
Enterococcal bacteraemia	5 (0.7)	4 (0.6)	0	0	0
Escherichia bacteraemia	5 (0.7)	3 (0.4)	1 (0.1)	0	0
Device related bacteraemia	4 (0.6)	2 (0.3)	1 (0.1)	0	0
Streptococcal bacteraemia	4 (0.6)	3 (0.4)	1 (0.1)	0	0
Pseudomonal bacteraemia	2 (0.3)	2 (0.3)	1 (0.1)	0	0
Corynebacterium bacteraemia	1 (0.1)	1 (0.1)	0	0	0

AML = acute myeloid leukaemia; N = total number of subjects; n = number of subjects; SCS = Summary of Clinical Safety
Source: Module 5.3.5.3 SCS Tables 4.1.3, 4.1.5, 4.1.9, 4.1.11, and 4.1.13

SVII.1.1.2.1.3. Bleeding

In Study AC220-A-U302, events of epistaxis were reported in 40 (15.1%) subjects in the quizartinib group and 29 (10.8%) in the placebo group were of Grade ≥3 in 3 (1.1%) and 1 (0.4%) subjects, respectively, and serious in only 1 (0.4%) subject in the quizartinib group (Module 5.3.5.3 SCS Tables 4.1.3, 4.1.5, and 4.1.11). There were no events of epistaxis associated with study drug discontinuation or with a fatal outcome (Module 5.3.5.3 SCS Tables 4.1.9 and 4.1.13).

In the 30 to 60 mg group of the All AML Pool, events of epistaxis were reported in 86 (12.9%) subjects, were of Grade ≥3 in 10 (1.5%) subjects, and serious in 1 (0.1%) subject (Module 5.3.5.3 SCS Tables 4.1.3, 4.1.5, and 4.1.11). There were no events of epistaxis associated with study drug discontinuation or with a fatal outcome (Module 5.3.5.3 SCS Tables 4.1.9 and 4.1.13).

SVII.1.1.2.2. Drug-Drug Interactions with QT Interval-Prolonging Drug

Dose-dependent QTc interval prolongation has been observed in human studies with quizartinib. Coadministration of quizartinib and other medications that prolong the QT interval on ECG may potentially increase the risk of subjects developing QTc interval prolongation.

In the 30 to 60 mg group of the All AML Pool, 599 (89.5%) subjects used at least 1 concomitant QT-prolonging medications with "known risk" according to the Arizona Center for Education and Research on Therapeutics at some point in the study. This suggests that subjects were able to tolerate concomitant therapy with drugs that are known to result in QT prolongation when considered essential for the care of the subjects.

Subgroup analysis by use of QT-prolonging medication showed that concomitant administration of QT-prolonging medications had no significant impact on the incidence of QT interval corrected by Fridericia's formula (QTcF) interval prolongation. In addition, concomitant administration of QT-prolonging drugs was not found to be a statistically significant covariate on baseline QTcF or maximum value of QTc changes (E_{max}) in a concentration-QTc model (Module 2.7.2 Section 3.4.2.1).

Serious ADRs related to QTc interval prolongation are an important identified risk for quizartinib, which is appropriately communicated in the SmPC. The potential for DDI with other QT-interval prolonging drugs is described in Section 4.5 of the SmPC, Interaction with other medicinal products and other forms of interaction.

Section 4.4 of the SmPC, Warnings and precautions for use includes recommendation that patients should be monitored more frequently with ECG if coadministration of VANFLYTA with medicinal products known to prolong the QT interval is required. No additional risk minimisation measures are proposed for this risk, and it will be evaluated and monitored as a part of the evaluation of the main risk of serious ADRs related to QTc interval prolongation. Risk minimisation measures for the main risk of serious ADRs related to QTc interval prolongation are discussed in Section Part V.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

The list of all quizartinib ADRs is included in Section 4.8 of the SmPC. The risks considered important identified and important potential risks for risk management planning are included in the sections below.

Important identified risks include serious ADRs related to QTc interval prolongation and increased incidence of ADRs due to DDI with strong CYP3A inhibitors. Important potential risks include embryo-foetal and reproductive toxicity.

Important Identified Risk 1: Serious ADRs Related to QTc Interval Prolongation
Frequency: In Study AC220-A-U302, TEAEs of ECG QT prolonged were reported in 36 (13.6%) subjects in the quizartinib group and 11 (4.1%) subjects in the placebo group. Events were of Grade ≥3 in 8 (3.0%) and 3 (1.1%) subjects in the quizartinib and placebo groups, respectively, and were serious in 1 (0.4%) subject in each treatment group. Treatment was interrupted for 7 (2.6%) subjects in the quizartinib group and 3 (1.1%) subjects in the placebo group, and discontinued for 2 (0.8%) subjects in the quizartinib group only. In the 30 to 60 mg group of the All AML Pool, TEAEs of ECG QT prolonged were reported in 133 (19.9%) subjects. Most subjects had events that were Grade 1 or Grade 2, 21 (3.1%) subjects had events of Grade ≥3, and 8 (1.2%) subjects had events reported as serious. The dose of quizartinib was interrupted for 21 (3.1%) subjects and discontinued for 4 (0.6%) subjects. In Study AC220-A-U302, treatment-emergent QTcF readings of >450 ms (Grade 1) were reported in 91 (34.3%) subjects in the quizartinib group and 48 (17.9%) subjects in the placebo group, readings of >480 ms (Grade 2) were reported in 20 (7.5%) subjects in the quizartinib group and 6 (2.2%) subjects in the placebo group, and readings of >500 ms (Grade 3) were reported in 6 (2.3%) subjects in the quizartinib group and 2 (0.7%) in the placebo group. In the 30 to 60 mg group of the All AML Pool, 284 (42.5%) subjects had a treatment-emergent QTcF reading of >450 ms, 75 (11.2%) subjects had a value >480 ms, and 17 (2.5%) subjects had a value >500 ms. In order to assess the frequency of torsade de pointes and arrhythmias potentially associated with QT prolongation, the Sponsor conducted an analysis of the pooled safety data from the AML groups, using the Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQ) torsade de pointes/QT prolongation (narrow and broad) plus the additional PTs of fall, presyncope, agonal rhythm, arrhythmia, cardiac flutter, paroxysmal arrhythmia, and death. In Study AC220-A-U302, 49 (18.5%) subjects in the quizartinib group and 30 (11.2%) subjects in the placebo group had at least 1 event in the torsade de pointes/QT prolongation SMQ; events were of Grade ≥3 in 18 (6.8%) in the quizartinib group and 8 (3.0%) subjects in the placebo group. The most frequently reported events (all grades) were ECG QT prolonged (36 [13.6%] and 11 [4.1%] subjects in the quizartinib and placebo groups, respectively), fall (5 [1.9%] and 7 [2.6%] subjects, respectively), syncope (7 [2.6%] and 5 [1.9%] subjects, respectively), and presyncope (4 [1.5%] and 7 [2.6%] subjects, respectively). In the 30 to 60 mg group of the All AML Pool, 173 (25.9%) subjects had at least 1 event in the torsade de pointes/QT prolongation SMQ, and 44 (6.6%) subjects had events of Grade ≥3. The most frequently reported events (all grades) were ECG QT prolonged (133 [19.9%] subjects), fall (25 [3.7%] subjects), syncope (20 [3.0%] subjects), and presyncope (10 [1.5%] subjects). At the recommended dosing regimen for the treatment of ND AML, ventricular arrhythmia events considered potentially associated with quizartinib included 2 cases of cardiac arrest with recorded ventricular

fibrillation (one with fatal outcome) in subjects with severe hypokalaemia, and 1 case of death (subject died in sleep with no cause identified). In total, 1 event of torsade de pointes occurred in the quizartinib development programme, at a dose higher than the currently proposed, and which occurred in a subject with additional risks factors (hypocalcaemia, sepsis with episodes of respiratory arrest, and underlying atrial fibrillation) for ventricular arrhythmia.
Seriousness: ECG QTc interval prolongation is an electrophysiological finding, generally without adverse clinical effect to the subject. QTc interval prolongation is a risk factor for the development of life-threatening or fatal cardiac arrhythmias (eg, torsade de pointes). The risk of QTc interval prolongation leading to clinically significant sequelae (ie, torsade de pointes) significantly increases when QTc interval is >500 ms. Torsade de pointes can be life-threatening or result in fatal cardiac arrest. When reported as an AE in the clinical studies with quizartinib, TEAEs of QTc interval prolongation have been mostly nonserious and of CTCAE Grade 1 and 2 severity. Most of the events in the torsade de pointes/QT prolongation SMQ were nonserious and resolved. In Study AC220-A-U302, 4 (1.5%) subjects in the quizartinib group and 2 (0.7%) subjects in the placebo group had serious events. Of the 4 serious events, cardiac arrest was reported in 2 (0.8%) subjects in the quizartinib group only. All other serious events were reported at most in 1 subject per treatment group: ECG QT prolonged (1 [0.4] subject in each treatment group), death and ventricular fibrillation (each in 1 [0.4%] subject in the quizartinib group). In the 30 to 60 mg group of the All AML Pool, a total of 20 (3.0%) subjects had serious events. The most frequently reported serious events were ECG QT prolonged (8 [1.2%] subjects) and syncope (6 [0.9%] subjects). Three (0.4%) subjects, of whom 2 in Study AC220-A-U302 (see above), had serious events of cardiac arrest (1 of the subjects also had a separate event of ventricular fibrillation reported), 1 (0.1%) subject had serious events of ventricular tachycardia, 1 (0.1%) subject had a serious event of fall, and 1 (0.1%) subject had a serious event of death. Two (0.3%) subjects had fatal events of cardiac arrest. Further details of these cases are available in Section SVII.3.1.
Risk-benefit impact: QTc interval prolongation is an ECG finding that is generally asymptomatic. However, QTc interval prolongation as a marker of impaired cardiac repolarisation and marked QTc prolongation is considered a potential risk factor for the development of severe or life-threatening cardiac arrhythmias. Severe or life-threatening arrhythmias could be associated with significant morbidity (hospitalisation, medical procedures, etc) and mortality. Torsade de pointes, although rare, is associated with a significant risk of sudden cardiac death. Monitoring of ECG and quizartinib dose modification is recommended to minimise the risk of the subject developing cardiac arrhythmias or torsade de pointes. The effects of QTc interval prolongation on individual quality of life were not assessed.

Important Identified Risk 2: Increased Incidence of ADRs due to DDI with Strong CYP3A Inhibitors
Frequency: Strong CYP3A inhibitors, such as azole antifungals, increase quizartinib plasma exposure by approximately 2-fold (see Section SVII.3.1). In the Phase 3 programme studies, quizartinib dose reduction for concomitant strong CYP3A4 inhibitor use was required. Data on the frequency of DDI between strong CYP3A inhibitors and quizartinib do not exist. The Sponsor has reviewed TEAE data from the AML Pool for concomitant use of strong CYP3A inhibitors. In the 30 to 60 mg group of the All AML Pool, 329 (49.2%) subjects took at least 1 strong CYP3A inhibitor concomitantly with quizartinib. A subgroup analysis of TEAEs did not reveal any notable differences in the types and overall frequency of TEAEs reported in subjects who concomitantly used a strong CYP3A4 inhibitor and those who did not. Concomitant use of strong CYP3A inhibitor was shown to be associated with a higher incidence of QTcF prolongation on ECG. The frequency of QTcF elevations >500 ms was observed in 11 (3.3%) subjects who concomitantly used strong CYP3A4 inhibitors and 6 (1.8%) subjects who did not. In addition, changes from Baseline in QTcF of >30 ms and >60 ms were reported in a higher proportion of subjects who concomitantly used strong CYP3A4 inhibitor compared with subjects who did not (203 [61.7%] vs. 185 [54.4%] and 43 [13.1%]) and 30 [8.8%] subjects, respectively).
Seriousness: DDIs with strong CYP3A inhibitors result in increased exposure to quizartinib and the likelihood of the subject experiencing AEs due to quizartinib. These can range from mild nonserious reactions to severe life-threatening or fatal events.
Risk-benefit impact: Increased exposure due to inhibition of quizartinib metabolism by strong CYP3A inhibitors can result in increased incidence of quizartinib toxicities, including QTc interval prolongation on ECG and torsade de pointes. Quizartinib dose should be reduced when used concomitantly with strong CYP3A inhibitors.

Potential risks considered important for inclusion in the list of safety concerns include embryo-foetal and reproductive toxicity.

Important Potential Risk 1: Embryo-Foetal and Reproductive Toxicity
Frequency: Nonclinical reproductive and developmental toxicity data for quizartinib are described in Table Part II: Module SII.1. Pregnancy was an exclusion criterion for the studies in the quizartinib clinical development programme. In addition, women of childbearing potential as well as male subjects were required to use reliable forms of contraception to prevent the occurrence of pregnancy or drug exposure to foetus. No pregnancy in a patient or female partner of a male patient treated with quizartinib occurred in the clinical development programme. No clinical data on the effect of quizartinib on fertility is available.
Seriousness: No pregnancy in a patient or female partner of a male patient treated with quizartinib occurred in the clinical development programme; however, any potential embryo-foetal or reproductive toxicity is expected to be serious.
Risk-benefit impact: Embryo-foetal toxicity due to quizartinib can result in foetal death or severe congenital abnormalities. Based on findings in animals, female and male fertility may be impaired with quizartinib treatment.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

In the sections below, safety data from the 30 to 60 mg group of the All AML Pool are presented as they provide an appropriate summary of the integrated safety profile at the target dosing regimen. Results from the other dose groups of the All AML Pool are discussed where relevant. Results from Study AC220-A-U302 are also presented where relevant.

SVII.3.1.1 Important Identified Risk: Serious ADRs Related to QTc Interval Prolongation

Risk groups or risk factors:

Quizartinib is known to be associated with dose-dependent prolongation of the QTc interval, which is a risk factor for the development of ventricular arrhythmias, including torsade de pointes.

Recognised risk factors for QTc prolongation include hypokalaemia, hypomagnesemia or hypocalcaemia, congenital long QT syndrome, concomitant use of anti-arrhythmic medicinal products or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Other risk factors include baseline QT prolongation, subclinical long QT syndrome, cardiac history (eg, congestive heart failure, bradycardia, myocardial infarction), the elderly, and the female population.

Individual patient risk factors for the development of torsade de pointes include congenital or acquired long QT syndrome, electrolyte abnormalities (hypokalaemia, hypomagnesemia, and hypocalcaemia), concomitant medications (eg, Class IA, Class IC, and Class III antiarrhythmic agents, phenothiazines, antiretroviral drugs, and tricyclic antidepressants), endocrine disorders, and cardiac disorders.

Strong CYP3A inhibitors, such as azole antifungals, increase quizartinib plasma exposure. QTc interval prolongation with quizartinib has been shown to be dose and concentration dependent, and increased exposure to quizartinib can result in higher incidence of QTc interval prolongation.

Characterisation of the risk:

Quizartinib is known to be associated with dose-dependent prolongation of the QTc interval that is substantially reduced and generally well managed at lower doses. The assessment of QTc prolongation in the clinical development programme evaluated TEAEs in the QT Prolongation/Torsade de Pointes SMQ plus additional selected PTs (fall, presyncope, agonal rhythm, arrhythmia, cardiac flutter, paroxysmal arrhythmia, and death) as well as QTcF interval data on ECG to provide the most comprehensive evaluation of the effect of quizartinib monotherapy on cardiac conduction.

In the 30 to 60 mg group of the All AML Pool, a total of 284 (42.5%) subjects had new QTcF values >450 ms and 17 (2.5%) subjects had new QTcF values >500 ms (Table Part II: Module SVII.11).

Table Part II: Module SVII.11: Summary of Electrocardiogram QTcF Intervals in Study AC220-A-U302 and in the 30 to 60 mg Group of the All Acute Myeloid Leukaemia Pool (Safety Analysis Set)

Maximum Postdose QTcF Interval Value (ms)	Study AC220-A-U302		All AML Pool Quizartinib 30 to 60 mg (N = 669) n (%)
	Quizartinib N = 265 n (%)	Placebo N = 268 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)
Increase >30 from Baseline	146 (55.1)	87 (32.5)	388 (58.0)
Increase >60 from Baseline	27 (10.2)	13 (4.9)	73 (10.9)

ECG = electrocardiogram; N = total number of subjects; n = number of subjects; QT = interval between the start of the Q wave and the end of the T wave; QTcF = QT interval corrected by Fridericia's formula; SCS = Summary of Clinical Safety

ECGs analysis is based on average of the triplicates (or multiple). Overall Baseline is defined as the last nonmissing value on or prior to the first dose date of study drug. Worst postbaseline value is summarised. Postbaseline is defined as occurring after first administration of study drug up to 30 days post last administration of study drug, including unscheduled visits. New implies a newly occurring ECG abnormality, which is defined as an abnormal ECG finding at postbaseline that is not present at Baseline.

Source: Module 5.3.5.3 SCS Table 7.1.1

Subgroup analysis of QT prolongation indicated that elevations >450 ms were more frequent in in females and subjects who used concomitant strong CYP3A inhibitors (Table Part II: Module SVII.12). 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. Similarly, concomitant administration of QT-prolonging medications had no significant impact on the incidence of QTcF interval prolongation. 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.

Table Part II: Module SVII.12: Electrocardiogram QTcF Data by Age, Sex, Strong Cytochrome P450 Inhibitor Use, and QT-prolonging Drug Use in the 30 to 60 mg Group of the All Acute Myeloid Leukaemia Pool (Safety Analysis Set)

	All AML Pool Quizartinib 30 to 60 mg n/N (%)			
	New >450 ms	New >480 ms	New >500 ms	Change from Baseline >60 ms
Age				
<60 years	167/401 (41.6)	38/401 (9.5)	8/401 (2.0)	40/401 (10.0)
60 to <65 years	40/81 (49.4)	12/81 (14.8)	4/81 (4.9)	15/81 (18.5)
65 to <75 years	66/164 (40.2)	18/164 (11.0)	4/164 (2.4)	15/164 (9.1)
≥75 years	11/23 (47.8)	7/23 (30.4)	1/23 (4.3)	3/23 (13.0)
Sex				
Male	104/319 (32.6)	29/319 (9.1)	7/319 (2.2)	18/319 (5.6)
Female	180/350 (51.4)	46/350 (13.1)	10/350 (2.9)	55/350 (15.7)
Concomitant use of QT-prolonging medication in AZCERT classification "known risk"				
Yes	257/599 (42.9)	68/599 (11.4)	15/599 (2.5)	69/599 (11.5)
No	27/70 (38.6)	7/70 (10.0)	2/70 (2.9)	4/70 (5.7)
Strong CYP3A inhibitor use				
Yes	139/329 (42.2)	39/329 (11.9)	11/329 (3.3)	43/329 (13.1)
No	145/340 (42.6)	36/340 (10.6)	6/340 (1.8)	30/340 (8.8)

AML = acute myeloid leukaemia; AZCERT = Arizona Center for Education and Research on Therapeutics; CYP = cytochrome P450; ECG = electrocardiogram; N = total number of subjects; n = number of subjects; QT = interval between the start of the Q wave and the end of the T wave; QTcF = QT interval corrected by Fridericia's formula; SCS = Summary of Clinical Safety

ECGs analysis is based on average of the triplicates (or multiple). Overall Baseline is defined as the last nonmissing value on or prior to the first dose date of study drug. Worst postbaseline value is summarised. Postbaseline is defined as occurring after first administration of study drug up to 30 days post last administration of study drug, including unscheduled visits.

New implies a newly occurring ECG abnormality, which is defined as an abnormal ECG finding at postbaseline that is not present at Baseline.

Source: Module 5.3.5.3 SCS Table 7.1.2

A model analysis of quizartinib concentration and QTc interval (C-QTc) on ECG was performed based on data from the pivotal Study AC220-A-U302.

In Study AC220-A-U302, a direct-response E_{max} model best described the C-QTcF relationship between quizartinib concentrations and QTcF. The median model-predicted ΔQTcF at C_{max} at steady state in subjects with ND AML in Study AC220-A-U302 during the Continuation Phase at 30 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 hypokalaemia, serum calcium and magnesium concentrations, age, body weight, sex, race, and use of QT-prolonging drugs, beta-blocker drugs and anthracycline. Age and hypokalaemia had an effect on the baseline QTcF. The covariate analysis on the drug effect model identified age, concurrent daunorubicin use, hypokalaemia, and calcium levels as statistically significant covariates on E_{max}. However, interindividual variability on E_{max} was increased after including the covariate effects, and these effects were not seen in the graphical analysis. In addition, age, daunorubicin use, and hypokalaemia effects were estimated with high uncertainty with relative standard error >34%. As a result, these covariate effects were not retained in the model. The remaining covariates had no effect on the baseline QTcF (Module 5.3.3.5 Exposure-response Report AC220-PMx010).

To further evaluate concomitant use of QT-prolonging medications with quizartinib, an additional evaluation was conducted using data from subjects who had matched concentrations and ECG measurements during the time of concomitant administration of QT-prolonging medications and during the time when those same subjects were not taking QT-prolonging medication. A within-subject analysis of the C-QTcF relationship in the presence and absence of QT-prolonging medications showed that concomitant administration of QT-prolonging medications had no impact on the observed QTcF increases associated with quizartinib concentrations (Module 2.7.2 Section 3.4.2.1).

In the 30 to 60 mg group of the All AML Pool, cardiac events potentially associated with QT prolongation were reported in 173 (25.9%) subjects (Module 5.3.5.3 SCS Table 4.1.27). Most subjects had events that were Grade 1 or Grade 2, 44 (6.6%) subjects had events of Grade ≥3, and 20 (3.0%) subjects had an event that was reported as serious. The dose of quizartinib was interrupted for 21 (3.1%) subjects and discontinued for 7 (10%) subjects due to cardiac events potentially associated with QTc interval prolongation.

The most common TEAEs in this category were events of ECG QT prolonged. A dose-dependent trend in events of ECG QT prolonged was observed with the highest incidence in the >60 mg group of the All AML Pool (Table Part II: Module SVII.13). The other common TEAEs identified by this MedDRA search included fall, syncope, and presyncope (Table Part II: Module SVII.13). On individual case review, these events had alternative aetiologies present, such as infections, vasovagal reaction, anaemia, and orthostatic hypotension; none of these events were associated with any evidence of ventricular arrhythmia as a cause of the event.

The incidence of ventricular arrhythmia was low at the recommended dose level. In Study AC220-A-U302, 2 subjects experienced treatment-emergent serious adverse events (TESAEs) of cardiac arrest (1 with fatal outcome) that were associated with recorded ventricular fibrillation on ECG (reported as a separate TEAE for 1 of the subjects) and occurred in the context of Grade 3 or 4 hypokalaemia. An additional subject 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 (Module 5.3.5.1 AC220-A-U302 CSR Section 10.4.1).

In addition to the above cases a comprehensive review of all potential cardiac arrhythmia events from the entire quizartinib development program revealed a single case of non-sustained torsade de pointes and 1 additional case of cardiac arrest, both of which occurred at higher quizartinib doses in subjects with some evidence of QTcF prolongation prior to the event. The event of non-sustained torsade de pointes occurred in a subject receiving quizartinib 90 mg with QTcF

prolongation (543 ms) at the time of 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 (Module 2.7.4 Section 2.1.5.4.1).

Table Part II: Module SVII.13: Treatment-emergent Adverse Events Identified by the QT Prolongation/Torsade de Pointes SMQ Search in Study AC220-A-U302 and in the All Acute Myeloid Leukaemia Pool

Preferred Term	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 identified events	**49 (18.5)**	**30 (11.2)**	**3 (10.0)**	**173 (25.9)**	**124 (32.5)**	**300 (27.8)**
ECG QT prolonged	36 (13.6)	11 (4.1)	3 (10.0)	133 (19.9)	106 (27.7)	242 (22.4)
Fall	5 (1.9)	7 (2.6)	0	25 (3.7)	8 (2.1)	33 (3.1)
Syncope	7 (2.6)	5 (1.9)	0	20 (3.0)	9 (2.4)	29 (2.7)
Presyncope	4 (1.5)	7 (2.6)	0	10 (1.5)	3 (0.8)	13 (1.2)
Cardiac arrest	2 (0.8)	0	0	3 (0.4)	3 (0.8)	6 (0.6)
Ventricular tachycardia	1 (0.4)	1 (0.4)	0	3 (0.4)	2 (0.5)	5 (0.5)
Loss of consciousness	1 (0.4)	1 (0.4)	0	2 (0.3)	1 (0.3)	3 (0.3)
Arrhythmia	0	0	0	0	2 (0.5)	2 (0.2)
Death	1 (0.4)	0	0	1 (0.1)	1 (0.3)	2 (0.2)
Cardio-respiratory arrest	0	0	0	0	1 (0.3)	1 (<0.1)
ECG QT interval abnormal	1 (0.4)	0	0	1 (0.1)	0	1 (<0.1)
Torsade de pointes	0	0	0	0	1 (0.3)	1 (<0.1)
Ventricular fibrillation	1 (0.4)	0	0	1 (0.1)	0	1 (<0.1)
Ventricular arrhythmia	0	1 (0.4)	0	0	0	0

AML = acute myeloid leukaemia; ECG = electrocardiogram; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects; QT = interval between the start of the Q wave and the end of the T wave; SCS = Summary of Clinical Safety; SMQ = Standardised MedDRA Queries

Percentage is calculated using number of subjects in the column heading as denominator. Adverse events were coded using the MedDRA version 24.0.

Source: Module 5.3.5.3 SCS Table 4.1.28

Potential mechanisms:

Blockade of I_{Ks} currents by quizartinib and its metabolite AC886 decreases the net repolarisation currents and prolongs cardiac repolarisation.

Preventability:

The risk of torsade de pointes with quizartinib is associated with its effect of prolonging cardiac repolarisation, manifested by prolongation of QTc interval on ECG. The risk of QTc interval prolongation leading to clinically significant sequelae (ie, torsade de pointes) significantly increases when QTc interval is >500 ms. Correspondingly, the measures to prevent QTc interval prolongation also apply to the risk of torsade de pointes.

The following recommendations are included in the SmPC:

- VANFLYTA should be initiated only if QTcF interval is <450 ms
- VANFLYTA is contraindicated in subjects with congenital long QT syndrome
- VANFLYTA should be used with caution in patients who are at a significant risk of developing QTc interval prolongation.
- The dose of VANFLYTA should be reduced when used concomitantly with strong CYP3A inhibitors as they may increase quizartinib exposure.
- Monitoring and correction of hypokalaemia and hypomagnesemia should be performed prior to and during treatment with VANFLYTA. More frequent monitoring of electrolytes and ECGs should be performed in patients who experience diarrhoea or vomiting.
- Patients should be monitored more frequently with ECG during coadministration of VANFLYTA with drugs known to prolong the QT interval.
- Quizartinib dose should be reduced for subjects with QTcF >480 ms. For subjects with QTcF >501 ms, quizartinib should be interrupted and restarted at a reduced dose when QTcF interval returns to <450 ms.
- Following dose initiation and escalation, ECGs should be performed at least once weekly for 2 weeks then as clinically indicated. ECG monitoring of the QT interval should be performed more frequently in patients who are at significant risk of developing QTc interval prolongation and torsade de pointes.
- VANFLYTA should be permanently discontinued in patients who develop recurrent QTcF ≥501 ms or torsade de pointes, polymorphic ventricular tachycardia or signs or symptoms of life-threatening arrhythmia.

For further details see SmPC Section 4.4.

Impact on the risk-benefit balance of the product:

QTc interval prolongation is an ECG finding that is generally asymptomatic. Data from the quizartinib clinical development programme indicate that significant QTc interval prolongation (eg, Grade ≥3) occurs infrequently at the proposed dose of 35.4 to 53 mg QD. The risk of QTc interval prolongation leading to clinically significant sequelae (ie, torsade de pointes)

significantly increases when QTc interval is >500 ms. QTc interval prolongation in patients receiving quizartinib can be effectively managed by dose reduction or interruption, serum electrolyte abnormalities management, and avoidance if possible, of the use of concomitant QT interval-prolonging drugs.

QTc interval prolongation as a marker of impaired cardiac repolarisation and marked QTc prolongation is a potential risk factor for the development of severe or life-threatening cardiac arrhythmias that could be associated with significant morbidity (hospitalisation, medical procedures, etc.) and mortality. Torsade de pointes is associated with a significant risk of sudden cardiac death. Torsade de pointes and other ventricular arrhythmias have been infrequently reported in the quizartinib clinical development programme. Monitoring of ECG and quizartinib dose modification is recommended to minimise the risk of the subject developing cardiac arrhythmias or torsade de pointes. The occurrence of torsade de pointes in a subject treated with quizartinib would require discontinuation of quizartinib therapy.

Potential public health impact:

Rough estimates of the size of the target population of patients with ND AML, which is *FLT3*-ITD positive, are available. The estimated size of the population expected to be treated with quizartinib is approximately 520 subjects per year in the 5 largest EU Member States (Germany, France, UK, Spain, and Italy), approximately 620 subjects per year in the US, and approximately 300 subjects per year in Japan.

Quizartinib is associated with the development of dose-dependent QTc interval prolongation, which is a risk factor for torsade de pointes. Significant QTc interval prolongation (ie, QTcF >500 ms) occurred in 2.5% of subjects receiving quizartinib at doses 30 to 60 mg of daily. There were no cases of torsade de pointes at the recommended quizartinib doses, and cardiac arrest/ventricular fibrillation occurred in <1% of subjects in the All AML Pool.

The requirement for ECG monitoring for QTc interval prolongation to prevent the development of torsade de pointes will represent an additional burden on the health system. The occurrence of acute cardiac arrhythmias such as torsade de pointes may have a short-term public health impact in terms of increased demand for emergency cardiac resuscitation. This public health impact is expected to be offset by improved patient outcomes and reduced complications from ND AML.

Evidence source(s) and strength of evidence:

Dose-dependent QTc prolongation was observed in the clinical development programme. Approximately 20% of subjects had TEAEs of ECG QT prolonged; however, most of these cases were mild and were manageable with dose modification or electrolyte correction, and very few events were serious or led to study drug discontinuation. QTc interval prolongation is a risk factor for the development of severe or life-threatening cardiac arrhythmias, including torsade de pointes, which is associated with a significant risk of sudden cardiac death. Torsade de pointes or other ventricular arrhythmias have been infrequently reported with the recommended quizartinib dosing regimen with QTc-based dose modification.

SVII.3.1.2 Important Identified Risk: Increased Incidence of ADRs due to DDI with Strong CYP3A Inhibitors

Risk groups or risk factors:

No specific risk factors are identified.

Characterisation of the risk:

For quizartinib, both the parent and the active metabolite (AC886) are metabolised by CYP3A. Therefore, strong CYP3A inhibitors, such as azole antifungals, increase quizartinib plasma exposure. Increased exposure of quizartinib may result in an increase in the adverse effects of quizartinib.

In a DDI study in healthy volunteers, concomitant use of quizartinib with ketoconazole, a strong CYP3A inhibitor, increased the exposure of quizartinib and its active metabolite AC886 compared to the use of quizartinib alone. Coadministration of ketoconazole (200 mg twice daily for 28 days) with single-dose administration of quizartinib resulted in increased C_{max} by 17% and AUC_{inf} by 94%. At steady state, exposure (C_{max} and area under the plasma concentration-time curve from time 0 to 24 h [AUC_{0-24h}]) was estimated to be increased by 86% and 96%, respectively. In the DDI study with fluconazole, a moderate CYP3A inhibitor, the predicted C_{max} and AUC at steady state were approximately 20% higher.

The Sponsor has reviewed TEAE data from the All AML Pool for concomitant use of strong CYP3A inhibitors. In the 30 to 60 mg group of the All AML Pool, 329 (49.2%) subjects concomitantly used at least 1 strong concomitant CYP3A during the study (Module 5.3.5.3 SCS Table 3.1.3). Within this subgroup, some differences in the incidence of events in the following categories were observed when comparing subjects who concomitantly used a strong CYP3A inhibitor (n = 329) and those who did not (n = 340; Module 5.3.5.3 SCS Table 4.1.2):

- The incidence of Grade ≥3 TEAEs, TESAEs (overall and study drug-related), and TEAEs associated with study drug interruption were reported more frequently (>5 pp higher incidence) in subjects who used strong CYP3A4 inhibitors than those who did not.

Despite these differences, the types and frequencies of TEAEs and those identified by the SMQ searches were generally consistent between subjects who used strong CYP3A inhibitors and those who did not (Module 5.3.5.3 SCS Table 4.1.15).

In a categorical summary of QT/QTcF elevations by concomitant use of strong CYP3A inhibitors in the 30 to 60 mg group of the All AML Pool, a QTcF of >500 ms was observed in 11 (3.3%) subjects who concomitantly used strong CYP3A inhibitors and 6 (1.8%) subjects who did not. A higher percentage of subjects had change from Baseline in QTcF of >30 ms (203 [61.7%] subjects and 185 [54.4%] subjects, respectively) and QTcF of >60 ms (43 [13.1%]) and 30 [8.8%] subjects, respectively). No other trends in ECG findings among subgroups could be identified (Module 5.3.5.3 SCS Table 7.1.2).

Potential mechanisms:

The mechanism for this risk is reduced metabolism of quizartinib due to CYP3A inhibition.

Preventability:

Adverse effects resulting from DDI can be prevented by appropriate restriction on the use of concomitant interacting drugs, as well as quizartinib dose reduction if concomitant use of a strong CYP3A inhibitor is required (see Section 4.5 of the SmPC, "*Interaction with other medicinal products and other forms of interaction*").

Impact on the risk-benefit balance of the product:

Increased exposure due to inhibition of quizartinib metabolism by strong CYP3A inhibitors can result in an increased incidence of quizartinib toxicities, including QTc interval prolongation on ECG and torsade de pointes. In the event that use of a strong CYP3A inhibitor is required, appropriate dose reductions of quizartinib should be undertaken to decrease the risk of subjects experiencing quizartinib-associated toxicities.

Potential public health impact:

Rough estimates of the size of the target population of patients with ND AML, which is *FLT3*-ITD positive, are available. The estimated size of the population expected to be treated with quizartinib is approximately 520 subjects per year in the 5 largest EU Member States (Germany, France, UK, Spain, and Italy), approximately 620 subjects per year in the US, and approximately 300 subjects per year in Japan.

No estimates of the absolute risk of increased incidence of ADRs due to DDI with strong CYP3A inhibitors are available.

Serum level monitoring of quizartinib is not required during concomitant use of strong CYP3A inhibitors. Public health impact is anticipated mainly from quizartinib toxicity due to higher quizartinib exposure, which can be severe or life-threatening and requires hospitalisation and potentially significant diagnostic and treatment efforts, thereby adding burden to the healthcare system. This public health impact is expected to be offset by improved patient outcomes and reduced complications from ND AML.

Evidence source(s) and strength of evidence:

Concomitant use of quizartinib with a strong CYP3A inhibitor increased the exposure of quizartinib and its active metabolite AC886 compared to the use of quizartinib alone in healthy volunteers. Coadministration of ketoconazole (200 mg twice daily for 28 days) with single-dose administration of quizartinib resulted in increased C_{max} by 17% and AUC_{inf} by 94%. At steady state, exposure (C_{max} and AUC_{0-24h}) was estimated to be increased by 86% and 96%, respectively. Increased quizartinib exposure may increase the risk of toxicity.

SVII.3.1.3 Important Potential Risk: Embryo-Foetal and Reproductive Toxicity

Risk groups or risk factors:

No specific risk factors have been identified.

Characterisation of the risk:

Nonclinical reproductive and developmental toxicity data for quizartinib are described in Table Part II: Module SII.1.

Pregnancy was an exclusion criterion for the studies in the quizartinib clinical development programme. In addition, women of childbearing potential as well as male subjects were required to use reliable forms of contraception to prevent the occurrence of pregnancy or drug exposure to foetus. No pregnancy in a patient or female partner of a male patient treated with quizartinib occurred in the clinical development programme.

Potential mechanisms:

The mechanism of this toxicity is unknown.

Preventability:

Data on the preventability of the risk to fertility are not available. The risk of embryo-foetal toxicity can be prevented by measures to prevent occurrence of pregnancy during quizartinib therapy or drug exposure to quizartinib during pregnancy, and the risk of infant exposure during breastfeeding can be prevented by measures to avoid breastfeeding during quizartinib therapy (see SmPC Section 4.4, "*Special warnings and precautions for use*" and SmPC Section 4.6, *"Fertility, Pregnancy, and Lactation*").

Impact on the risk-benefit balance of the product:

Embryo-foetal toxicity due to quizartinib can result in foetal death or severe congenital abnormalities. The risks to the foetus should be weighed against the benefits of treatment in patients.

Based on findings in animals, female and male fertility may be impaired with treatment with quizartinib.

Potential public health impact:

Rough estimates of the size of the target population of patients with ND AML, which is *FLT3*-ITD positive, are available. The estimated size of the population expected to be treated with quizartinib is approximately 520 subjects per year in the 5 largest EU Member States (Germany, France, UK, Spain, and Italy), approximately 620 subjects per year in the US, and approximately 300 subjects per year in Japan.

No estimates of the absolute risk of embryo-foetal or reproductive toxicity are available.

In the short term, public health impact is expected to arise through the need for hospitalisation, potentially significant diagnostic and treatment efforts, antenatal and postnatal care for women, and children exposed to quizartinib during pregnancy. In the long term, outcomes of significant permanent disabilities due to congenital abnormalities will impact public health with a need for rehabilitation and nursing support. Impaired fertility due to previous quizartinib treatment may result in requirement for infertility treatment in the affected patients.

Evidence source(s) and strength of evidence:

Based on findings in animals, quizartinib may cause embryo-foetal harm when administered to a pregnant woman. No cases of embryo-foetal toxicity were observed in the clinical development programme.

Based on findings in animals, female and male fertility may be impaired with quizartinib treatment.

SVII.3.2 Presentation of Missing Information

Not applicable.

PART II: MODULE SVIIISUMMARY OF THE SAFETY CONCERNS

The safety concerns for quizartinib are presented in Table Part II: Module SVIII.1.

Table Part II: Module SVIII.1: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Serious ADRs related to QTc interval prolongation Increased incidence of ADRs due to DDI with strong CYP3A inhibitors
Important potential risks	Embryo-foetal and reproductive toxicity
Missing information	Not applicable

ADR = adverse drug reaction; CYP = cytochrome P450; DDI = drug-drug interaction; QT = interval between the start of the Q wave and the end of the T wave; QTc = corrected QT interval

PART III PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Not applicable.

III.2 Additional Pharmacovigilance Activities

Table Part III.1: Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.2: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities, which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities, which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

Not applicable.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

All identified and potential safety concerns with quizartinib will be managed with routine risk minimisation activities, that is, the warnings and precaution information contained within the product information and package leaflet, and will be discussed in aggregate safety reports. For each of the identified and potential safety concerns, in the context of observed efficacy in the target indication (ie, ND *FLT3*-ITD positive AML), the Investigator's Brochure, the proposed SmPC, and package leaflet will be used to communicate and manage risk. These safety reference documents will be periodically reviewed and updated in accordance with updated safety specifications and required action plans.

For the important identified risk of serious ADRs related to QTc interval prolongation, the Applicant is proposing additional risk minimisation measures in the form of a Healthcare Professional (HCP) Guide and a Patient Card (PC) (see Section Part IV:V.2 for details).

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Important Identified Risks	
Safety concern	**Routine risk minimisation activities**
Serious ADRs related to QTc interval prolongation	Contraindication in SmPC Section 4.3 for subjects with congenital long QT syndrome. Inclusion in the list of ADRs in Section 4.8 of the SmPC. Warning in Section 4.4 of the SmPC with specific information on ECG monitoring, discontinuation, and/or reversibility. Dose adjustment guidelines in Section 4.2 of the SmPC. Guidance on correction of electrolyte imbalance is described in Section 4.4 of the SmPC.
Increased incidence of ADRs due to DDI with strong CYP3A inhibitors	Recommendations for quizartinib dose adjustment if concomitant use of strong CYP3A inhibitors is described in Section 4.2 of the SmPC. Information on DDIs in Section 4.5 of the SmPC.
Important Potential Risks	
Safety concern	**Routine risk minimisation activities**
Embryo-foetal and reproductive toxicity	Warning in Section 4.4 of the SmPC Information on risk of embryo-foetal and reproductive toxicity in Section 4.6 of the SmPC.
Missing information	
Not applicable	

ADR = adverse drug reaction; CYP = cytochrome P450; DDI=drug-drug interaction; ECG = electrocardiogram; QT = interval between the start of the Q wave and the end of the T wave; QTc = corrected QT interval; SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimisation Measures

For the important identified risk of serious ADRs related to QTc interval prolongation , additional risk minimisation measures of an HCP Guide and a PC are proposed. The proposed draft key messages of the additional risk minimisation activities are provided in Annex 6.

Additional risk minimisation 1: HCP Guide

Objectives:

The objective of the HCP Guide is to reinforce prescriber's awareness about the risk of serious ADRs related to QTc interval prolongation and the risk minimisation measures included in the quizartinib SmPC by providing HCPs with a reference guide about appropriate monitoring of QTc prolongation, how to appropriately interrupt or reduce the dose of quizartinib, and manage other risk factors for QTc prolongation, such as serum electrolyte abnormalities and concomitant QT-prolonging medications.

Rationale for the additional risk minimisation activity:

A concise and easy-to-use reminder/reference material in the form of a 1-page HCP reference guide will improve the adherence to the key risk minimisation measures for the risk of serious ADRs related to QTc interval prolongation.

Target audience and planned distribution path:

The target audience of the HCP will be prescribers of quizartinib. All potential prescribers will be provided with the HCP Guide to keep and use as a reminder/quick reference material on initial placement on the product on the market, with periodic redistribution.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The Applicant will track and analyse the distribution rates of the HCP Guide among prescribers of VANFLYTA. The incidence of serious ADRs related to QTc interval prolongation in the postmarketing setting using routine pharmacovigilance activities will be evaluated and reported in each Periodic Safety Update Report.

Additional risk minimisation 2: PC

Objectives:

The objective of the PC is intended to ensure that special information regarding VANFLYTA and the risk of serious ADRs related to QTc interval prolongation is held by the patient at all times and reaches the relevant HCP as appropriate. The PC will notify the patient, caregiver, or other treating HCP of the risk of serious ADRs related to QTc interval prolongation, its signs and symptoms and the appropriate actions to be taken to prevent the occurrence of the risk.

Rationale for the additional risk minimisation activity:

HCPs who are not prescribers of VANFLYTA should be informed of the risk minimisation measures for VANFLYTA that impact on their clinical practice (eg, the risk of DDI with strong CYP3A inhibitors or medications with a QT-prolonging effect). Patients/caregivers should be informed about the signs or symptoms of serious ADRs related to QTc interval prolongation and when to seek attention from an HCP.

Target audience and planned distribution path:

The target audience of the PC will be patients receiving VANFLYTA and caregivers, and other treating HCPs providing care for the patient. A key design feature of the PC will be the ability to carry the PC with ease (ie, it can fit in a wallet). The PC will be included in each product pack.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The incidence of serious ADRs related to QTc interval prolongation in the postmarketing setting using routine pharmacovigilance activities will be evaluated and reported in each Periodic Safety Update Report.

V.3 Summary of Risk Minimisation Measures

Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious ADRs related to QTc interval prolongation	Routine risk minimisation measures: Contraindication in SmPC Section 4.3 for subjects with congenital long QT syndrome. Inclusion in the list of ADRs in Section 4.8 of the SmPC. Warning in Section 4.4 of the SmPC with specific information on ECG monitoring, discontinuation, and/or reversibility. Dose adjustment guidelines in Section 4.2 of the SmPC. Guidance on correction of electrolyte imbalance is described in Section 4.4 of the SmPC. Additional risk minimisation measures: HCP Guide to reinforce prescriber's awareness about the risk of serious ADRs related to QTc interval prolongation and the risk minimisation measures. PC to ensure that special information regarding VANFLYTA and the risk of serious ADRs related to QTc interval prolongation is held by the patient at all times and reaches the relevant HCP as appropriate.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Increased incidence of ADRs due to DDI with strong CYP3A inhibitors	Routine risk minimisation measures: Recommendations for quizartinib dose adjustment if concomitant use of strong CYP3A inhibitors is described in Section 4.2 of the SmPC. Information on DDIs in Section 4.5 of the SmPC. No additional risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Embryo-foetal and reproductive toxicity	Routine risk minimisation measures: Warning in Section 4.4 of the SmPC Information on risk of embryo-foetal and reproductive toxicity in Section 4.6 of the SmPC. No additional risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

ADR = adverse drug reaction; CYP = cytochrome P450; DDI = drug-drug interaction; HCP = healthcare professional; QT = interval between the start of the Q wave and the end of the T wave; QTc = corrected QT interval; SmPC = Summary of Product Characteristics

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR VANFLYTA (QUIZARTINIB DIHYDROCHLORIDE)

This is a summary of the RMP for VANFLYTA. The RMP details important risks of VANFLYTA and how these risks can be minimised.

VANFLYTA's SmPC and its package leaflet give essential information to HCPs and patients on how VANFLYTA should be used.

This summary of the RMP for VANFLYTA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of VANFLYTA's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

VANFLYTA is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by VANFLYTA single agent maintenance therapy for adult patients with ND AML that is *FLT3*-ITD positive (see SmPC Section 4.1 for the full indication). It contains quizartinib as the active substance, and it is given by oral administration.

Quizartinib is a potent oral second-generation Class III receptor tyrosine kinase inhibitor with potent activity against FLT3 both in vitro and in vivo. FLT3 is expressed in blood-forming precursor cells, and signalling through FLT3 promotes these cells' proliferation and differentiation. *FLT3* is mutated in approximately 30% of subjects with AML; the mutations include ITD of the juxtamembrane domain of FLT3 and point mutations, usually in the kinase domain. Both types of mutations activate FLT3 and contribute to leukaemic transformation of blood-forming cells. Quizartinib selectively inhibits survival pathways that block cell death by

inhibiting FLT3 receptor signalling. Quizartinib thus inhibits proliferation of FLT3-dependent cell lines.

Further information about the evaluation of VANFLYTA's benefits can be found in VANFLYTA's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of VANFLYTA, together with measures to minimise such risks and the proposed studies for learning more about VANFLYTA risks, are outlined below.

- Measures to minimise the risks identified for medicinal products can be the following:
  - Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs.
  - Important advice on the medicine's packaging.
  - The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
  - The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of VANFLYTA, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of VANFLYTA is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of VANFLYTA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of VANFLYTA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table II.1: List of Important Risks and Missing Information

Important identified risks	• Serious ADRs related to QTc interval prolongation • Increased incidence of ADRs due to DDI with strong CYP3A inhibitors
Important potential risks	• Embryo-foetal and reproductive toxicity
Missing information	Not applicable.

ADR = adverse drug reaction; CYP = cytochrome P450; DDI = drug-drug interaction; QT = interval between the start of the Q wave and the end of the T wave; QTc = corrected QT interval

II.B Summary of Important Risks

Important identified risks include QTc interval prolongation/torsade de pointes, DDIs with strong CYP3A inhibitors, and DDIs with strong or moderate CYP3A inducers. Important potential risks considered important for inclusion in the list of safety concerns include embryo-foetal and reproductive toxicity.

Important Identified Risk 1: Serious ADRs Related to QTc Interval Prolongation	
Evidence for linking the risk to the medicine	Dose dependent QTc prolongation was observed in the clinical development programme; QTcF prolongation was observed more frequently at quizartinib doses >60 mg. Approximately 28% of subjects had TEAEs of ECG QT prolonged; however, most of these cases were mild and were manageable with dose modification or electrolyte correction, and very few events were serious or led to study drug discontinuation. QTc interval prolongation is a risk factor for the development of severe or life-threatening cardiac arrhythmias, including torsade de pointes, which is associated with a significant risk of sudden cardiac death. Torsade de pointes or other ventricular arrhythmias have been infrequently reported in the quizartinib clinical development programme.
Risk factors and risk groups	Recognised risk factors for QTc prolongation include hypokalaemia, hypomagnesemia or hypocalcaemia, congenital long QT syndrome, concomitant use of antiarrhythmic medicinal products or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Other risk factors include baseline QT prolongation, subclinical long QT syndrome, cardiac history (eg, congestive heart failure, bradycardia, myocardial infarction), the elderly, and the female population. Individual patient risk factors for the development of torsade de pointes include congenital or acquired long QT syndrome, electrolyte abnormalities (hypokalaemia, hypomagnesemia, and hypocalcaemia), concomitant medications (eg, Class IA, Class IC, and Class III antiarrhythmic agents, phenothiazines, antiretroviral drugs, and tricyclic antidepressants), endocrine disorders, and cardiac disorders. Strong CYP3A inhibitors, such as azole antifungals, increase quizartinib plasma exposure. QTc interval prolongation has been shown to be dose and concentration dependent, and increased exposure

Important Identified Risk 1: Serious ADRs Related to QTc Interval Prolongation	
	to quizartinib can result in higher incidence of QTc interval prolongation.
Risk minimisation measures	Routine risk minimisation measures: Contraindication in SmPC Section 4.3 for subjects with congenital long QT syndrome. Inclusion in the list of ADRs in Section 4.8 of the SmPC. Warning in Section 4.4 of the SmPC with specific information on ECG monitoring, discontinuation, and/or reversibility. Dose adjustment guidelines in Section 4.2 of the SmPC. Guidance on correction of electrolyte imbalance is described in Section 4.4 of the SmPC. Additional risk minimisation measures: HCP Guide to reinforce prescriber's awareness about the risk of serious ADRs related to QTc interval prolongation and the risk minimisation measures. PC to ensure that special information regarding VANFLYTA and the risk of serious ADRs related to QTc interval prolongation is held by the patient at all times and reaches the relevant HCP as appropriate.

Important Identified Risk 2: Increased Incidence of ADRs due to DDI with Strong CYP3A Inhibitors	
Evidence for linking the risk to the medicine	Concomitant use of quizartinib with a strong CYP3A inhibitor increased the exposure of quizartinib and its active metabolite AC886 compared to the use of quizartinib alone in healthy volunteers. Coadministration of ketoconazole (200 mg twice daily for 28 days) with single-dose administration of quizartinib resulted in increased C_{max} by 17% and AUC_{inf} by 94%. At steady state, exposure (C_{max} and AUC_{0-24h}) was estimated to be increased by 86% and 96%, respectively. Increased quizartinib exposure may increase the risk of toxicity.
Risk factors and risk groups	No specific risk factors are identified.
Risk minimisation measures	Routine risk minimisation measures: Recommendations for quizartinib dose adjustment if concomitant use of strong CYP3A inhibitors is described in Section 4.2 of the SmPC. Information on DDIs in Section 4.5 of the SmPC. No additional risk minimisation measures.

Important Potential Risk 1: Embryo-Foetal and Reproductive Toxicity	
Evidence for linking the risk to the medicine	Based on findings in animals, quizartinib may cause embryo-foetal harm when administered to a pregnant woman. No cases of embryo-foetal toxicity were observed in the clinical development programme. Based on findings in animals, female and male fertility may be impaired with treatment with quizartinib.
Risk factors and risk groups	No specific risk factors have been identified.
Risk minimisation measures	Routine risk minimisation measures: Warning in Section 4.4 of the SmPC Information on risk of embryo-foetal and reproductive toxicity in Section 4.6 of the SmPC. No additional risk minimisation measures.

II.C PostAuthorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

Not applicable.

II.C.2 Other Studies in Postauthorisation Development Plan

Not applicable.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

There are no specific follow-up forms.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Draft key messages of the additional risk minimisation measures:

Prior to the launch of VANFLYTA in each Member State, the Marketing Authorisation Holder (MAH) must agree on the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at reinforcing the prescriber's and patient/caregiver's awareness about the risk of serious ADRs related to QTc interval prolongation, and the actions to be taken to minimise the occurrence of the risk in patients receiving VANFLYTA.

The MAH shall ensure that in each Member State where VANFLYTA is marketed, all HCPs and patients/caregivers who are expected to prescribe, dispense, and use VANFLYTA have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The SmPC
- HCP Guide

The HCP Guide will contain the following key elements:

- Description of serious ADRS related to QTc interval prolongation that have occurred with quizartinib
- Detailed description of the recommended VANFLYTA dosing regimen: starting dose and dose escalation criteria
- Detailed description of VANFLYTA dose interruption, dose reduction, and treatment discontinuation based on QTc interval duration
- VANFLYTA dose modification for concomitant strong CYP3A inhibitors use
- Management of other comedications that are known to cause QT prolongation
- Frequency of ECG monitoring
- Serum electrolyte monitoring and management

The patient information pack:

- Package leaflet
- PC

The PC will contain the following key elements:

- A warning message for HCPs that VANFLYTA treatment may increase the risk of serious ADRs related to QTc interval prolongation
- Important information for HCPs not involved in the regular care of the patient about patient management related to QTc prolongation

- Important information for patients/caregivers about signs or symptoms of serious ADRs related to QTc interval prolongation and when to seek attention from an HCP
- Contact details of the VANFLYTA prescriber