14 September 2023
EMA/443555/2023
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Vanflyta

International non-proprietary name: quizartinib

Procedure No. EMEA/H/C/005910/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Table of contents

# List of abbreviations

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransaminase |
| AML | acute myeloid leukaemia |
| AML-MRC | AML with myelodysplasia-related changes |
| AST | aspartate aminotransaminase |
| ATC | Anatomical Therapeutic Chemical (Classification) |
| ATP | adenosine triphosphate |
| AUC | area under the concentration-time curve |
| AUC0-inf | area under the concentration-time curve from time zero extrapolated to infinity |
| BMI | body mass index |
| bpm | beats per minute |
| CEBPA | CCAAT enhancer-binding protein alpha |
| CI | confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| C-KIT | mast/stem cell growth factor receptor (SCFR), a receptor tyrosine kinase protein that in humans is encoded by the KIT gene |
| Cmax | maximum plasma concentration |
| Cmax,ss | steady-state maximum plasma concentration |
| C-QTc | relationship between quizartinib concentrations and QTc interval |
| C-QTcF | relationship between quizartinib concentrations and QTcF interval |
| CR | complete remission |
| CRc | composite complete remission |
| CRF | case report form |
| CRi | complete remission with incomplete hematologic recovery |
| CRia | (Protocol definition): Met all specified criteria for CR except for incomplete hematological recovery (residual neutropenia <1 × 109/L) with or without complete platelet recovery. RBC and platelet transfusion independence is not required |
| CRib | All criteria for CR or CRp met, except for recent RBC or platelet transfusion |
| CRO | clinical research organisation; contract research organisation |
| CRp | complete remission with incomplete platelet recovery |
| CTCAE | Common Terminology Criteria for Adverse Events |

| | |
|---|---|
| CYP | cytochrome P450 |
| CYP3A | cytochrome P450 3A |
| DMC | data monitoring committee |
| DSI | Daiichi Sankyo, Inc. |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EOT | end of treatment |
| eCRF | electronic case report form |
| eDISH | evaluation of drug-induced serious hepatotoxicity |
| EFS | event-free survival |
| FAB | French-American-British |
| FDA | Food and Drug Administration |
| FLAG-IDA | fludarabine, cytarabine, and G-CSF with idarubicin |
| FLT3 | Feline McDonough Sarcoma-like tyrosine kinase 3 |
| FLT3-ITD | Feline McDonough Sarcoma-like tyrosine kinase 3 internal tandem duplication |
| GCP | Good Clinical Practices |
| G-CSF | granulocyte-colony stimulating factor |
| GGT | gamma glutamyl transferase |
| GSD | group sequential design |
| GVHD | graft versus host disease |
| HPβCD | hydroxypropyl-β-cyclodextrin |
| HR | hazard ratio |
| HSCT | hematopoietic stem cell transplantation |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IDH | isocitrate dehydrogenase |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| IRIS | International Randomized Study of Interferon and STI571 (trial) |
| IRT | Interactive Response Technology |
| ITD | internal tandem duplication |
| ITT | Intent-to-Treat |
| IWG | International Working Group |
| JM | juxtamembrane |
| LFS | leukaemia-free survival |
| LFT | liver function test |

| | |
|---|---|
| LoDAC | low-dose cytarabine |
| LQTS | long QT syndrome |
| MDS | myelodysplastic syndrome |
| MEC | mitoxantrone, etoposide, and intermediate-dose cytarabine |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRD | minimal residual disease |
| ms | millisecond |
| NCI | National Cancer Institute |
| NPM1 | nucleophosmin 1 |
| NR | no response |
| OS | overall survival |
| PCI | potentially clinically important |
| PD | progressive disease |
| P-gP | P-glycoprotein |
| PGX | pharmacogenomic(s) |
| PK | pharmacokinetic(s) |
| PPS | Per-Protocol Analysis Set |
| PPX | pharmacoproteomic(s) |
| PR | partial response |
| PT | preferred term |
| QRS | interval between the R and S wave |
| QT | interval between the start of the Q wave and the end of the T wave |
| QTc | corrected QT interval |
| QTcF | QTc with Fridericia's correction factor |
| RBC | red blood cell(s) |
| RDI | relative dose intensity |
| RTK | receptor tyrosine kinase |
| SAC | statistical analysis centre |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SEER | Surveillance, Epidemiology, and End Results |
| SMQ | Standardized MedDRA Query |
| SOC | system organ class |
| STAT5 | signal transducer and activator of transcription 5 |
| SVT | supraventricular tachycardia |

| | |
|---|---|
| t-AML | therapy-related AML |
| TBL | total bilirubin |
| TEAE | treatment-emergent adverse event |
| TESAE | treatment-emergent serious adverse event |
| TK | tyrosine kinase |
| TKI | tyrosine kinase inhibitor |
| ULN | upper limit of normal |
| US | United States |
| WBC | white blood cell(s) |
| WHO | World Health Organization |
| WT | wild type |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Daiichi Sankyo Europe GmbH submitted on 23 June 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Vanflyta, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 April 2021

Vanflyta, was designated as an orphan medicinal product EU/3/09/622 on 23 March 2009 in the following condition: Treatment of acute myeloid leukaemia.

On 19 September 2023, during the ongoing initial application procedure, the applicant withdrew the Orphan designation.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was removed from the Union Register of designated orphan medicinal products on 19 September 2023. More information on the COMP's review can be found in the orphan designation withdrawal assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/vanflyta.
The applicant applied for the following indication:

*VANFLYTA is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) positive (see section 5.1).*

## *1.2. Legal basis and dossier content*

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

## *1.3. Information on paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0281/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0281/2021 was not yet completed as some measures were deferred.

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

## *1.5. Applicant's request(s) for consideration*

### 1.5.1. New active substance status

The applicant requested the active substance quizartinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

## *1.6. Protocol assistance*

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

The protocol assistance pertained to the following quality and clinical aspects:

Quality:

- Genotoxic impurity control strategy, starting materials, control of metal impurities, drug substance specification, drug product intermediate specifications, drug product intermediate method of manufacture, drug product specifications, dissolution analytical procedure, drug product and drug product intermediate shelf-life.
- Starting material, revised control strategy and adequacy of the revised quality development proposal.

Clinical:

- Phase 3 study AC220-007 design, in particular the inclusion/exclusion criteria, dose, endpoints, comparator, and the statistical plan.
- If patient population included in phase 2 Study AC220-002 (FLT3-ITD positive patients with relapsed/refractory AML) constitutes a high medical need population that has no available therapy
- Acceptability of the planned analyses to characterise the potential clinical benefit of treatment with the medicinal product.
- Acceptability of the use of a historical control group to illustrate and quantify the clinical benefit.
- Possibility of the Study AC220-002 to support a marketing authorisation application in combination with positive data from the confirmatory Study AC220-007 and if the Study AC220-002 could be basis for a CMA.
- Development of a companion diagnostic test for FLT3-ITD status.
- Further questions were presented on the overall study design for Study AC220-007 with further defined inclusion/exclusion criteria including a in order to determine the FLT3-ITD(+) status, the dose for the study based on the Phase 2 dataset, the dose adjustment guidelines based on the completed drug-drug interaction study AC220-015, endpoints of the study, comparators and the amended statistical plan.

- Agreement was sought that the patient population included in the Phase 2 Studies AC220-002 and 2689-CL-2004 (FLT3-ITD(+) patients with relapsed/refractory AML) constitute a high unmet medical need in a population that has limited available therapy.
- If the total sample size from the Phase 2b study 2689-CL-2004 and from the Phase 2 study AC220-002 is sufficient for an adequate efficacy and safety database to support a starting quizartinib dose of 60 mg daily in relapsed/refractory FLT3-ITD (+) AML, and if this dataset could support a conditional approval of quizartinib for the proposed indication of relapsed or refractory FLT3-ITD(+) AML.
- Acceptability of the use of historical control data.
- Acceptability of the tablet formulation to be used in the Phase 3 study based on the Phase 1 relative bioavailability study in healthy volunteers (Study AC220-014).
- Phase 3 study design to support a full approval for newly diagnosed FLT-3 ITD(+) AML. Acceptability of the secondary objectives and endpoints, PROs, population, inclusion and exclusion criteria, criteria to define FLT3–ITD(+) patients, stratification factors, local and central testing of FLT3-ITD for randomisation, randomisation plan, choice of standard chemotherapy regimens, dose regimen and duration of quizartinib treatment.
- Justifications for sample size, effect size, type I error control.
- Adequacy of the statistical analyses and methods, timing of the interim analysis.
- Acceptability of the Phase 3 study to support approval for this indication.
- Safety database

## *1.7. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Janet Koenig

| | |
|---|---|
| The application was received by the EMA on | 23 June 2022 |
| The procedure started on | 18 August 2022 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 4 November 2022 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 21 November 2022 |
| The CHMP Co-Rapporteur's Assessment was circulated to all CHMP and PRAC members on | 22 November 2022 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 15 December 2022 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 22 March 2023 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint | 2 May 2023 |

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|---|---|
| Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on | |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 12 May 2023 |
| The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on | 25 May 2023 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 19 June 2023 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 05 July 2023 |
| SAG was convened to address questions raised by the CHMP on<br>The CHMP considered the views of the SAG as presented in the minutes of this meeting. | 10 July 2023 |
| The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on | 20 July 2023 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 11 August 2023 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 1 September 2023 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vanflyta on | 14 September 2023 |
| The CHMP adopted a report on similarity of Vanflyta with Dacogen, Rydapt, Mylotarg, Vyxeos Liposomal, Xospata, Daurismo, and Tibsovo on | 14 September 2023 |
| Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product on | 14 September 2023 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

Proposed Indication:

"VANFLYTA is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following

consolidation, for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) positive".

## 2.1.2. Epidemiology and risk factors, screening tools/prevention

Acute myeloid leukaemia is the most common acute leukaemia in adults (Siegel, 2022; De Kouchkovsky, 2016).Kouchkovsky, 2016). The incidence of AML in Europe is estimated at 2.5 to 6 per 100,000 people (Lubeck, 2016). The incidence of AML increases with age, ranging from 1.8 cases per 100,000 people aged <65 years to 17.6 cases per 100,000 people aged >65 years. More than half of the patients with newly diagnosed AML in developed countries are >65 years of age, with a median age at diagnosis of 67 years (Heuser, 2020).

Overall, the outcome of patients with AML is poor, with a 5-year survival rate of 40%, which rapidly declines with increasing age at diagnosis (Thein, 2013). Outcome is influenced by multiple factors, both disease specific (eg, cytogenetic and/or molecular genetic alterations, including FLT3, nucleophosmin 1 [NPM1], and others) and patient specific such as age, Eastern Cooperative Oncology Group (ECOG) performance status, organ function, and other comorbidities (Döhner, 2017). Age is the most prominent patient-specific risk factor, while chromosomal aberrations/genetic mutations have been considered the strongest disease-specific risk factors (Kottaridis, 2001). The assessment of genetic mutations, including FLT3, as prognostic factors has become increasingly important for risk assessment and in the treatment of AML, as recommended by both the European LeukemiaNet and the National Comprehensive Cancer Network (NCCN) guidelines (Döhner, 2017; Pollyea, 2021). There is evidence that the incidence of FLT3-ITD mutations decreases with age, with an incidence of up to 35% in patients between 20 and 59 years compared with 16% to 20% in patients >60 years (Konig, 2015). In contrast, FLT3-TKD mutations have not been associated with a consistent prognostic impact (Mead, 2007).

## 2.1.3. Biologic features

Acute myeloid leukaemia is a heterogeneous hematologic malignancy characterised by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow and/or other tissues.

FMS-like tyrosine kinase 3 is a transmembrane tyrosine kinase in the Class III split kinase domain family of RTKs. It is normally expressed on immature hematopoietic progenitors, as well as on some mature myeloid and lymphoid cells. Furthermore, FLT3 plays a role in the regulation of survival, proliferation, and differentiation of hematopoietic progenitor cells (Kazi, 2019). Overexpression of the FLT3 receptor occurs in nearly all cases of AML and mutations in FLT3 represent one of the most common genetic alterations, occurring in approximately 30% of adult patients with newly diagnosed AML (Papaemmanuil, 2016; Kennedy, 2020).

There are 2 types of FLT3 mutations: FLT3-ITD and point mutations or deletion in the tyrosine kinase domain (TKD; FLT3-TKD). The FLT3-ITD (In-frame internal tandem duplications) mutation is more common than the TKD mutation, and these are found in 20% to 25% and 7% to 10% of all AML cases, respectively. In-frame internal tandem duplications within the FLT3 gene (FLT3-ITD) occur most commonly in exon 14, encoding the juxta membrane (JM) domain. The JM domain inhibits activation of the receptor by steric hindrance, preventing the tyrosine kinase domain (TKD) from assuming an active conformation. Presence of an ITD causes loss of this inhibitory effect, resulting in activation of the TKD causing ligand-independent, or constitutive, FLT3 receptor signalling, and thereby promote cytokine-independent AML cell survival and proliferation. The FLT3-ITD mutations are associated with a higher leukaemic burden with marked leukocytosis and higher blast percentage.

## 2.1.4. Clinical presentation, diagnosis

It is well established that the presence of an *FLT3*-ITD mutation confers an unfavorable prognosis, with relapse being the principal cause of treatment failure for the majority of these patients. On average, the median time to relapse for patients with *FLT3*-ITD (+) AML in first remission is estimated at approximately 9 months (Ciolli, 2004; Fröhling, 2002; Kottaridis, 2001). Moreover, approximately 75% of patients with *FLT3*-ITD (+) AML at diagnosis continue to have the ITD mutation at relapse, suggesting that *FLT3*-ITD may function as a driver mutation responsible for disease progression (Daver, 2019; Krönke, 2013).

At initial presentation, patients with newly diagnosed AML harboring *FLT3*-ITD mutations present commonly with a high leukaemic burden, such as increased white blood cell (WBC) counts and a high percentage of blasts in the peripheral blood and bone marrow. When treated with combination chemotherapy alone, *FLT3*-ITD (+) AML is associated with a higher rate of relapse (Levis, 2004) and inferior overall survival (OS) than compared with FLT3 WT disease (Kottaridis, 2001; Yanada, 2005; Thiede, 2002; Fröhling, 2002; Whitman, 2001).

## 2.1.5. Management

Chemotherapy has long been the mainstay of treatment for patients with newly diagnosed AML. In patients eligible for induction chemotherapy, cytarabine in combination with an anthracycline remains the standard therapy in newly diagnosed AML, regardless of cytogenetic or molecular abnormalities, with CR achieved in 60% to 85% of adults who are ≤60 years of age and 40% to 60% in adults >60 years of age (Döhner, 2017). For subjects who achieve a CR, the current guidelines recommend that subjects must be offered postinduction therapy to eradicate residual disease and prevent relapse. Available options for consolidation include chemotherapy and/or allogeneic-hematopoietic stem cell transplantation (allo-HSCT), depending on the risk group. Allogeneic-hematopoietic stem cell transplantation has improved the prognosis of patients with AML, but relapse remains high and non-relapse mortality associated with allo-HSCT is as high as 20% (Styczyński, 2020).

The clinical management of AML with FLT3 mutations has been transformed by the development of multikinase inhibitors targeting FLT3 mutations. The current approach is to combine them with conventional chemotherapy to increase the cytotoxic effect against leukaemia cells and reverse the poor prognosis for AML patients with FLT3 mutations (Döhner, 2017; Pollyea, 2021). The standard of care for patients with newly diagnosed FLT3-ITD (+) AML includes 2 distinct approaches based on patient age (ranges <60 years and ≥60 years). For AML patients with FLT3 mutations who are <60 years of age and who are eligible for standard induction and consolidation chemotherapy, the NCCN and European LeukemiaNet guidelines recommend that midostaurin be added to standard chemotherapy as part of frontline treatment. This recommendation is based on the results of the RATIFY study in newly diagnosed AML subjects with FLT3 mutations (internal tandem duplication [ITD] and/or TKD) (Stone, 2017). For AML patients with FLT3 mutations who are ≥60 years old and who are benefiting from intensive cytarabine-based induction therapy, the NCCN also recommends that midostaurin be added to standard chemotherapy (Pollyea, 2021). For AML subjects with FLT3-ITD who are unable to tolerate intensive chemotherapy, azacytidine or decitabine alone or in combination with sorafenib or venetoclax with hypomethylating agents are recommended (Pollyea, 2021).

In the European Union (EU), maintenance treatment is approved only for midostaurin in patients who are in CR after induction and consolidation chemotherapy, but not after allo-HSCT (Heuser, 2020). Significant improvements in survival outcomes of patients with *FLT3*-ITD (+) AML have been reported with allo-HSCT compared with chemotherapy or autologous HSCT; however, relapse following allo-HSCT remains high in these patients compared with those without *FLT3*-ITD mutations, with a higher

2-year relapse incidence (30% versus 16%; p = 0.006) and lower leukaemia-free survival (58% versus 71%; p = 0.04), respectively (Schlenk, 2014); Döhner, 2017).

Given the poor prognosis of patients with *FLT3*-ITD (+) AML and the high risk of relapse, the unmet medical need remains high and new treatment options are urgently needed.

## 2.2. About the product

Quizartinib is a Type II inhibitor of the receptor tyrosine kinase FLT3. Type II inhibitors, including quizartinib, binds the inactive conformation (Zorn, 2015, Smith 2015). Generally, type II inhibitors are more selective than type I inhibitors, as the inactive conformation preferred by type II inhibitors is thought to be more kinase specific than the active conformation (Davis 2011). Quizartinib and its major metabolite AC886 competitively bind to the adenosine triphosphate (ATP) binding pocket of FLT3 with high affinity (Kd=1.3 nM and 0.54 nM, respectively). Quizartinib and AC886 inhibit FLT3 kinase activity by crossing the cell membrane and interacting with the ATP-binding site of the intracellular TKD and competitively inhibit ATP binding, preventing autophosphorylation of the receptor, thereby inhibiting further downstream FLT3 receptor signalling and blocking FLT3-ITD-dependent cell proliferation. Type II inhibitors interact with a hydrophobic region immediately adjacent to the ATP-binding site that is only accessible when the receptor is in the inactive conformation, and thereby prevent receptor activation and block FLT3-ITD-dependent cell proliferation.

At clinically relevant concentrations, quizartinib and AC886 also bind with less affinity to KIT and have little or no affinity for other receptor tyrosine kinases.

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX11

## 2.3. Type of application and aspects on development

As of August 2021, the overall quizartinib clinical programme consisted of 26 sponsored clinical studies, including 13 studies in either newly diagnosed or R/R AML, 1 study in solid tumours, and 12 single-dose studies in healthy subjects and subjects with hepatic impairment. The dose of quizartinib administered in these studies ranged from 12 to 450 mg QD. Of the 13 studies conducted in subjects with AML, 10 are completed studies.

The quizartinib clinical development programme for newly diagnosed FLT3-ITD (+) AML comprises a pivotal Phase 3 study, AC220-A-U302 (N = 539) and 2 completed Phase 1 studies in subjects with newly diagnosed AML, Studies 2689-CL-0005 (N = 18) and AC220-A-J102 (N = 7). In addition, 1 Phase 1 study, 2689-CL-0011 (N = 13), in subjects who received quizartinib as maintenance following allo-HSCT, has been completed.

In the EU, orphan drug designation was granted on 23 Mar 2009, and Protocol Assistance was received from the Committee for Medicinal Products for Human Use on 24 Sep 2015 for the development of quizartinib for the treatment of newly diagnosed AML (see below). The original Pediatric Investigational Plan was first approved on 22 Jul 2016.

## *2.4. Quality aspects*

## 2.4.1. Introduction

The finished product is presented as film-coated tablets containing 17.7 mg or 26.5 mg of quizartinib, which is present as quizartinib dihydrochloride.

Other ingredients are: (tablet core): hydroxypropylbetadex, microcrystalline cellulose, magnesium stearate, (film-coating): hypromellose, talc, triacetin, titanium dioxide, yellow iron oxide (26.5 mg tablet only).

The product is available in aluminium/aluminium perforated unit dose blisters.

## 2.4.2. Active substance

### *2.4.2.1. General information*

The chemical name of quizartinib dihydrochloride is 1-(5-tert-butyl-1,2-oxazol-3-yl)-3-(4-{7-[2-(morpholin-4-yl)ethoxy]imidazo[2,1-b][1,3]benzothiazol-2-yl}phenyl)urea corresponding to the molecular formula $C_{29}H_{32}N_6O_4S*2HCl$. It has a relative molecular mass of 633.59 and the following structure:

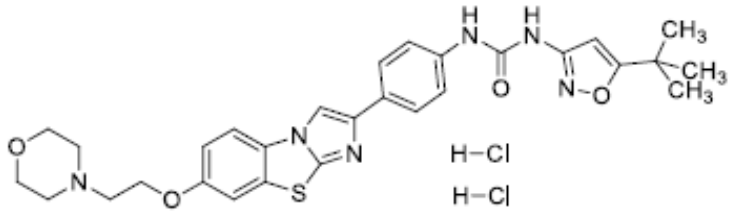



**Figure 1. Quizartinib dihydrochloride active substance structure**

The chemical structure of quizartinib was elucidated by a combination of halide titration, ultraviolet (UV) spectrum, infrared (IR) spectroscopy, $^{1}$H-NMR spectroscopy, $^{13}$C NMR spectroscopy, proton-proton correlation spectroscopy (COSY), heteronuclear multiple-bond correlation spectroscopy (HMBC), heteronuclear single-quantum correlation spectroscopy (HSQC), mass spectrometry and single crystal X-Ray structure determination.

The active substance is a white to off-white solid, slightly hygroscopic, very slightly soluble in acidic aqueous medium and its solubility decreases with pH. Quizartinib has a non-chiral molecular structure.

Polymorphism has been observed for quizartinib dihydrochloride. The solid state properties of the active substance were measured by a polymorph screen of quizartinib dihydrochloride produced a total of nine unique XRPD patterns (designated A through I) as well as amorphous material. The active substance is manufactured in the Form B which is the most thermodynamically stable. All of these other forms were either solvates or hydrates and all were found to convert to Form B upon drying. It should be noted that the active substance is rendered amorphous in the finished product by spray-drying manufacturing process.

#### *2.4.2.2. Manufacture, characterisation and process controls*

The commercial active substance manufacturing process consists of three chemical transformations (with isolation of intermediates) followed by a final salt formation step. It is a convergent synthesis with both arms of equal length (two steps).

The process uses well-defined starting materials with acceptable specifications. The proposed starting materials were the subject of pre-submission Scientific Advice from EMA and were assessed in a previous centralised MAA. The justification of the choice of starting material was considered acceptable and it was concluded that the proposed starting materials ensure sufficient portion of the process is performed under GMP.

The manufacturing process is sufficiently well described and the overall control strategy was considered adequate to control the process leading to an active substance of intended and consistent quality. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of Quality by Design (QbD). The critical process parameters were identified by a combination of prior knowledge and multivariate Design of Experiments (DoEs). Based on these studies, proven acceptable ranges (PARs) were proposed for a number of unit operations of the manufacturing process of the active substance. In response to questions raised during the procedure, and in line with EMA Q&A on "Improving the understanding of NORs, PARs, DSp and normal variability of process parameters" (EMA/CHMP/CVMP/QWP/354895/2017), the applicant revised the proposed PARs so that the flexibility in the commercial manufacturing process of the active substance is limited to a single PAR for each unit operation (i.e. a Design Space is not claimed). A traditional approach is maintained in the control strategy (with in-process controls for reaction monitoring and intermediates' specifications). The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the finally approved PARs.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. The currently proposed version (B3) of the manufacturing process was developed at proposed commercial manufacturing site and it has undergone only minor adjustments from previous version (B2) which produced stability and toxicology batches. Late stage clinical batches were obtained from these processes at the proposed commercial scale. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance packaging complies with Ph. Eur. chapter 3.1.3 and Regulation EC 10/2011 as amended.

#### *2.4.2.3. Specification*

The active substance specification includes tests for: appearance, identity (IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), counter-ion assay (Ph. Eur.), and residue on ignition (Ph. Eur.).

The tests included in the specifications are in line with the requirements of ICH Q6A. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

An extensive discussion on the impurities control strategy has been presented, both in 3.2.S.2.3 as well as in 3.2.S.3.2. About 28 impurities are discussed in detail. Actual and potential impurities occurring at all stages have been discussed in detail.

The applicant argues that quizartinib active substance is exempted from ICH M7 requirements for impurity limits setting as: 1) quizartinib is indicated for advanced cancer disease as defined in the scope of ICH S9 and exposure to mutagenic impurities in these cases would not significantly add to the cancer risk of the active substance, and herewith impurities could be controlled at acceptable levels for non-mutagenic impurities, and 2) quizartinib itself appears to be genotoxic according to the performed Ames test. 1) and 2) combined means that the ICH M7 guideline would not apply for quizartinib and instead the impurities could be set in line with ICH Q3A/B guidelines.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. The results from forced degradation, confirming the stability-indicating power of the HPLC impurity test procedure, were provided. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (including 8 batches manufactured at commercial scale) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

#### *2.4.2.4. Stability*

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial packagefor up to 48 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The primary batches are manufactured according to process B2 while the proposed commercial process is the more recent process B3 however, considering the minor differences between the two versions of the process this was not considered to have a significant effect on the stability profile of the active substance.

The following parameters were tested: appearance, organic impurities assay, moisture (every time point), microbial limits and X-ray powder diffraction (annually). The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. Despite a somewhat variable impurity profile at time zero, the study results show that the active substance quizartinib dihydrochloride is highly stable and no clear trends are observed, notably towards degradation.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions (Acidic, Basic, Oxidative, Thermal) were also provided on one batch. The results show no significant changes after storage. The physical and chemical properties, appearance, IR, XRPD pattern, assay, related substance and water remain the same compared to unstressed control.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable.

## 2.4.3. Finished medicinal product

### *2.4.3.1. Description of the product and Pharmaceutical development*

The finished product is presented as immediate release film-coated tablets containing 17.7 mg or 26.5 mg of quizartinib, which is present as quizartinib dihydrochloride. The 17.7 mg tablets are white, round shaped film-coated tablets, 8.9 mm in diameter and debossed with "DSC 511" on one side and the 26.5 mg tablets are yellow, round shaped film-coated tablets, 10.2 mm in diameter and debossed with "DSC 512" on one side.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The formulation development was supported by clinical development, each modified formulation from the form used in Phase 1 (powder in bottle dissolved at the clinical site in a 5% hydroxypropyl-β-cyclodextrin (HPβCD) solution) to the form used in Phase 3 (film-coated tablets), was justified by the need to simplify preparation of the oral solution at the clinical site and reduce time required to dissolve the active substance.

The solubility of quizartinib dihydrochloride is highly pH dependent; it increases as the pH deceases. At pH 2.0 or above it becomes practically insoluble. At pH below 2, quizartinib is very slightly soluble. The solution of quizartinib dihydrochloride at concentrations greater than 1 mg/mL tend to form a gel. Active substance particle size distribution is not subject to specification given that during the manufacturing process quizartinib is dissolved in water.

At the highest dosage strength of 26.5 mg the active substance is not completely soluble in 250 mL of aqueous media over the range from pH 2.2 to 8.0. Quizartinib demonstrates low permeability and has thus been classified as a BCS class 4 compound (low solubility/low permeability).

The major excipient is the hydroxypropyl-β-cyclodextrin (HPβCD) which increases the quizartinib solubility and prevents gel formation. The ratio of the active substance to HPβCD was set at 1:10. The other inactive ingredients are microcrystalline cellulose, magnesium stearate and colour coating mixture.

The active substance to HPβCD ratio (1:10) has been shown to be an important parameter to the bioavailability of the finished product. Since this ratio has not changed from the Phase 1 clinical study to commercial formulation, it is considered that there is no significant difference between commercial formulation and clinical trial formulations.

Vanflyta 17.7 mg and 26.5 mg tablets are manufactured from the same blend by adjusting the compression weight. The manufacturing process is considered as a non-standard process. The tablet formulation is based on an amorphous solid dispersion of quizartinib dihydrochloride and hydroxypropyl-β-cyclodextrin (HPβCD) in a 1:10 ratio, mixed with microcrystalline cellulose and magnesium stearate to form the common final blend. The final blend is compressed to manufacture the core tablets which are then coated.

Pharmaceutical development of the finished product contains QbD elements. The starting point for the process development work was based on an initial risk assessment identifying the potential interactions between unit operations and critical quality attributes (CQAs). It was estimated what factors could be judged less important and what factors required further studies. All parameters relevant to QTPP were identified from an Ishikawa diagram, and analysed using a detailed risk assessment failure mode and

effects analysis (FMEA) approach to establish those process parameters (CPPs) associated with critical material attributes (CMAs) affecting the critical quality attributes (CQAs).

The acceptance criteria for the critical material attributes, were determined by examination of the manufacturing capability of the Phase 3 clinical and registration stability batches and performance of structured experimental studies. The process understanding have been generated through prior knowledge and use of multivariate experimental plans (DoEs). To establish critical process parameters (CPPs), many potential–CPPs have been selected and studied with well described design of experiments (DoEs) (full factorial designs at two levels with centre points) and with well-defined ranges.

The development of the dissolution method was conducted in two steps, the first step was the selection of the testing conditions and the second step was the evaluation of the discriminating power. To evaluate the discriminating power of the proposed dissolution method, studies assessing purposeful changes in the ratio of active substance to HPβCD in the SDD, crystallinity in the finished product and differences in tablet hardness and film coat level were conducted using quizartinib tablets 26.5 mg. The method is considered discriminatory.

The choice of materials for the container and closure for spray dried dispersion intermediate, bulk tablets and finished product have been adequately justified with stability study. The primary packaging of the finished product is aluminium/aluminium perforated unit dose blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

#### *2.4.3.2. Manufacture of the product and process controls*

The manufacturing process consists of four main steps: manufacture of the amorphous solid dispersion intermediate, blending, tabletting and film-coating.

Design spaces are proposed in the preparation of the amorphous solid dispersion and the tableting operations. Proven acceptable ranges have been defined for the relevant CPPs. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs and Design Spaces.

Formal process validation of the manufacturing process will be conducted post-approval. A process validation protocol summarising the full studies intended to be conducted at commercial scale, has been provided.

#### *2.4.3.3. Product specification*

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form; appearance, identification (HPLC, UV), uniformity of dosage units (Ph. Eur.), assay (HPLC), related substances (HPLC), dissolution (Ph. Eur.), water content (KF) and microbiological quality (Ph. Eur.).

The finished product is released on the market through traditional final product release testing. The specifications are in line with ICH Q6A and Ph. Eur. general monograph for film-coated tablets. The limits proposed for the specified impurity in the finished product at release and end of shelf-life are considered justified based on the available batch release and stability data and furthermore, the impurity is considered qualified and hence there is no safety concern. The limit for unspecified impurities is in line with ICH Q3B identification threshold (MDD 60 mg) and therefore acceptable. The

proposed limits for total impurities in the tablets at release correspond to the maximum allowed content in spray-dried dispersion intermediate.

A risk assessment for potential elemental impurities in quizartinib tablets has been performed according to ICH Q3D. No routine or monitoring tests for elemental impurities of the finished product are needed.

The risk of carryover of any N-nitrosamine species from the quizartinib active substance is negligible as nitrous acid and nitrite salts are not used in the process. Additionally, the Raney Nickel reduction in Step 2 of the manufacturing process would eliminate any nitrosamines introduced prior to that step. In addition, for the finished product for all its components, manufacturing stages, and used packaging, no risks were identified for formation or contamination with nitrosamine impurities. And finally, quizartinib dihydrochloride tablets are intended for the treatment of patients with advance cancer under the scope of ICH S9. Therefore, in line with the principles of ICH M7 (R1), additional controls for nitrosamine impurities in the finished product, beyond those required under the ICH Q3 guidelines are not warranted.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for n=8 for 17.7 mg tablets, n=13 for 26.5 mg tablets batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

#### *2.4.3.4. Stability of the product*

Stability data from three commercial scale batches of finished product for each strength stored for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing and in addition in PCTFE/PVC//Al.

Samples were tested for appearance, dissolution, assay, impurities and water content. The analytical procedures used are stability indicating. The stability results show relatively little degradation and only one impurity (AC012917) increases over time; this increase is more pronounced under accelerated conditions but its content remains within the specification limit. A similar trend is noticed for content in total impurities. As discussed above, a downward trend in dissolution results was observed on storage for product packaged in PCTFE/PVC//Al blisters. Nevertheless the product remained within specification at long term conditions. This slowing down of dissolution was not seen in product packed in the proposed Al/Al blisters.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products, and one batch was subjected to thermal cycling (freeze and thaw) study.

The applicant proposed to calculate the shelf-life starting with compression of SDD with the other excipients. To support this proposal, the applicant has put on stability one batch of each strength of tablets manufactured from "aged" SDD (24 months, the shelf-life proposed for this intermediate). The data provided show a stability profile similar to the other stability batches; 24 months long term results are available. Based on this extended stability data, this approach to calculating the start of shelf-life can be accepted. The applicant further committed to continue for at least 3 years the stability programme on the tablets made with aged SDD.

Based on available stability data, the proposed finished product shelf-life of 3 years without special storage condition as stated in sections 6.3 and 6.4 of the SmPC, are acceptable.

#### *2.4.3.5. Adventitious agents*

No excipients derived from animal or human origin have been used.

## 2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. Design spaces have been proposed for two steps in the manufacture of the finished product. The design spaces have been adequately verified.

At the time of the CHMP opinion, there was a minor unresolved quality issue, having no impact on the Benefit/Risk ratio of the product, which pertain to stability data for the quizartinib tablets 17.7 mg and 26.5 mg manufactured with aged SDD. This point is put forward and agreed as recommendation for future quality development.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

## 2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used as proposed. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

## 2.4.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant has committed to provide 3 years stability data for the quizartinib tablets 17.7 mg and 26.5 mg manufactured with aged SDD.

# *2.5. Non-clinical aspects*

## 2.5.1. Pharmacology

#### *2.5.1.1. Primary pharmacodynamic studies*

The applicant demonstrated the selectivity and potency of quizartinib to inhibit FTL3 *in vitro*: with a biochemical competition binding assay the biochemical potency and selectivity of quizartinib was determined against a panel of 441 kinases. Quizartinib binds with the highest affinity to FLT3 (Kd(WT) = 1.3 nM, Kd(ITD) = 9.4 nM) and with less affinity to KIT (Kd = 4.9 nM). It also binds to a few other

class III RTKs including CSF1R/FMS (Kd = 9.6 nM), PDGFRα (Kd = 14 nM), and PDGFRβ (Kd = 8.4 nM), and non-class III RTK, RET (Kd = 7.1 nM), and with lesser affinity to FLT1 (Kd = 44 nM), FLT4 (Kd = 49 nM), and DDR1 (Kd = 81 nM). Thus, quizartinib is highly potent against the selected class III RTKs. Also AC886, a major metabolite of quizartinib, binds with the highest affinity to FLT3 (Kd(WT) = 0.54 nM, Kd(ITD) = 5.8 nM) and with less affinity to KIT (Kd = 0.97 nM). It also binds to a few other class III RTKs including CSF1R/FMS (Kd = 8.6 nM), PDGFRα (Kd = 3.6 nM), and PDGFRβ (Kd = 1.8 nM), and non-class III RTK, RET (Kd = 14 nM).

Quizartinib at concentrations of 0.8 to 20 nM inhibited significantly the FLT3-ITD kinase activity (i.e., autophosphorylation) in MV4-11 cells, a human leukaemia cell line that expresses the FLT3-ITD mutation. Besides, quizartinib was found to be a highly potent inhibitor of FLT3-dependent cell proliferation in this MV4-11 cell line (IC50 = 0.3 nM) and to have more than a 1,000-fold weaker activity against the FLT3 independent cell proliferation of the RS4;11 control cell line. Near complete inhibition was observed at around 10 nM quizartinib or AC866. Similar inhibitory effects on FLT3 phosphorylation and cell proliferation were reported for the major metabolite AC886.

Resistance to quizartinib is related to mutations (F691L and D835) and reduction in SPRY3 or GSK3 expression leading to re-activation of downstream FGF/Ras/ERK or Wnt signalling.

*In vivo*, the pharmacology of quizartinib was tested in different mouse models. The temporal effect of quizartinib treatment on the expression of p-FLT3 and total FLT3 protein was examined in subcutaneous human leukaemia MV4-11 tumours in female mice. Mice were treated at 96 to 0.25 h prior to tumour collection with a single dose of 10 mg/kg quizartinib. Phosphorylated FLT3 and total FLT3 protein in tumour lysates were measured, and the ratio of p-FLT3 to total FLT3 (p/tFLT3 ratio) was calculated and normalised against the 0.25 h vehicle time point to report the normalised p/tFLT3 ratio (i.e., the % p-FLT3). A time-dependent reduction of p-FLT3 was observed, and the maximal effect was at 1, 2, and 6 h post-dose with 6%, 4%, and 7% p-FLT3, respectively. Levels of % p-FLT3 rebounded at 48 and 96 h post-dose, but levelled off at approximately 60%.

The efficacy of quizartinib was also tested in a tumour xenograft model using MV4-11 cells, which were grown as subcutaneous tumours in female athymic nude mice. The mice were treated PO with 1, 3 and 10 mg/kg/day quizartinib for 28 days. Quizartinib demonstrated a strong dose-dependent antitumour activity, already seen at 1 mg/kg/day. The activity was nearly maximal at 3 mg/kg/day and at 10 mg/kg QD no tumour regrowth after dosing discontinuation and during the entire 32-day follow-up observation period was shown. No group mean body-weight loss or other toxicity was observed for any of the treatment groups. At a lower dose of 0.5 mg/kg for 10 days, tumour growth was inhibited by quizartinib, while a reduction in tumour volume was seen when quizartinib was combined with cytarabine and daunorubicin.

In a disseminated engraftment model, the activity of quizartinib was determined using the non-obese diabetic/severe combined immunodeficient (NOD/SCID) mice that were pre-treated with cyclophosphamide followed by intravenous administration of MV4-11 cells that disseminated to bone marrow. Then, the mice were treated PO with 0.1, 1, or 10 mg/kg/day quizartinib for 31 days or at 1 or 10 mg/kg/day for 150 days (labelled "continuously"). Quizartinib dosed for 31 days at 0.1, 1, and 10 mg/kg QD provided an increased life span (ILS) of 12%, 55%, and >250%, respectively, compared to vehicle. At 1 mg/kg/day, quizartinib dosed continuously for 150 days gave an ILS of 153% and provided a markedly higher survival advantage compared to 31-day dosing. The study was terminated prior to reaching 50% mortality in the 10 mg/kg/day continuous dosing group, yielding an ILS of >250%.

#### *2.5.1.2. Secondary pharmacodynamic studies*

Quizartinib did not show activity with an IC50 value below 2 µM against a diverse panel of 118 non-kinase enzymes, receptors, channels, and transporters in a screen test, demonstrating its selectivity.

A secondary pharmacodynamics screen has been performed for the metabolite AC886. A significant response of ≥50% inhibition at 10 µM was observed for acetyl cholinesterase, ACES (64%); sodium channel, site 2 (72%); and adenosine transporter (53%). The determination of $IC_{50}$ or Ki is considered unnecessary given the unbound plasma levels of AC886 in patients around 3 nM.

#### *2.5.1.3. Safety pharmacology programme*

No safety pharmacology studies have been performed concerning the central nervous system and the respiratory functions. In the general toxicity studies, no effects on these organs were observed.

In different *in vitro* models quizartinib showed clearly several effects on the cardiovascular system. However, due to the high protein binding profile of both quizartinib and its metabolite AC886 (≥99%), the unbound Cmax values for quizartinib and AC886 were estimated to be approximately 1%, and therefore, the concentration range of 1 to 30 µM were 100- to 10,000-fold higher than unbound Cmax values in human. In addition, dispersed canine cardiomyocytes were used for INa, and ICa-L assays. To overcome this difficulty, additional ion channel assays for hERG current, IKs, INa, INa,L, and ICa-L were conducted using cells stably expressing human genes.

In hERG transfected HEK293 cells quizartinib and metabolite AC886 inhibited the potassium channels (IKr) significantly by 16% and 12% respectively at 3 µM. hKvLQT1/minK potassium channels expressed in HEK293 cells (IKs) were significantly inhibited to a maximum of 68% and 27% resp., with IC50s of ca. 0.3 µM and ca. 2.9 µM resp. Neither quizartinib nor AC886 showed significant inhibitory effects on sodium current INa and late sodium current INa,L at up to 3 µM in HEK293 cells and also not on cloned L-type calcium channels ICa-L expressed in Chinese hamster ovary cells.

The effects of quizartinib on the cardiovascular system were determined in male cynomolgus monkeys using a telemetry system. The monkeys were dosed orally with 3, 10, and 30 mg/kg quizartinib and quizartinib resulted in QT prolongation at doses approximately 2 times the RHD of 53 mg/day based on Cmax. The NOAEL was approximately 0.4 times the RHD based on Cmax. Quizartinib primarily inhibited IKs with a maximum inhibition of 67.5% at 2.9 µM. The maximum inhibition of IKs by AC886 was 26.9% at 2.9 µM. Quizartinib and AC886 at 3 µM statistically significantly inhibited hERG currents by 16.4% and 12.0%, respectively. Neither quizartinib nor AC886 inhibited INa, INa-L and ICa-L at any concentration tested.

#### *2.5.1.4. Pharmacodynamic drug interactions*

No pharmacodynamic drug interaction studies with quizartinib have been conducted.

### 2.5.2. Pharmacokinetics

The pharmacokinetics (PK) of quizartinib (AC220), its major and pharmacologically active metabolite AC886 have been investigated upon single dose intravenous (IV) or oral (PO) administration in mouse (nu/nu mice), rat (Sprague Dawley (SD), and Long Evans (pigmented)), dog (Beagle dogs) and monkey (Cynomolgus monkeys). Multiple dose toxicokinetics (TK) was examined upon daily oral administration, which is the intended clinical route. The majority of the doses were prepared using the same formulation as the one that was used in the pivotal toxicity studies, although radiolabelled drug

was incorporated when appropriate. In addition, analytical methods for determination of quizartinib in formulations used to conduct single- and repeated-dose oral toxicology studies were validated.

**Methods of analysis**

Concentrations of quizartinib in rat, dog, and monkey plasma (EDTA), and its major metabolite AC886 in rat and monkey plasma were determined by adequately validated methods (5 to 1000 ng/mL) of mass spectrometry (LC MS/MS) or by high performance liquid chromatography (HPLC) using ultraviolet (UV) detection (formulations) following solid phase extraction or liquid-liquid extraction. Methods were validated for sensitivity, selectivity, carry over, linearity, accuracy, repeatability, precision, sample dilution analysis, and sample long-term stability. Metabolites were characterised and quantified by HPLC with radioactivity detection and their chemical structures were elucidated by LC-MS/MS and, when possible, co-elution with non-radiolabelled standards. Distribution and excretion were analysed by measuring radioactivity in samples of plasma, tissues, and excreta from animals dosed with [$^{14}$C]quizartinib using liquid scintillation counting (LSC) and by quantitative whole-body autoradiography. Analytical methods using high performance liquid chromatography (HPLC) with ultraviolet detection (HPLC-UV) method for the determination of quizartinib, spiked with impurities, formulated in 5% to 22% 2-hydroxypropyl-β-cyclodextrin (HPβCD) were validated for determination of quizartinib concentrations in solutions used to conduct single- and repeated-dose oral toxicology studies.

**Absorption**

*In vitro* membrane permeability of quizartinib through Caco-2 cell monolayers was moderate. P-gp (P-Glycoprotein)(MDR1)-mediated transport of quizartinib was evaluated using MDR1-expressing cells (MDCKII-MDR1 cells). Based on transcellular transport in the Bl-to-Ap direction and inhibition by the P-gp model inhibitors, quizartinib was considered to be a P-gp substrate. An *in vitro* study investigating BCRP-mediated transcellular transport in BCRP-expressing LLC-PK1 cells showed that the major human metabolite AC886 was a substrate for human BCRP, while quizartinib was not.

Plasma exposure following single dose oral administration of quizartinib to mice was dose proportional in the dose range tested (0.1 – 300 mg/kg) as measured by AUCinf. Absorption was fast (Tmax 1-2h) and (apparent) elimination moderate (T1/2 ~4h). At the higher dose range (100 & 300 mg/kg) absorption was delayed leading to higher Tmax (4h) and 40-80% lower Cmax than expected based on the dose. In addition, the PK profiles suggest an increase of (apparent) elimination half-life with increasing dose cq quizartinib exposure to >20 h at the highest dose but elimination was only measured up to 24h after dosing. The PK of the major, active metabolite, AC886 was found to be comparable to the PK of quizartinib with a Cmax value of 0.77-fold and an exposure ($AUC_{inf}$) of 0.95-fold the values found with quizartinib. The exposure ($C_{max}$ and $AUC_{inf}$) using 5% HP$\beta$CD was found to be about 2-fold higher than when using 22% HP$\beta$CD.

Plasma exposure ($C_{max}$, AUC) following single dose oral administration of quizartinib to rats was dose proportional in the dose range tested in both genders (3 – 30 mg/kg). Exposure in female rats was slightly higher (po 1.7-fold; IV 1.5-fold) than the values found in males. Absorption was fast ($T_{max}$ 1-2h) with the lower doses and elimination moderate ($T_{1/2}$ 5-6h). At the higher dose range (100 & 300 mg/kg) absorption was delayed leading to higher Tmax (4h) and, with the 300 mg/kg dose, a 50% lower Cmax than expected. In addition, the PK profiles suggest an increase of elimination half-life with increasing dose cq quizartinib exposure to >20 h at the highest dose but elimination was only measured up to 24h after dosing. Bioavailability (Fpo) was ~46% using 22% HP$\beta$CD as vehicle and food seemed to double the oral bioavailability. Clearance was found to be low (0.4 L/h.kg) and volume of distribution high (2.5-3.4 L/kg). The PK of the major, active metabolite, AC886 was found to be comparable to the PK of quizartinib with a Cmax value of 0.64-fold and an exposure ($AUC_{inf}$) of 0.67-fold the values found with quizartinib, indicating an incomplete metabolisation to AC886 in rats. When

the major metabolite AC886 was dosed to male rats, a low oral bioavailability (Fpo) of 6.9% was found. Terminal elimination half-life ($T_{1/2}$ = 3.4-3.7h) was also lower than found when dosing with quizartinib indicating a faster clearance (metabolism) of AC886 than quizartinib. This may indicate that the formation of AC886 from quizartinib is the rate limiting step in the metabolic clearance of quizartinib.

The PK profile of quizartinib upon multiple oral dose administration (1 and 10 mg/kg) to male and female rats was found to be comparable to single dose administration, with a slight increase in $T_{max}$, and an about 2-fold increase in $C_{max}$ and $AUC_{0-24}$ on Day28 as compared to Day1. Exposure (AUC) and $C_{max}$ was comparable in females and males. Elimination half-life could not be assessed properly as the last time point was at 24h post administration, but seemed to increase with repeated dosing and with dose level. The exposure of the major metabolite AC886 seemed to follow the quizartinib exposure and was slightly lower (0.7 – 1.0) with the low dose but the AC886/quizartinib ratio decreased with increasing dose and time (0.3).

Plasma exposure (AUC) following single dose oral administration of quizartinib to dogs was dose proportional in the tested dose range (1 – 25 mg/kg). Exposure in females was about 1.5- to 2.7-fold higher than the values found in males. Absorption was fast ($T_{max}$ 1-2h) and elimination moderate (T1/2 6-9h). At the highest dose tested (25 (M) & 10 (F) mg/kg) an increase of elimination half-life was found (T1/2 11h). Bioavailability (Fpo) was ~40% using HP$\beta$CD as vehicle. Clearance was found to be low (0.3 L/h.kg) and volume of distribution high (3.4 L/kg).

Several (~17) different liquid and solid formulation vehicles were tested in the dog. The effect of food was variable and dependent on the formulation used. The AC886 exposure was dependent of the formulation used and varied from 0.08 to 0.56 the quizartinib exposure ($AUC_{inf}$).

Plasma exposure ($C_{max}$, AUC) following single dose oral (3 mg/kg in 22% HP$\beta$CD) and intravenous (1 mg/kg) administration of quizartinib was studied in male and female cynomolgus monkeys. Absorption was fast ($T_{max}$ 1.5h) but exposure modest with a low oral bioavailability of 14%, a short elimination half-life ($T_{1/2}$ ~2h) and with a high clearance (1.7 L/h.kg) and volume of distribution (~5 L/kg). No gender difference was found. The PK of the major, active metabolite, AC886 was found to be comparable to the PK of quizartinib, but with higher plasma levels, i.e. $C_{max}$ value 3.5- to 6.5-fold and exposure ($AUC_{inf}$) 7.9- to 9.2-fold quizartinib, indicating fast and extensive conversion to AC886 in the monkey.

As compared to human, rat and dog, a fast conversion of quizartinib to AC886 was found in the monkey leading to a low exposure, a low $T_{1/2}$ and a low oral bioavailability. The elimination half-life ($T_{1/2}$) found in humans (73h) is longer than expected based on the mouse, rat and dog (4 – 7h). Accumulation of exposure (TK studies, $AUC_{0-24}$) upon multiple dosing was low in dog (0.6-0.9x) and rat (1.2-2.7x), but 2.8-4.6x in monkey, which is not in line with the short (2 h) elimination half-life. In humans an accumulation ratio of 4.9 was found, which is in line with the higher elimination half-life (73 h).

**Distribution**

Plasma protein binding (PPB) was determined by an ultracentrifugation method at 50, 500 and 2500 ng/mL. Quizartinib and the main metabolite AC886 showed a very high PPB in the mouse, rat, dog, monkey and human (≥99%). Unbound quizartinib plasma concentration (Fu) seems to be about 3- and 5-fold higher in human (1.0%) as compared to dog, monkey (0.3%) and rat or mouse plasma (0.2%) at the clinically relevant concentrations but it should be noted that the variance (CV%) of the measurement is high (9-36%). PPB of AC886 in dog plasma seemed to be concentration dependent showing with increasing concentrations a 3-fold increase in PPB. Unbound AC886 plasma concentration was 0.3% in human plasma as compared 0.1%, 0.2%, 0.5% and 0.6% in mouse, rat, monkey and

dog, respectively, at the clinically relevant concentrations. Using equilibrium dialysis, quizartinib seemed to display a similar, very high, binding to an has (human serum albumin) containing buffer as to total plasma, but the poor solubility/low recovery may have confounded the results. The poor solubility of quizartinib in the presence of alpha-1-acid glycoprotein (AAGP) suggests binding to AAGP is insufficient to keep the compound in solution.

In human blood, the blood to plasma (B/P) ratio of quizartinib was >0.9, which is indicative of distribution or adsorption to the blood cells, and decreased from 1.48 to 0.97 with increasing blood concentrations (10 – 4000 ng/ml). A similar blood concentration dependent decline in B/P ratio was found for the major, active, metabolite AC886 (3.4 to 1.3). The higher B/P ratios for both compounds are indicative of higher red blood cell (RBC) compartmentalisation. At the clinically relevant plasma concentrations, the human B/P ratio is ~1.3 for quizartinib and ~3 for AC886. Therefore, it is concluded that quizartinib at clinically relevant concentrations is predominantly present in the red blood cell compartment (50%-70%), while for AC886 this is more than ~80%. The impact of quizartinib and AC886 concentration and haematocrit (20% – 50%) on blood/plasma partition was also investigated in human blood. The ratio of blood to plasma concentration values for quizartinib were relatively consistent at approximately 1.0 with a range of 0.79 to 1.30 with considerable overlap taken variability into consideration. The B/P values for AC886 ranged from 1.36 to 3.19 and demonstrated a trend for increase at lower blood concentrations and higher haematocrit levels.

In blood partitioning tests, quizartinib and AC886 were spiked to rat, dog, and monkey blood and each blood sample was processed on ice or at 37°C for 2 h. In contrast to human blood, no time- or temperature-dependent partitioning of quizartinib and AC886 between the plasma and blood cell fractions were noted in rat and dog blood. On the other hand, in monkey blood AC886 concentrations were approximately 4-fold higher on ice than those at 37°C, whereas quizartinib concentrations was not affected by either on ice or at 37°C. The blood to plasma (B/P) ratios of quizartinib were not given but were calculated to be ~0.7 for rat and dog, i.e. 20% in RBC, and 1.0 for monkey and independent of concentration added (20 – 2000 ng/ml). The B/P ratio for AC886 was ~0.8 and 1.2 for rat and dog, respectively.

Tissue distribution was investigated using QWBA in pigmented male Long-Evans (LE) and albino male and female Sprague Dawley (SD) rats following administration of a single oral dose of [$^{14}$C]-labelled quizartinib. A rapid and wide distribution of $^{14}$C-label was demonstrated in the rat, with maximum tissue concentrations at 2 h or 4 h post-dose (mostly Tissue/Plasma (T/P) ratio <10), with the exception of the testes (24 h). The highest concentrations of radioactivity were found in the contents of the alimentary canal (T/P ratio up to 31), while a moderate exposure (T/P ratio 4 – 9) was found in lung, adrenal, pancreas and in organs associated with metabolism and excretion (liver and kidney). At 24h post dose, radioactivity was below 2-fold plasma $C_{max}$ in all tissues. In rats, quizartinib-related radioactivity following either IV or oral dosing crossed the blood brain barrier but, T/P levels were low (0.1 – 0.3) and radioactivity was not detected in CSF. Reproductive organs were included among the tissues examined, but no studies have been carried out regarding pregnant or nursing animals, studying placental transfer, foetal exposure or excretion in milk.

In pigmented LE rats a similar distribution and decline of radioactivity over the course of the study was found, but elimination was incomplete at 336 h post-dose and measurable tissue concentrations were seen in eye uveal tract, meninges, small intestine, pigmented skin, adrenal gland, spleen, and liver at this time point. Binding to melanin was evident as pigmented skin accumulated about 9-fold more radioactivity than non-pigmented skin. The time course of distribution of radioactivity in the pigmented uvea of the eye and pigmented skin of Long-Evans rats suggested a reversible association of [$^{14}$C]quizartinib-derived radioactivity with melanin with a tissue half-life of 348 h and 138 h, respectively.

**Metabolism**

*In vitro* intrinsic clearance of quizartinib was low in rat, dog, monkey and human hepatocytes with a $T_{1/2}$ >700 min and in mouse, rat and human liver microsomal incubations with $T_{1/2}$ >60 min, while clearance was modest in dog liver microsomes ($T_{1/2}$ 33 min) and high in cynomolgus monkey liver microsomes ($T_{1/2}$ 19 min). In human liver S9 fraction 84% of quizartinib was unchanged after 60 min indicating also a low *in vitro* clearance.
Using recombinant human CYP enzyme incubations, CYP3A4/5 was identified as the major CYP isoform responsible for the metabolism of quizartinib and of AC886. CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 isoforms appeared to have little contribution. AC886 formation from quizartinib was detected only with CYP3A4 and CYP3A5.

A mass balance study in rats and dogs using $^{14}$C-labelled quizartinib (single dose, oral) showed that, as in humans, two main labelled peaks were detected in plasma, of which unchanged quizartinib accounted for 74% or 59% and the major human metabolite AC886 for 22% or 16% in rats or dogs, respectively. In addition, in dog plasma a morpholino N-oxide metabolite (22%), eluting at 42 min, was detected.

In urine, 9 and 7-20 $^{14}$C-labelled peaks, which included quizartinib and AC886, were detected in rat and dog, respectively, with in total 1.4% and only 0.5% of administered $^{14}$C-labelled quizartinib. In both rat and dog faeces almost 90% of $^{14}$C-label was found, consisting of at least 15 - 22 $^{14}$C-labelled peaks, including unchanged quizartinib (rat 22% & dog 34%), AC886 (8.5% & 13%), M40.1 (12% & 5%, morpholino N-oxidation), M25.7 (6% & 10%, isoxazole-ring opening) and M23.4 (11%, rat only). The other peaks were below 5%. No gender differences were found.

Results from an unlabelled study performed in bile cannulated rat indicated that in bile 6.0% of unchanged compound was found. In addition to M19 and M1 (AC886), several other metabolites were detected. Metabolite profiling indicated that the major metabolic pathways for quizartinib include oxidation (M19', M1/AC886) and conjugation (M1-sulphate) of the isoxazole moiety, and oxidation (M14, M49, M38) and cleavage (M2', M49, M48) of the morpholino group, which is consistent with metabolic pathways in humans.

**Excretion**

Excretion was determined in [$^{14}$C]quizartinib mass balance studies in rats, dogs at 168 h and humans at 336 h post-dose. Total recovery was high in rat (95%) and dog (91%) at 168 h post-dose, and 78% in humans at 336 h. Quizartinib was found to be primarily excreted as metabolites via faeces in both animals and humans. In rats and dogs, these ADME studies showed that less than 2% of total quizartinib-related radioactivity was recovered from the urine, while more than 89% of radioactivity was recovered, via biliary excretion, in faeces. In humans, urinary excretion was also low (<2%), while 76% was recovered in faeces.

## 2.5.3. Toxicology

### *2.5.3.1. Single dose toxicity*

Single-dose toxicity was assessed in Sprague-Dawley rats, beagle dogs and cynomolgus monkeys up to 300 mg/kg, 200 mg/kg and 400 mg/kg quizartinib dihydrochloride respectively. Mortality only occurred in female rats treated with ≥150 mg/kg. In dogs, no severe treatment-related findings were observed, with the exception of slight bodyweight loss in the female dog treated with ≥40 mg/kg.

Bodyweight loss was also observed in monkeys treated with ≥100 mg/kg, accompanied with reduced food intake and soft/loose/liquid faeces.

### *2.5.3.2. Repeat dose toxicity*

Repeat-dose toxicity studies were conducted in Sprague-Dawley rats, beagle dogs and cynomolgus monkeys given quizartinib dihydrochloride for up to 13 weeks, including a 4-week recovery period for all pivotal studies. Exposure levels to quizartinib were low for dogs (13 weeks, up to 10 mg/kg/day, margin-of-exposure (MOE): 1.14-1.59) and monkeys (13 weeks, up to 12 mg/kg/day, MOE: 0.52-0.98) and relatively higher in rats (13 weeks, up to 10mg/kg/day, MOE: 7.90-10.37).

Quizartinib-related observations were observed in principal target organs such as the bone marrow and lymphoid organs in all three species, accompanied by related haematological and clinical chemistry parameters. Dose-dependent bone marrow hypocellularity correlated with decreased white and red blood cell indices in rats treated with ≥3 mg/kg/day, dogs treated with 15 mg/kg/day and monkeys treated with ≥10/6 mg/kg/day. In both dogs and monkeys these observations mainly recovered, where as in rats these observations only partially resolved after a 30-day recovery period. NOAELs for severe haematopoietic inhibition are 3 mg/kg/day for rats (MOE: 1.42-1.51) and monkeys (MOE: 0.07-0.10) and 5 mg/kg/day for dogs (MOE: 0.41-0.54). These effects on haematopoietic tissues can be interpreted as exaggerated pharmacology and are likely relevant for humans.

Lymphoid atrophy in the thymus was observed in a dose-dependent manner in all three species in the pivotal studies (13 weeks, rats and dogs treated with ≥1 mg/kg/day, monkeys treated with ≥10 mg/kg/day). In addition, lymphoid atrophy in the spleen was also observed in monkeys treated with ≥10 mg/kg/day (28 days) and ≥3 mg/kg/day (13 weeks). Rats treated with 60/30 mg/kg/day and dogs treated with ≥ 50/25 mg/kg/day also showed splenic lymphoid atrophy, but not in the 13 weeks study. These observations were reversible in all species after a 4-week recovery period.

Liver toxicity appeared in all species. Rats treated with ≥15 mg/kg/day for 28 days or ≥3 mg/kg/day for 13 weeks only demonstrated elevated liver enzyme (AST/ALP/ALT) levels, but no histological changes in the liver. In monkeys, 28 days treatment at the high dose also led to elevated liver enzymes, but additional increases in bilirubin levels and histological changes (single cell/centrilobular necrosis, hepatocellular vacuolation) were only observed in monkeys after 13 weeks. Dogs showed elevated AST, ALT, ALP and bilirubin levels when treated with ≥50/25 mg/kg/day for 28 days or 15 mg/kg/day for 13 weeks. This was accompanied with single cell necrosis, sinusoidal cell activation and hepatocellular vacuolation. NOAELs for hepatotoxicity are 5 mg/kg/day for rats (MOE: 0.96-1.01), 3 mg/kg/day for monkeys (MOE: 0.07-0.10) and 5 mg/kg/day for dogs (MOE: 0.41-0.54). Liver is a target organ of toxicity, likely relevant for humans. Birefringent crystal depositions in the dog liver and rat kidney were observed in the pivotal repeat-dose toxicity studies. The crystals found in the dog liver and rat kidney were considered composed of quizartinib and several metabolites (53 in dog; 17 in rat), without significant protein components.

Reversible tubular basophilia without any clinical chemistry correlates was also observed in the kidney of dogs treated with ≥ 50/25 mg/kg/day for 28 days and ≥1 mg/kg/day for 13 weeks. In addition, all male dogs treated with 15 mg/kg/day showed non-birefringent renal tubular pigment deposits. Similar situation has been observed in Rats. Elevated urea and creatinine levels were observed in monkeys treated with ≥ 3 mg/kg/day, but no correlating histological changes in the kidneys were observed at any dose level. NOAELs for renal toxicity are 3 mg/kg/day for rats (MOE: 1.42-1.51) and 30/12 mg/kg/day monkeys (MOE: 0.52-0.98) and 15 mg/kg/day for dogs (MOE: 0.52-0.92). Kidney is a target organ of toxicity, likely relevant for humans.

Toxicity in reproductive organs was also observed in rats and monkeys. Male rats treated with 60/30 mg/kg/day for 28 days or 10 mg/kg/day for 13 weeks showed germ cell necrosis and atrophy of the seminiferous epithelium in the testes accompanied by aspermia in the epidydimides observed at approximately 8 times the recommended human dose (RHD) based on AUC. This was also observed for male monkeys treated with ≥10/6 mg/kg/day for 13 weeks observed at approximately 0.5 times the RHD based on AUC and for both species this finding was not observed after a 4-week recovery period. Female rats treated with ≥ 1 mg/kg/day for 13 weeks showed non-reversible abnormal epithelial mucification of the vagina and when treated with ≥ 3 mg/kg/day ovarian cysts. In female rats, ovarian cysts and vaginal mucosal modifications were observed at doses approximately 10 times the RHD based on AUC. Female monkeys showed reversible atrophy of the uterus, ovary and vagina at ≥10/6 mg/kg/day for 13 weeks observed at doses approximately 0.3 times the RHD based on AUC. NOAELs for reproductive organ toxicity are 3 mg/kg/day for rats (MOE: 1.42-1.51) and monkeys (MOE: 0.07-0.10) and 15 mg/kg/day for dogs (MOE: 0.52-0.92).

#### *2.5.3.3. Genotoxicity*

The genotoxic potential of quizartinib was evaluated in a bacterial reverse mutation assay, mammalian cell (mouse lymphoma thymidine kinase) mutagenicity assay, chromosome aberration assay in human lymphocytes, rat bone marrow micronucleus assays following a single or 28-day repeat oral dosing of quizartinib, and a transgenic rodent (TGR) mutation assay (Big Blue Assay in Fisher 344 rats). Quizartinib tested positive in the bacterial reverse mutation assay in strains TA98 and TA100, but was negative in the chromosome aberration assay, mammalian cell mutation and in the single dose rat bone marrow micronucleus assay. A rat micronucleus assay conducted in conjunction with the 28-day general toxicology study had an equivocal result, as there were significant increases in micronucleated immature erythrocytes. However, these were within the range of historical controls. The second *in vivo* assay, TGR assay was negative, which overrules the positive *in vitro* findings in the Ames test.

#### *2.5.3.4. Carcinogenicity*

Quizartinib is intended to be administered in patients with advanced cancers; therefore, carcinogenicity studies are not deemed necessary consistent with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline S9, "Nonclinical Evaluation for Anticancer Pharmaceuticals" (ICH S9, 2009).

#### *2.5.3.5. Reproductive and developmental toxicity*

Embryo-foetal toxicity studies were conducted in a dose range-finding study and a definitive GLP study in time mated SD rats from Gestation Day (GD) 6 to GD 17, the period of organogenesis. Foetal toxicity was evident at 6 mg/kg/day, primarily consisting of lower foetal weights and effects on skeletal ossification. Teratogenicity was also observed at the same dose as evidenced by high incidence of foetal malformations (anasarca). Foetotoxicity and teratogenicity were observed at doses approximately 3 times the RHD based on AUC. The NOAEL is 2 mg/kg/day (MOE: 0.53) for general toxicity and reproduction in dams and for embryo-foetal development.

The juvenile toxicity studies were conducted in a dose range-finding and definitive studies in juvenile male and female Sprague-Dawley rats. This study identified no other findings as observed in adult rats. Primary target organs were the bone marrow and male reproductive organs. The NOAEL was set at 0.3 mg/kg/day for juvenile rats (MOE: 0.07). The juvenile toxicity studies are not relevant for the current application for adult patients only.

#### *2.5.3.6. Toxicokinetic data*

#### *2.5.3.7. Local tolerance*

No specific animal studies have been conducted to evaluate local tolerance since quizartinib is intended to be used by oral treatment. Quizartinib was tested for antigenicity in guinea pigs and based on the results not considered to be a contact sensitiser in guinea pigs. Due to a low potential for physical and physiological addition, no dependence studies were conducted with quizartinib.

#### *2.5.3.8. Other toxicity studies*

The potential toxicities of 5 impurities (AB200631, AC016778, AC016679, AC016928 and AC012917) were evaluated in a 28-day repeat dose oral toxicity study in rats (Study No. 1258-023). In the study, quizartinib spiked with impurities induced some changes including decreased thymus, spleen, and testes weights and increased ALT/AST values. Although it was considered to be related to the addition of impurities, they were concluded to be non-adverse.

Considering phototoxicity, while it is possible that quizartinib accumulates in melanin-containing tissues after repeated administration of quizartinib at the dosage and administration for which the application is being filed, quizartinib was concluded not to have phototoxic potential; no treatment-related changes were seen either in ophthalmology or histopathology of the eye or skin in rats, dogs, or cynomolgus monkeys; and the frequency of Grades ≥3 Skin and subcutaneous tissue disorders SOC, eye disorders SOC, and potentially relevant clinical findings was low. Therefore, the risk of quizartinib-induced phototoxicity in patients is considered low.

Ocular and dermal irritation studies were conducted in rabbits to support workplace safety. Based on the results, quizartinib is considered to be a mild irritant to ocular tissue of the rabbit and a slight irritant to the skin of the rabbit.

## 2.5.4. Ecotoxicity/environmental risk assessment

**Table 1. Summary of main study results**

| **Substance (INN/Invented Name):** quizartinib (free base) | | | |
|---|---|---|---|
| **CAS-number (if available):** 950769-58-1 | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD 123 | log $D_{ow}$ 4.88 (pH 5)<br>log $D_{ow}$ >5.33 (pH 7, 9) | |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Bioaccumulation | log $K_{ow}$ | >5.33 | |
| | BCF | <1192 L/kg$_{ww}$ | not B |
| Persistence | ready biodegradability | not readily biodegradable | |
| | DegT50 | parent<br>$DT_{50\ water}$: 3.8; 3.8 d<br>$DT_{50\ sediment}$: 185; 84 d<br>$DT_{50\ system}$: 4.5; 4.9 d<br><br>metabolite WS1<br>$DT_{50\ water}$: 88; >1000 d<br>$DT_{50\ sediment}$: >1000; 456 d<br>$DT_{50\ system}$: >1000; 584 d | $DT_{50}$ values corrected to 12°C.<br><br>Both values determined using lake sediment.<br><br>Conclusion: |

| | | | | | |
|---|---|---|---|---|---|
| | | metabolite WS2<br>$DT_{50\ water}$: 82.6; >1000 d<br>$DT_{50\ sediment}$: 571; >1000 d<br>$DT_{50\ system}$: 420; >1000 d | | | parent: potentially P<br>WS1: P/vP<br>WS2: P/vP |
| Toxicity | NOEC fish | P.M. | | | P.M. |
| | CMR | no data, substance not registered in C&L inventory | | | |
| **PBT-statement:** | Quizartinib is not PBT, nor vPvB | | | | |
| ***Phase I*** | | | | | |
| ***Calculation*** | **Value** | **Unit** | | | **Conclusion** |
| $PEC_{surface\ water}$ | 0.006 | µg/L | | | > 0.01 threshold: N |
| Other concerns (e.g. chemical class) | potential endocrine disruptor | A targeted ERA was performed | | | |
| ***Phase II Physical-chemical properties and fate*** | | | | | |
| **Study type** | **Test protocol** | **Results** | | | **Remarks** |
| Adsorption-Desorption | OECD 106 | $K_{oc\ sludge}$ = 436.4; 484.9 L/$kg_{oc}$<br>$K_{oc\ soil}$ = 14359; 27677; 44275 L/$kg_{oc}$ | | | |
| Ready Biodegradability Test | OECD 301B | not readily biodegradable | | | |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | parent<br>$DT_{50\ water}$: 1.8; 1.8 d<br>$DT_{50\ sediment}$: 87.2; 39.6 d<br>$DT_{50\ system}$: 2.1; 2.3 d<br><br>metabolite WS1<br>$DT_{50\ water}$: 41.5; >1000 d<br>$DT_{50\ sediment}$: >1000; 215 d<br>$DT_{50\ system}$: >1000; 275 d<br><br>metabolite WS2<br>$DT_{50\ water}$: 38.9; >1000 d<br>$DT_{50\ sediment}$: 269; >1000 d<br>$DT_{50\ system}$: 198; >1000 d | | | $DT_{50}$ values at 20°C.<br><br>Both values determined using lake sediment.<br><br>Significant shifting to sediment observed. |
| ***Phase IIa Effect studies*** | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Fish, acute toxicity test / *O. latipes* | OECD 203 | LC50 | >0.57 | mg/L | mortality |
| ***Phase IIb Studies*** | | | | | |
| Bioaccumulation | OECD 305 (dietary) | $BCF_{KgL}$ | <1192 | L/$kg_{ww}$ | normalised to 5% lipids |
| Sediment dwelling organism/*C. riparius* | OECD 218 | EC10 | 181 | mg/$kg_{dw}$ | emergence, not normalised to o.c. content |
| Sediment dwelling organism/*L. variegatus* | OECD 225 | NOEC | 500 | mg/$kg_{dw}$ | reproduction; not normalised to o.c. content |

*Conclusions on studies for quizartinib*

Quizartinib is not PBT, nor vPvB.

The ERA cannot be finalised since a chronic, fish reproduction study is missing.

The applicant has provided a commitment to submit the ongoing OECD 240 study and an updated ERA as soon as the study is finalised. The sediment risk assessment should be based on test results that are not normalised to organic carbon content and the $PEC_{sediment}$ should be calculated using the highest $K_{f\ soil}$ (not normalised).

## 2.5.5. Discussion on non-clinical aspects

The inhibition of tumour cell growth, through inhibition of FLT3-ITD kinase activity (i.e. phosphorylation) was demonstrated on MV4-11 AML cell line, after treatment with quizartinib or AC866 compared the RS4;11 cell line (full FLT3). The effects were more marked in the MV4-11 cell line compared to RS4;11 and the IC50 of quizartinib was 0.3 nM. Quizartinib binds with high affinity not only to FLT3 but also, albeit with less affinity, to KIT and RET. The active metabolite AC886 binds with high affinity not only to FLT3 but also, although with less affinity, to KIT and PDGFRβ. Inhibition of these other kinases are likely to play a minor role in the efficacy of quizartinib.

Four *in vivo* studies have been provided on MV4-11 model in mice, 3 with a localised model and 1 on a disseminated one. In the localised tumour models, a time–dependent reduction of phosphorylated FLT3 was retrieved after administration of quizartinib as a single dose, and the maximal effect was reached at 6h post dose (7% of p-FLT3). However, the method to determine expression could not be assessed as the provided SOP for p/tFLT3 determination only lists materials. A rebound in p-FLT3 was observed starting at 48h post dose. Dose-dependent inhibition of quizartinib of tumour growth was demonstrated from 1 to 10 mg/kg, on a 28-day treatment and no regrowth until 32 days after discontinuation of quizartinib dihydrochloride was observed. At a lower dose of 0.5 mg/kg for 10 days, tumour growth was inhibited by quizartinib, while a reduction in tumour volume was seen when quizartinib was combined with cytarabine and daunorubicin. In the disseminated MV4-11 model, quizartinib demonstrated efficacy by prolonged survival rate correlated with delayed disease onset, as measured by clinical signs and detection of circulating MV4-11 cells in peripheral blood and bone marrow. The efficacy of quizartinib was superior after 150 days treatment as compared to 31 days of treatment in NOD/SCID mice subcutaneously inoculated with MV4-11.

Any secondary pharmacodynamic interaction of quizartinib or AC886 as tested against a diverse panel of 118 non-kinase enzymes, receptors, channels, and transporters has shown the high selectivity of quizartinib and its major metabolite (AC886) and any other interaction has been considered not clinically relevant.

Besides mutations in FLT3 leading to resistance, there is a theoretical possibility of strong CYP3A4 inducers and strong CYP3A4 inhibitors resulting in altered concentrations quizartinib in the bone marrow, which might lead to dose adjustments.

It appears that both quizartinib and AC886 induced blockade of hERG current and IKs, and thereby caused QT prolongation by a decrease in the net repolarisation currents also at lower concentrations than measured before. The effect on IKs was more dominant than that on hERG current. The IKs IC50 of quizartinib of 0.3 µM (ca. 168 ng/ml) is between the human Cmax at 60 mg of 112 ng/ml (Day 1) and 487 ng/ml (Day15) and could therefore be relevant. Although no account is given here for the high protein binding of the compound and its metabolite, clear effects on QT prolongation have been seen in humans and is marked as a possible side effect which could increase the risk of ventricular arrhythmias or torsade de pointes.

The pharmacokinetic behaviour of quizartinib was evaluated in Sprague-Dawley rats, Beagle dogs and Cynomolgus monkeys upon IV and oral administration and, only after oral administration, in nu/nu mice. Repeat dose toxicokinetics (TK) was studied upon 4 and 13 week oral dosing in rat, dog and monkey.

The IV pharmacokinetics in rat and dog was characterised by low plasma clearance values (0.4 L/h.kg) but was high in monkey (1.7 L/h.kg). The volume of distribution was high in all preclinical species, with values ranging from 2.9 to 4.8 L/kg. The terminal elimination half-life ranged from 4 h in mouse, 5 h in

rat, 7 h in dog and 2 h in monkey, which is much lower than the terminal elimination half-life of 73 h found in human.
Oral absorption was moderately fast in all preclinical species with peak concentrations occurring about 1-4, 2-4, 1-2 and ~2 hours after dosing in mice, rats, dogs and monkeys, respectively, and increased with increasing dose or administration. In general, no gender differences were found. An *in vitro* study investigating BCRP-mediated transcellular transport in BCRP-expressing LLC-PK1 cells showed that the major human metabolite AC886 was a substrate for human BCRP, while quizartinib was not. The applicant will investigate *in vitro* if quizartinib is an inhibitor of BCRP at the highest concentration possible to elucidate if quizartinib is an inhibitor of BCRP at maximal intestinal concentrations.

Oral bioavailability from a HPβCD solution formulation, which was used in the toxicity studies, was 45% in rat and 41% in dog but only 14% in monkey. No large food effect was found in rats and dogs using the HPβCD formulation but this was variable and depended on the formulation used. In humans no food effect was found. Accumulation of exposure upon multiple dosing was low in dog (0.6-0.9x) and rat (1.2-2.7x) but 2.8-4.6x in monkey, which is not in line with the short (2 h) elimination half-life. In humans an accumulation ratio of 4.9 was found.

Plasma protein binding (PPB) of quizartinib was extremely high across all species examined, including human (>99%). Unbound quizartinib plasma concentration (Fu) at the clinically relevant concentrations seems to be about 3- and 5-fold higher in human (1.0%) as compared to dog, monkey (0.3%) and rat or mouse plasma (0.2%). The major human metabolite AC886 was also highly protein bound (>99%). Unbound AC886 plasma concentration was 0.3% in human plasma at the clinically relevant concentrations as compared 0.1%, 0.2%, 0.5% and 0.6% in mouse, rat, monkey and dog, respectively. In addition, quizartinib has preferential partitioning into red blood cells in monkey (blood to plasma (B/P) ratio 1.0) and human (1.3) but less in rat or dog (B/P 0.7). More prominent results were found with AC886 with B/P ratios of 3.0, 0.8 and 1.2 for human, rat and dog, respectively.

Biotransformation of quizartinib in rat, dog and human primarily involves enzymatic oxidation but was low in plasma, and unchanged quizartinib was the primary drug-related component in rat (74%), dog (59%) and in human (77%). In addition, in humans, AC886 was identified as the major, active, human metabolite, representing 16% of total exposure. AC886 is also present in plasma of preclinical toxicology species (22 & 16% in rat & dog) *in vivo*. In dog, also a morpholino N-oxide metabolite (22%) was found. The exposure (AUC) ratio of AC886/quizartinib upon single dosing was 0.9 in mouse, 0.7 in rat and 0.2 in dog and human but 8.6 in monkey. Upon multiple dosing, AC886/quizartinib ratio decreased with increasing dose and time in the rat (0.3) but increased in human (0.6). *In vitro* metabolism experiments showed that quizartinib, and AC886, showed a slow, limited metabolism, predominantly by CYP3A4/3A5.
Excretion of [$^{14}$C]-labelled quizartinib and associated radioactivity via faeces (biliary excretion) was the major route of elimination in the tested preclinical species (rat and dog) and also in human.
Renal clearance plays a minimal role (<2%) in all species.

The toxicological profile of quizartinib has been evaluated during single and repeat-dose toxicity studies in rats, dogs, and cynomolgus monkeys. The main target organs are bone marrow, liver and kidney with less severe effects on the thymus, and reproductive organs (ovary, vagina and testes). The main safety concerns identified during non-clinical studies include QTc prolongation, myelosuppression, lymphoid depletion, gastrointestinal toxicity, and liver and kidney function abnormalities. Those effects are usually retrieved for oncolytic agents; more specifically, bone marrow and lymphoid tissues are the main targets in AML therapy. Birefringent crystal depositions in the dog liver and rat kidney were observed in the pivotal repeat-dose toxicity studies.

Quizartinib underwent a complete genotoxicity tests battery *in vitro* and *in vivo*, with respect to gene mutations in bacteria and mammalian cells. The Ames test was positive, when quizartinib was tested at dose level up to the maximum recommended dose (5000 µg/plate) with or without metabolic activation, in contrast to its negative result mammalian cell mutation (mouse lymphoma thymidine kinase) assay. Quizartinib was negative in a chromosome aberration assay or in a single dose rat bone marrow micronucleus assay. In human lymphocytes, no increases in chromosomal aberration were observed in absence or presence of metabolic activation at all concentrations tested. No increases in micronucleus frequency were found in micronucleus assays in rat as a single dose, PO at dosage levels up to 100 mg/kg (next to the MTD). Micronucleus assay conducted in conjunction with the 28-day toxicity study in rats showed a slight but statistically significant increase in the incidence of micronucleated immature erythrocytes. However, none of the individual values or the group means fell outside the historical control range. It appears that no exposure data are available for micronucleus study (single dose), but exposure was assessed during 28-day micronucleus study and some margin of exposure exist in rats. A further *in vivo* transgenic rodent mutation assay was conducted in Fisher 344 Big Blue rats. The assay was negative, indicating no mutagenic potential of quizartinib in this model, which overrules the positive *in vitro* findings in the Ames test. Exposure was not assessed in this assay, and no TK is available for this strain of rats. Sufficient exposure at the high dose can be assumed however, based on TK from SD rats. Overall, it can be concluded that quizartinib has low genotoxic potential.

Quizartinib is intended to be administered in patients with advanced cancers; therefore, carcinogenicity studies are not deemed necessary consistently with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline S9, "Nonclinical Evaluation for Anticancer Pharmaceuticals" (ICH S9, 2009). The lack of dedicated carcinogenicity studies is acceptable.

Fertility studies in animals have not been conducted with quizartinib. However, adverse findings in male and female reproductive systems were observed in repeat dose toxicity studies in rats and monkeys. In female rats, ovarian cysts and vaginal mucosal modifications were observed at doses approximately 10 times the RHD based on AUC. Findings in female monkeys included atrophy of the uterus, ovary, and vagina; observed at doses approximately 0.3 times the RHD based on AUC. In male rats, testicular seminiferous tubular degeneration and failure of sperm release were observed at approximately 8 times the RHD based on AUC. Findings in male monkeys included germ cell depletion in the testes; observed at approximately 0.5 times the RHD based on AUC. After a four-week recovery period, all these findings except the vaginal mucosal modifications in the female rats were reversible. In embryo foetal reproductive toxicity studies, embryo foetal lethality and increased post-implantation loss were observed at maternally toxic doses. Foetotoxicity (lower foetal weights, effects on skeletal ossification) and teratogenicity (foetal abnormalities including oedema) were observed at doses approximately 3 times the RHD based on AUC. Quizartinib is considered to be potentially teratogenic. No pre- and postnatal studies were performed. Considering the patient population, this is agreed. Based on these data and as a general warning women of childbearing potential should undergo pregnancy testing within 7 days before starting treatment with quizartinib, should use effective contraception during treatment and for at least 7 months after the last dose. Male patients with female partners of childbearing potential should use effective contraception during treatment with quizartinib and for at least 4 months after the last dose.

The potential toxicities of 5 impurities were evaluated in a 28-day repeat dose oral toxicity study in rats (Study No. 1258-023). In the study, quizartinib spiked with impurities induced some changes including decreased thymus, spleen, and testes weights and increased ALT/AST values. Although it was considered to be related to the addition of impurities, they were concluded to be non-adverse.

Considering phototoxicity, while it is possible that quizartinib accumulates in melanin-containing tissues after repeated administration of quizartinib at the dosage and administration for which the application is being filed, quizartinib was concluded not to have phototoxic potential; no treatment-related changes were seen either in ophthalmology or histopathology of the eye or skin in rats, dogs, or cynomolgus monkeys; and the frequency of Grades ≥3 Skin and subcutaneous tissue disorders SOC, eye disorders SOC, and potentially relevant clinical findings was low. Therefore, the risk of quizartinib-induced phototoxicity in patients is considered low.

With respect to the environmental risk assessment (ERA), it is concluded that Quizartinib is not PBT, nor vPvB. The ERA, however, cannot be finalised since a chronic, fish reproduction study is missing. The applicant has provided a commitment to submit the ongoing OECD 240 study and an updated ERA as soon as the study is finalised. The sediment risk assessment should be based on test results that are not normalised to organic carbon content and the $PEC_{sediment}$ should be calculated using the highest $K_{f\ soil}$ (not normalised).

## 2.5.6. Conclusion on the non-clinical aspects

The pharmacological, pharmacokinetic and toxicological properties of quizartinib are sufficiently evaluated and described. There are no remaining issues from a non-clinical point of view. There is a commitment regarding the Environmental Risk Assessment as reported in the discussion above.

# *2.6. Clinical aspects*

## 2.6.1. Introduction

### *GCP aspects*

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

## 2.6.2. Clinical pharmacology

### *2.6.2.1. Pharmacokinetics*

Quizartinib is administered (as quizartinib dihydrochloride) in combination with standard chemotherapy at a dose of 35.4 mg (2 × 17.7 mg) once daily for two weeks in each cycle of induction. For patients who achieve complete remission (CR) or complete remission with incomplete haematologic recovery (CRi), quizartinib is administered at 35.4 mg once daily for two weeks in each cycle of consolidation chemotherapy followed by quizartinib single-agent maintenance therapy initiated at 26.5 mg once daily. After two weeks the maintenance dose is increased to 53 mg (2 × 26.5 mg) once daily if the QT interval corrected by Fridericia's formula (QTcF) is ≤ 450 ms. Single-agent maintenance therapy may be continued for up to 36 cycles.

The starting dose should be reduced to 17.7 mg once daily when quizartinib is given in combination with a strong CYP3A inhibitor. The drug product is an immediate release, solid oral dosage form film-coated tablet. The tablets are available in two strengths, 17.7 mg and 26.5 mg free base.

The applicant performed several clinical studies investigating the pharmacokinetics of quizartinib and its pharmacologically active metabolite AC886 (see Table 2).

**Table 2. PK studies in humans**

| study | PK objectives | dose and formulation |
|---|---|---|
| **healthy volunteers** | | |
| AC220-006* | absorption, metabolism, and excretion | 53 mg (spray-dried powder in bottle) |
| AC220-A-U107 | absolute oral bioavailability | 53 mg (commercial tablet) |
| AC220-014 | relative bioavailability and dose proportionality of commercial tablet | single dose of 26.5, 53, and 79.5 mg (spray-dried powder in bottle and commercial tablet) |
| AC220-019 | food effect | single dose of 26.5 mg (commercial tablet) |
| **patients** | | |
| 2689-CL-0011 | PK following multiple dosing | 26.5, 35.4, 53, and 79.5 mg once daily (spray-dried powder in bottle and commercial tablet) |
| 2689-CL-2004 | PK following multiple dosing | 26.5 to 53 mg once daily (commercial tablet) |
| 2689-CL-0005 | PK following multiple dosing | 35.4 to 53 mg once daily (commercial tablet) |
| AC220-007 | PK following multiple dosing | 17.7 to 53 mg once daily (commercial tablet) |
| AC220-A-J101 | PK following multiple dosing in Japanese patients | 17.7 to 53 mg once daily (commercial tablet) |
| AC220-A-J102 | PK following multiple dosing in Japanese patients | 17.7 to 35.4 mg once daily (commercial tablet) |
| AC220-A-J201 | PK following multiple dosing in Japanese patients | 17.7 to 53 mg once daily (commercial tablet) |
| AC220-A-U302 | PK following multiple dosing | 17.7 to 53 mg once daily (commercial tablet) |
| **special populations** | | |
| AC220-016 | effect of mild or moderate hepatic impairment on PK | 26.5 mg (commercial tablet) |
| AC220-A-U105 | effect of moderate hepatic impairment on PK | 26.5 mg (commercial tablet) |
| **DDI studies with quizartinib as victim** | | |
| AC220-015 | effect of ketoconazole and fluconazole on PK of quizartinib | 26.5 mg (commercial tablet) |
| AC220-A-U106 | effect of efavirenz (a moderate CYP3A inducer) on the PK of quizartinib | 53 mg (commercial tablet) |
| AC220-018 | effect of gastric pH modification by lansoprazole on PK of quizartinib | 26.5 mg (commercial tablet) |
| **DDI studies with quizartinib as perpetrator** | | |
| AC220-A-U104 | effect of quizartinib on the PK of P-glycoprotein substrate dabigatran etexilate | 53 mg (commercial tablet) |

Modelling

Population PK (PopPK) modelling

*Objective*

The population pharmacokinetic analyses aimed at:

- developing a population model describing the PK characteristics of quizartinib, including associated inter-individual variability and residual unexplained variability and evaluating the impact of selected covariates on the quizartinib parameters that exhibit inter-individual variability.

- extending the quizartinib model to describe the PK characteristics of AC886, including associated inter-individual variability and residual unexplained variability and evaluating the impact of selected covariates on the AC886 parameters that exhibit inter-individual variability.
- deriving secondary PK parameters ($AUC_{ss}$ and $C_{max,ss}$) in the AC220-A-U302 study that can be used in the exposure-response (ER) analysis and in the graphical comparison of quizartinib and AC886 exposure across region/country subgroups

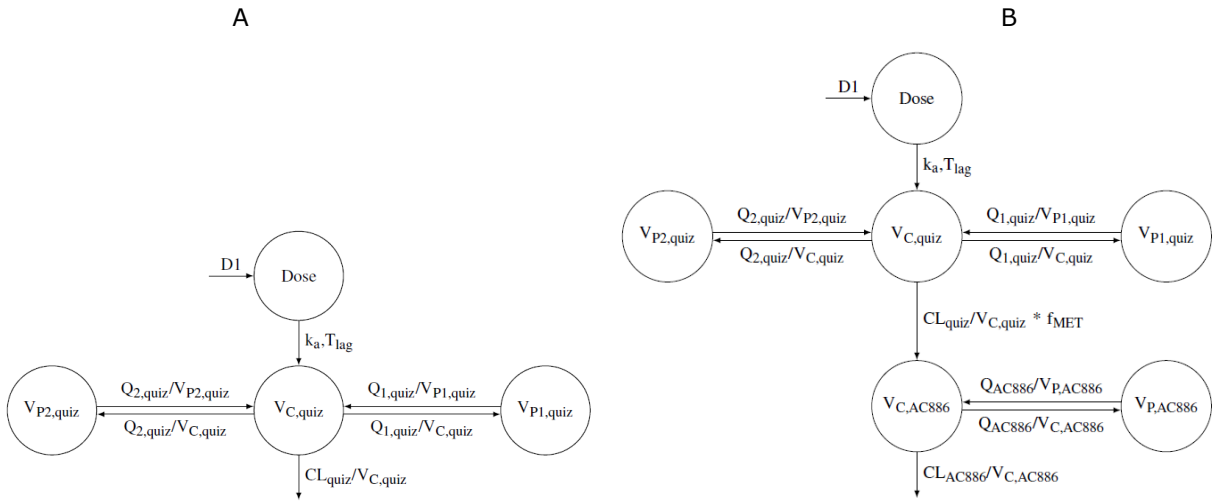
*Data*

The following studies in healthy volunteers were included: AC220-014, AC220-015, AC220-016, AC220-018, AC220-A-U105. The following studies in patients were included: 2689-CL-0005, 2689-CL-0011, 2689-CL-2004, AC220-A-J101, AC220-A-J102, AC220-A-J201, AC220-007 and AC220-A-U302. During the analysis, observations below the lower limit of quantification (LLOQ) were excluded. The observed and predicted quizartinib and AC886 concentrations associated with absolute conditional weighted residuals (CWRES) >5 were excluded from the data set to avoid undue influence of outliers. A total of 1710 observations were excluded for quizartinib and 2499 for AC886. A PopPK model was developed with a total of 14160 quizartinib and 13399 AC886 observations following oral administration of quizartinib from 932 subjects (273 healthy subjects and 659 patients).

*Population pharmacokinetic model*

A population pharmacokinetic model was developed using non-linear mixed effects modelling software (NONMEM, version 7.4.4). Model evaluation was conducted using standard goodness-of-fit plots and numerical diagnostics. The PK of quizartinib was best described by a three-compartment model with sequential zero- and first-order absorption and a first-order elimination from the central compartment (see figure 2).

**Figure 2. PopPK model for quizartinib (A) and AC886 (B)**




The covariates evaluated were: body weight; weak, moderate and strong CYP3A inducers; weak, moderate and strong CYP3A inhibitors; race; relapsed/refractory (R/R) subjects; newly diagnosed AML subjects; age; gender; region (Japan, mainland China, Taiwan, Hong Kong, and Korea); Asians living in other countries; creatinine clearance, alanine aminotransferase, alkaline phosphatase, total bilirubin, and albumin; hepatic impairment by NCI-ODWG criteria; acid reducing agent, proton pump inhibitor; and formulation.

Physiologically Based Pharmacokinetic (PBPK) modelling

PBPK modelling was performed to predict the drug-drug interaction (DDI) between quizartinib and the substrates of UGT1A1. The base PBPK model was developed based on a combination of *in vitro* and clinical PK data of a single IV 50 µg dose of $^{14}$C-quizartinib and an oral 53 mg dose of quizartinib in healthy subjects (study AC220-A-U107). The model was further validated using clinical data after multiple dosing of quizartinib to AML patients (study 2689-CL-2004). Simulated PK profiles, $AUC_{inf}$ or $AUC_{tau}$, and $C_{max}$ of quizartinib following a single dose of 26.5 to 53 mg to healthy subjects and repeat oral doses of 26.5 mg once daily and 53 mg once daily to AML subjects were within 2-fold of observed data. The developed quizartinib PBPK model was used to predict the DDI potential between quizartinib and raltegravir (built-in PBPK model in Simcyp Simulator version 20).

Exposure-response modelling

The overall aim of the exposure-response analysis was to further support the quizartinib dosing regimen. The exposure-response relationships were evaluated for:

- *Efficacy*: overall survival (OS), event free survival (EFS) based on the definition of induction treatment failure as failure to achieve complete remission (CR) within 42 days from the start of the last cycle of induction chemotherapy, and remission rate defined as CR, CR with minimal residual disease (MRD) negativity, composite CR (CRc), CRc with MRD negativity.
- *Safety*: Fridericia-corrected QT interval (QTcF) and the first occurrence of treatment emergent adverse events (TEAEs) of any grade, TEAEs of grade greater or equal to 3, serious TEAEs, TEAEs leading to dose reduction/interruption, TEAEs leading to dose discontinuation, events in the torsade de pointes (TdP)/QT prolongation Standardized MedDRA Query (SMQ), infection, haemorrhages, hepatotoxicity and myelosuppression. Additionally, a graphical exploration of the relationship between QT and the interval between two R waves on electrocardiogram (ECG) (RR) was performed to investigate if the QT interval appropriately shortens at high heart rates after quizartinib treatment.

The exposure-response modelling was mainly performed for study AC220-A-U302. A total of 268 patients treated with placebo and 244-263 patients treated with quizartinib were included for the efficacy and safety evaluation. The exposure metrics for quizartinib in plasma were derived using the empirical Bayes estimates of the individual PK parameters based on the final population PK model. The exposure metric was defined as predicted quizartinib $AUC_{0\text{-}24,ss}$ following 40 mg once daily in the induction phase. Overall survival was found to be related to quizartinib exposure. No exposure-response relationship was identified for remission rate and EFS based on the definition of induction treatment failure as failure to achieve CR within 42 days from the start of the last cycle of induction chemotherapy. NPM1 mutation was found to be associated with significantly higher rates of CR and CRc, irrespectively of quizartinib treatment. An $E_{max}$ model best described the relationship between quizartinib concentration and QTcF. No exposure-response relationship was identified for the probability of the first occurrence of TEAEs of any grade, TEAEs of grade greater or equal to 3, serious TEAEs, TEAEs leading to dose reduction/interruption, TEAEs leading to dose discontinuation, events in the TdP/QT prolongation SMQ, infection, haemorrhages, hepatotoxicity and myelosuppression.

Analytical

Quizartinib and AC886 were measured in plasma using a sufficiently validated LC-MS/MS method. Furthermore, validated analytical methods were developed for the determination of quizartinib and its metabolites in urine and faeces.

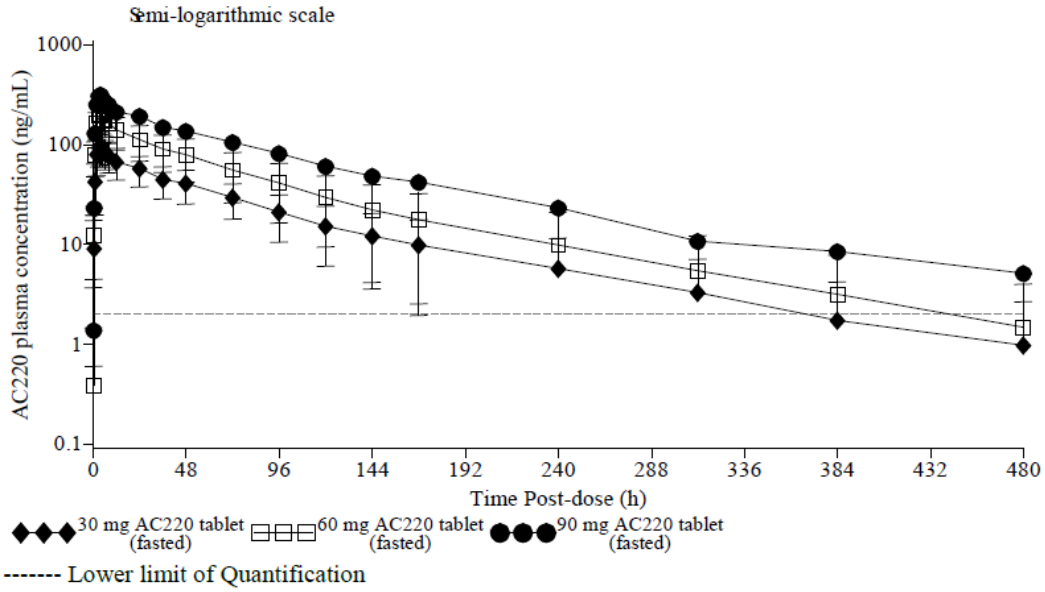
Absorption

The *in vitro* permeability of quizartinib in Caco-2 cells was 0.981 × $10^{-6}$ cm/s at a concentration of 10 µM suggesting that quizartinib is a low permeable compound. This was confirmed in an *in vitro* study using MDCK cells.

Following oral single dose administration under fasted conditions, the absolute oral bioavailability of a 53 mg dose was ~71% and ranged from 58% to 79% for the different individuals.

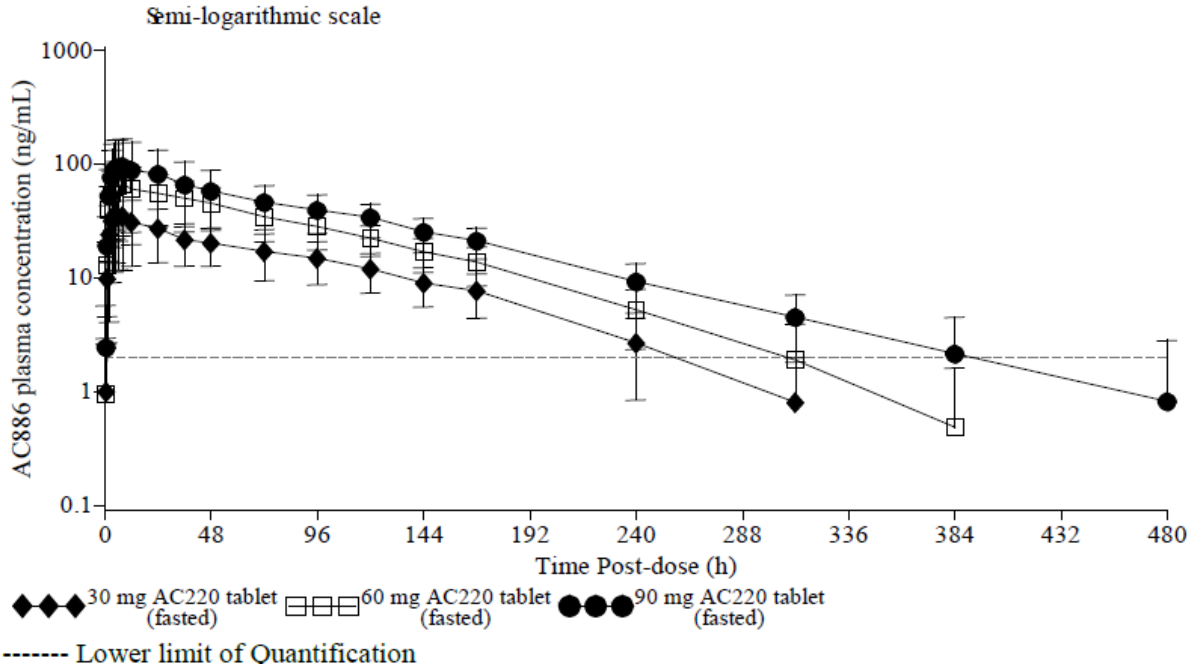
The time to maximum observed plasma concentration ($t_{max}$) of quizartinib is approximately 4 hours in healthy volunteers independent of the dose. At a dose of 26.5 mg quizartinib, the mean maximum concentration ($C_{max}$) ranged from 89 to 105 ng/mL and the mean exposure ($AUC_{inf}$) ranged from 5909 to 9626 ng ×h/mL. At a dose of 53 mg quizartinib, the mean maximum concentration ($C_{max}$) ranged from 178 to 238 ng/mL and the mean exposure ($AUC_{inf}$) ranged from 10899 to 25900 ng ×h/mL. Plasma concentration – time curve is shown in Figure 3.

**Figure 3. Arithmetic mean (±SD) plasma concentration-time profiles for quizartinib (AC220) following single oral dose administration of 26.5 mg, 53 mg and 79.5 mg quizartinib (30 mg, 60 mg, and 90 mg quizartinib dihydrochloride)**




For the major metabolite AC886, the mean $t_{max}$ ranged from 5 to 6 hours. At a dose of 26.5 mg quizartinib, the mean $C_{max}$ ranged from 13 to 32 ng/mL and the mean $AUC_{inf}$ ranged from 1970 to 3560 ng ×h/mL. At a dose of 53 mg quizartinib, the mean $C_{max}$ ranged from 34.4 to 51.3 ng/mL and the mean $AUC_{inf}$ ranged from 4550 to 6278 ng ×h/mL. At clinically relevant doses of 26.5 and 53 mg, the parent-metabolite ratio is approximately 0.39 for the AUC and 0.21 for the $C_{max}$ in healthy subjects. Plasma concentration – time curve is shown in Figure 4.

**Figure 4. Arithmetic mean (±SD) plasma concentration-time profiles for AC886 following single oral dose administration of 26.5 mg, 53 mg and 79.5 mg quizartinib (30 mg, 60 mg, and 90 mg quizartinib dihydrochloride)**




No data was provided on the intra-individual variability in healthy volunteers. The inter-individual variability is 25 to 82% for quizartinib and 26 to 83% for AC886. Quizartinib and AC886 $C_{max}$ and AUC are dose proportional over a dose range of 26.5 to 79.5 mg quizartinib in healthy volunteers. Based on the half-lives of quizartinib and AC886 (63 to 136 h for quizartinib and 54 to 135 h for AC886) and the once daily dosing, accumulation is expected with once daily dosing to healthy volunteers.

The 17.7 mg dose was only investigated in the patient population. No PK data are available in healthy volunteers following the clinical starting dose of 35.4 mg or following repeated dosing. However, since the PK is dose proportional for quizartinib and AC886 over the dose range of 26.5 mg to 79.5 mg quizartinib, the PK for the clinical dose can be calculated.

Based on population pharmacokinetic modelling in newly diagnosed AML patients, at 35.4 mg/day, steady state during induction therapy, the geometric mean (%CV) Cmax of quizartinib and AC886 was estimated to be 140 ng/mL (71%) and 163 ng/mL (52%), respectively, and the geometric mean (%CV) AUC0-24h was 2,680 ng•h/mL (85%) and 3,590 ng•h/mL (51%), respectively.

During consolidation therapy at 35.4 mg/day, steady state, the geometric mean (%CV) Cmax of quizartinib and AC886 was estimated to be 204 ng/mL (64%) and 172 ng/mL (47%), respectively, and the geometric mean (%CV) AUC0-24h was 3,930 ng•h/mL (78%) and 3,800 ng•h/mL (46%), respectively.

During maintenance therapy at 53 mg/day, steady state, the geometric mean (%CV) Cmax of quizartinib and AC886 was estimated to be 529 ng/mL (60%) and 262 ng/mL (48%), respectively, and the geometric mean (%CV) AUC0-24h was 10 200 ng•h/mL (75%) and 5 790 ng•h/mL (46%), respectively.

Distribution

Quizartinib and AC886 are highly plasma-protein bound with measured values of ≥99%. The blood-to-plasma ratio of quizartinib and AC886 are concentration dependent, indicating saturation of the

distribution to erythrocytes. At clinically relevant plasma concentrations, the blood-to-plasma ratio is ~1.3 for quizartinib and ~2.8 for AC886.

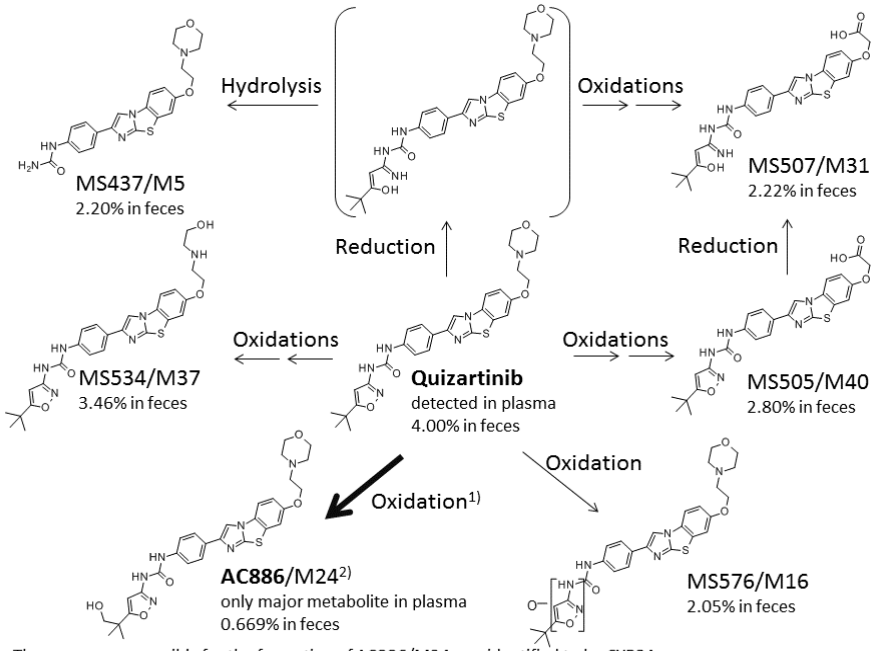
The volume of distribution was 275 following an IV dose of 50 µg radiolabelled quizartinib. The apparent volume of distribution ($V_d$/F) was 453 L in healthy volunteers, which is in the same range considering the absolute oral bioavailability.

Metabolism

*In vitro* studies show that AC886 is a metabolite of quizartinib and is formed by CYP3A4 and CYP3A5. AC886 is further metabolised to several metabolites by CYP3A4 (main contributor) and CYP3A5. The steady-state AC886-to-quizartinib AUC0-24h ratio during maintenance therapy was 0.57.

In humans, the metabolism profile was investigated in plasma, urine and faeces. However, the applicant investigated the metabolism profile in plasma in the plasma samples taken at 2 hours to 6 hours. Quizartinib has a half-life of ~75 hours. The sampling period is too close to the dose administration to accurately determine the metabolism profile; less than 1/10$^{th}$ of the elimination half-life. In plasma, the parent compound is the major component and AC886 is the major metabolite (~16% of the administered dose), with large intra-individual variability. In urine, radioactivity is only excreted as metabolites. In faeces, radioactivity is mainly excreted as metabolites (4% is excreted as parent and ~43% as metabolites; with the rest not identified). In total 41 metabolites were observed in faeces. Based on the provided data quizartinib is most likely mainly metabolised to AC886. The biotransformation route of AC886 is not clear. The proposed biotransformation pathway is shown in the Figure 5.

**Figure 5. Human biotransformation pathway of quizartinib**




1) The enzyme responsible for the formation of AC886/M24 was identified to be CYP3A
2) AC886 undergoes further metabolism (putative secondary metabolites: M14, M18, M19, M20, M26).
3) Most of other metabolites (not shown in this pathway) were minor (<2% in feces) .

Transporters

Quizartinib is a substrate of P-glycoprotein, but not of BCRP, OATP1B1, OATP1B3, OCT1, OAT2, MATE1, and MRP2. AC886 is a substrate of P-glycoprotein and BCRP, but not of OATP1B1, OATP1B3, MATE1, and MRP2.

Excretion

After absorption, the majority of the radioactivity is eliminated in faeces (also when taking the low recovery into account).

The half-life of quizartinib in healthy volunteers ranged from 63 to 136 h and is independent of the administered dose. The elimination half-life of AC886 is 54 to 135 h (independent of the dose).

***Special populations***

Mild and moderate renal impairment, mild and moderate hepatic impairment based on Child-Pugh criteria, age, and gender do not seem to have a clinically relevant impact the PK of quizartinib and AC886 (data not shown). The plasma protein binding appears higher in subjects with moderate hepatic impairment compared to normal hepatic function (data not shown). However, the plasma protein binding was still >99% for both subject groups. There are no data on the effect of severe hepatic impairment on the PK of quizartinib and AC886. At a body weight of 37 kg, the $C_{max}$ and AUC of quizartinib and AC886 increased by 1.7-fold compared to a body weight of 75 kg. At a body weight of 153 kg, the $C_{max}$ and AUC of quizartinib and AC886 decreased by 1.7-fold compared to a body weight of 75 kg. The applicant provided information (data not shown) that the lower exposure in patients with a body weight of 153 kg did not affect the efficacy to a significant extent. Furthermore, no exposure-safety relationship was observed, thus a low body weight does not appear to lead to an increase in safety issues.

Quizartinib and AC886 are metabolised by CYP3A4 and 3A5. CYP3A5 function resulted in a lower $C_{max}$ and AUC of quizartinib and a higher $C_{max}$ and AUC for AC886. The net effect is a lower Cmax and AUC for quizartinib + AC886. These results indicates that CYP3A5 contributes to the overall metabolism of quizartinib. However, the sum of quizartinib+AC886 exposures lies entirely within the 80% to 125% bound and is therefore not considered clinically relevant.

***Pharmacokinetic interaction studies***

DDIs with quizartinib as perpetrator

At maximal intestinal concentrations, quizartinib may be an inhibitor of P-glycoprotein, but is not an inhibitor of CYP3A4. A clinical DDI study with dabigatran etexilate indicated that quizartinib is not a clinically relevant inhibitor of P-glycoprotein at the maximal oral dose. Co-administration of quizartinib and dabigatran etexilate (a P-gp substrate) increased total and free dabigatran Cmax by 1.12-fold and 1.13-fold, respectively, and increased total and free dabigatran AUCinf by 1.13-fold and 1.11-fold, respectively. Quizartinib is a weak P-gp inhibitor, and no dose modification is recommended when P-gp substrates are co-administered with quizartinib. It is currently unknown if quizartinib is an inhibitor of BCRP at maximal intestinal concentrations. The applicant will investigate *in vitro* if quizartinib is an inhibitor of BCRP at the highest concentration possible to elucidate if quizartinib is an inhibitor of BCRP at maximal intestinal concentrations.

At maximal portal vein concentration, quizartinib is not an inhibitor of OATP1B1, OATP1B3, and OCT1.

At maximal systemic concentrations, quizartinib and AC886 are not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A, and the transporters P-glycoprotein, BCRP, OATP1B1, OATP1B3, OCT1, OCT2,

OAT1, OAT3, MATE1, MATE2-K and BSEP. In addition, quizartinib and AC886 are not time-dependent inhibitors of CYP. Quizartinib inhibits UGT1A1 with an estimated *in vitro* Ki of 0.78 µM. Based on a physiologically based pharmacokinetic (PBPK) analysis, quizartinib was predicted to increase the Cmax and AUCinf of raltegravir (a UGT1A1 substrate) by 1.03-fold% which was not considered clinically relevant. Quizartinib is not an inducer via AhR, CAR and PXR at the concentrations investigated at clinically relevant systemic concentrations. Higher concentrations could not be investigated due to cytotoxicity of quizartinib. However, there are some uncertainties regarding study XT1330187.

DDIs with quizartinib as victim

*In vitro*, it was elucidated that quizartinib and AC886 are mainly metabolised by CYP3A4 and 3A5. Furthermore, quizartinib is a substrate of P-glycoprotein and AC886 a substrate of BCRP.

Co-administration of ketoconazole (200 mg twice daily for 28 days), a strong CYP3A/P-gp inhibitor, with a single dose of quizartinib increased quizartinib maximum plasma concentration ($C_{max}$) and area under the curve (AUCinf) by 1.17-fold and 1.94-fold, respectively, and decreased AC886 Cmax and AUCinf by 2.5-fold and 1.18-fold, respectively, compared to quizartinib alone. At steady state, quizartinib exposure (Cmax and AUC0-24h) was estimated to be increased by 1.86-fold and 1.96-fold, respectively, and AC886 exposure (Cmax and AUC0-24h) decreased by 1.22-fold and 1.17-fold, respectively.

In contrast, Co-administration of fluconazole (200 mg twice daily for 28 days), a moderate CYP3A inhibitor, with a single dose of quizartinib increased quizartinib and AC886 Cmax by 1.11-fold and 1.02-fold, respectively, and AUCinf by 1.20-fold and 1.14-fold%, respectively. This change was not considered clinically relevant. Therefore, no dose reduction of quizartinib is necessary if co-administered with a moderate or weak CYP3A inhibitor.

A clinical DDI study with a moderate CYP3A4 inducer (efavirenz) resulted in a 9.7-fold decrease in quizartinib AUC and a 26-fold decrease in AC886 AUC. Therefore, co-administration of strong and moderate CYP3A inducers with quizartinib should be avoided due to possible lack of efficacy.

The proton pump inhibitor lansoprazole decreased quizartinib $C_{max}$ by 1.16-fold and $AUC_{inf}$ by 1.05-fold. This decrease in quizartinib absorption was not considered clinically relevant. Quizartinib can therefore be co-administered with gastric acid reducing agents (ARAs), such as proton pump inhibitors, H2 blockers, and antacids.

Co-administration of quizartinib with other medicinal products that prolong the QT interval may further increase the incidence of QT prolongation. Caution should be used when co-administering medicinal products that prolong the QT interval with quizartinib.

### *2.6.2.2. Pharmacodynamics*

#### *Mechanism of action*

Quizartinib is an inhibitor of the receptor tyrosine kinase FLT3. Quizartinib and its major metabolite AC886 competitively bind to the adenosine triphosphate (ATP) binding pocket of FLT3 with high affinity. Quizartinib and AC886 inhibit FLT3 kinase activity, preventing autophosphorylation of the receptor, thereby inhibiting further downstream FLT3 receptor signalling and blocking FLT3-ITD-dependent cell proliferation.

**Primary pharmacology**

The applicant demonstrated the selectivity and potency of quizartinib to inhibit FTL3 *in vitro*: with a biochemical competition binding assay the biochemical potency and selectivity of quizartinib was determined against a panel of 441 kinases. Quizartinib binds with the highest affinity to FLT3 (Kd = 1.3 nM) and with less affinity to KIT (Kd = 4.9 nM) and a few other class III RTKs.

**Analytical methods for FLT3-ITD biomarker detection**

The sponsor utilises the Navigate BP FLT3-ITD Mutation Assay for the determination of FLT3-ITD mutation status from bone marrow and/or blood samples to prospectively select subjects for entry into Study AC220-A-U302. This is a molecular assay that employs polymerase chain reaction (PCR) and capillary electrophoresis technology. Since the ITD mutation always occurs in exons 14 and 15 of the FLT3 gene, which includes the juxtamembrane domain and the N-terminal part of the kinase domain, this region, when amplified by PCR using a single set of DNA primers that flank the region, yields ITD mutant reaction products that are greater in size than 330 base pairs (bp) as well as nonmutant (FLT3 wild type) product. The lengths of ITDs have been reported to range in size from 3 bp to 400 bp, but they are most often between 15 bp and 150 bp. The FLT3-ITD Mutation Assay uses a fragment size analysis method to resolve and detect the different-sized PCR products. In this method, the PCR primers that target exons 14 and 15 of the FLT3 gene are conjugated with differential fluorescent dyes, and the PCR products are separated and detected by capillary electrophoresis.

The assay utilises genomic DNA isolated from ethylenediaminetetraacetate (EDTA)- or heparin anticoagulated peripheral blood or bone marrow. Three control samples are included in each assay run: the No-Template control (water); the Negative Control (nonmutant cell line DNA); and the Low Positive Control (mixing mutant cell line DNA with nonmutant cell line DNA such that the percent mutant is in the range of 6% to 10%).

Clinical Trial Assay Analytical Validation

Navigate BP performed a series of studies to validate the analytical performance of the FLT3-ITD Mutation.

A bridging study (IVS-062-005-01-001, report submitted with the response to LOQ) assessed concordance between the CTA and the *in vitro* assay developed to be the companion diagnostic at Invivoscribe (IVS; San Diego, CA, US, LeukoStrat® CDx FLT3 Mutation Assay). Samples from 1029 subjects from the clinical study, including screen failures, were retrospectively analysed and showed agreement with PPA 94.2% (91.8%, 96.0%) and NPA 99.4% (98.3%, 99.9%).

In this study mean ITD insert size was detected with 56.33 and 55.96 bp by CTA and CDx, respectively, with ranges from 6-243 and 4-259 bp, respectively. Only 33 and 26 samples, respectively, had ≥100 bp in the pivotal study population.

The detailed results of the clinical validation assessed in the bridging study will be submitted as part of the CDx submission, where appropriate.

**Study AC220-002**

Thia was a Phase 2 Open-Label, AC220 Monotherapy Study in Patients with AML With and Without FLT3-ITD Activating Mutations. The initial starting dose of quizartinib was 200 mg/day, reduced in Protocol Amendment 4 to 135 mg/day for males and 90 mg/day for females.

Within the FLT3-ITD (-) cohorts, patients could be subdivided into non-detectable for FLT3-ITD and detectable ≤10% FLT3-ITD allelic ratio for some analyses.

Within the FLT3-ITD (+) cohorts, patients with >10% to <25% FLT3-ITD allelic ratio were considered to have a low allelic ratio, patients with 25% to 50% allelic ratio were considered to have an intermediate allelic ratio, and patients with >50% allelic ratio FLT3-ITD were considered to have a high allelic ratio.

Quizartinib reduced phosphorylation of its intended target, FLT3, as well as the downstream signalling protein STAT5 in the peripheral blood of the AML patients. Additionally, it reduced kinase insert domain for tyrosine (KIT) phosphorylation, although to a less degree relative to FLT3 and STAT5.

Of the 292 patients tested, 26% were negative for the FLT3-ITD mutation. It was therefore analysed if the FLT3-ITD status had an effect on responses. Phospho- and total FLT3 signals for ITD+ patients were significantly higher before treatment compared to FLT3-ITD patients. After quizartinib treatment, there were significantly greater reductions in p/tFLT3 signal ratios at day 2, as well as greater reductions in tFLT3 levels at day 8. Similarly, there were significantly greater reductions in p/tSTAT5 signal ratios at both days 2 and 8 after treatment for ITD+ subjects vs. ITD- subjects.

**Study 2686-CL-2004**

This was a Phase 2, Randomised, Open Label Study of the Safety and Efficacy of Two Doses of Quizartinib in Subjects with FLT3-ITD Positive Relapsed or Refractory AML.

Quizartinib inhibited FLT3 phosphorylation in the PIA assay with ITD(+) cells to medians of 98.6% and 99.2% for 30 and 60 mg, respectively, with undiluted plasma sampled on days 8 or 15.

After dilution, in FLT3-ITD(+) cells and in THP-1 cells (FLT3-WT) pFLT3 inhibition was significantly higher in the subjects receiving 60 mg than 30mg.

The $IC_{90}$ (plasma concentration of quizartinib + AC886 that resulted in a 90% inhibition of kinase activity) were 182 nM in FLT3-ITD cells, 1160 nM in FLT3-WT cells, and 3977 nM in KIT cells.

**Figure 6. Plasma quizartinib + AC886 levels vs PIA IC90 values**

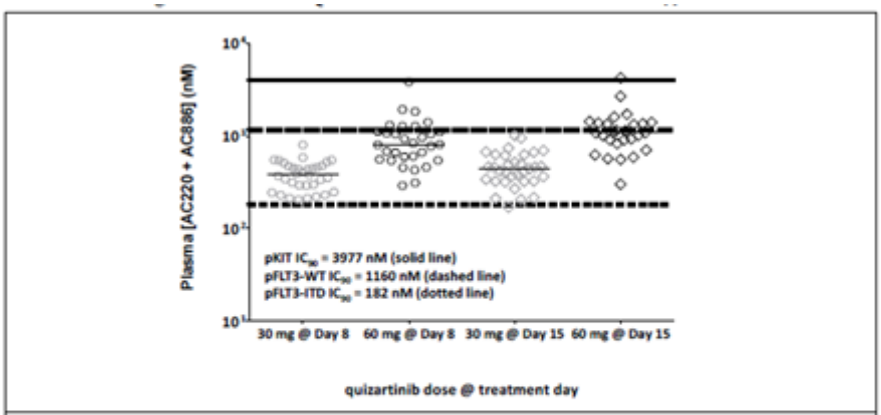



**Figure 12. Plasma quizartinib (AC220) and AC886 concentrations with PIA $IC_{90}$ values.** Predose, combined plasma concentrations for each subject at day 8 (hexagons) or day 15 (diamonds) after 30 mg/day (gray symbols) or 60 mg/day (black symbols) quizartinib treatment. Average inhibitory concentrations that result in 90% inhibition ($IC_{90}$) of phosphorylation in the FLT3-ITD (dotted line), FLT3-WT (dashed line), or KIT (solid line) PIA assay are indicated. Bars indicate median plasma concentrations of 382 nM (30 mg) and 808 nM (60 mg) at day 8, and 441 nM (30 mg) and 1097 nM (60 mg) at day 15.

In conclusion, the 30mg and 60mg doses of quizartinib should result in very strong inhibitory effects on FLT3-ITD phosphorylation activity *in vivo*, with reduced, but still robust activity on FLT3-WT, and with largely reduced inhibition of KIT activity.

***Secondary pharmacology***

*Concentration-QTcF (C-QTcF) Analysis in Study AC220-A-U302*

The quizartinib plasma concentration-QTcF (C-QTcF) relationship in Study AC220-A-U302 was best described by a maximum effect (Emax) model. The median model-predicted change from baseline of QTcF at Cmax,ss during the Continuation Phase at 30 mg and 60 mg were 18.4 ms (90% confidence interval [CI] 16.3, 20.85) 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 medications, beta-blocker drugs, and anthracycline. Age and hypokalaemia had an effect on the baseline QTcF. Sex, body weight, race, serum magnesium concentration, and concomitant administration of QT-prolonging medications or beta-blockers were not found to be statistically significant covariates on baseline QTcF or Emax. Additionally, the C-QTcF relationship from the current analysis in the newly diagnosed AML subjects in Study AC220-A-U302 appeared to be similar to that from the previous analysis in the R/R AML subjects in Study AC220-007. Further evaluation of the C-QTcF relationships using data from subjects who had matched concentrations and electrocardiogram (ECG) measurements during the time of concomitant administration of QT-prolonging medications, and during the time when those same subjects were not taking QT-prolonging medications, showed that the concomitant administration of QT-prolonging medications had no impact on the observed QTcF increases associated with quizartinib concentrations.

**Relationship between plasma concentration and effect**

*Exposure-response (ER) for efficacy (OS)*

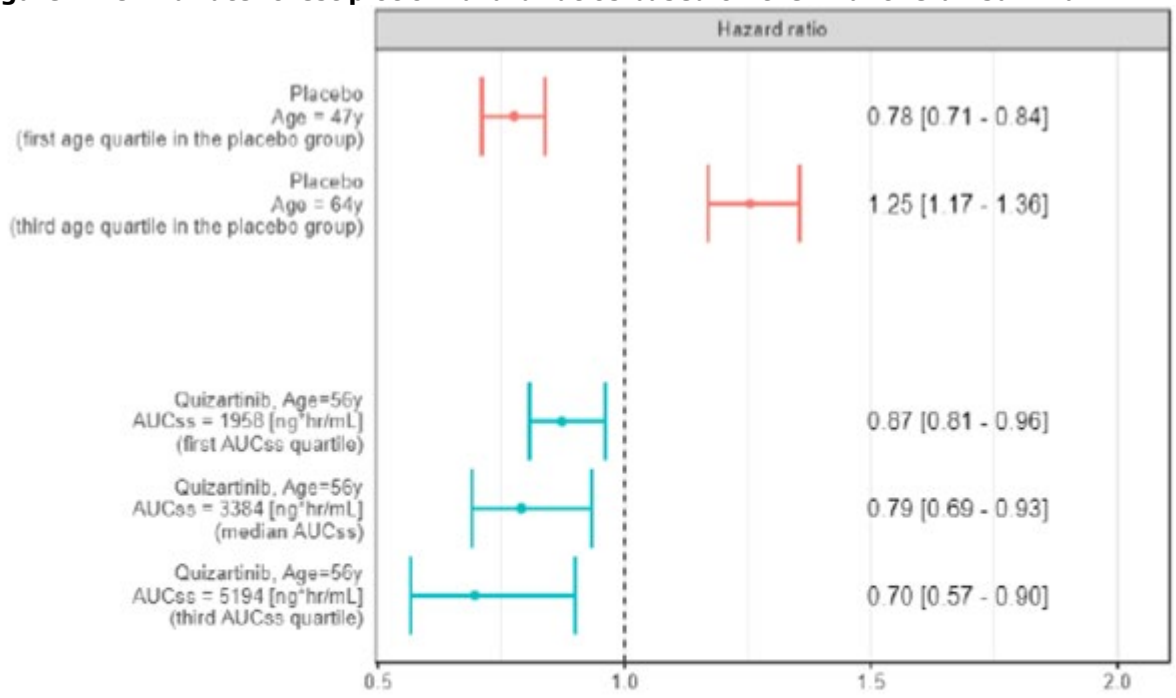
Different exposure metrics were evaluated in the ER analysis. The average daily exposures up to the event were inherently associated with a confounding factor related to the design in Study AC220-A-U302 where the target quizartinib dose was 40 mg in the Induction and Consolidation Phases, followed by an initial dose at 30 mg for 15 days and escalation to 60 mg in the Continuation Phase. Since the majority of subjects in the highest exposure quartile were those that survived into the Continuation Phase and escalated to 60 mg, it implied the loss of the causality in the relationship between exposure and response, and a model-based analysis of these metrics would have led to a biased ER relationship. This confounding was further exacerbated by the treatment phase effect that was found for quizartinib PK where it was observed that subjects had a higher quizartinib exposure during the Continuation Phase compared to the Induction Phase. On the other hand, the AUCss at the nominal starting dose of 40 mg during the Induction Phase was independent of dose escalation and phase-varying PK and was therefore selected as the exposure metric to be tested in the model-based analysis.

The OS was described using a parametric time-to-event (TTE) model where the base hazard followed a Gompertz distribution. In the model, age was a significant covariate for baseline hazard. After accounting for the effect of age, a statistically significant effect of quizartinib exposure was found, where higher exposure was associated with longer OS. The final model predicted a median (95% CI) hazard ratio for quizartinib compared to a placebo of 0.790 (0.690,0.933) at the median quizartinib exposure (Figure 7). The estimated slope was relatively uncertain (RSE 37%) and led to a modest ER relationship. This is likely a result of the small range of AUCss at 40 mg, which is uniquely driven by the variability in individual apparent CL of quizartinib (CLquiz) and relative bioavailability (Frel) values. There was an overlap in the Cis between subgroups (age, race, WBC, ECOG, FLT3-ITD).

Thus, age was a statistically significant covariate on the baseline hazard for OS, with older subjects being at higher risk. OS was found to be related to quizartinib exposure, defined by predicted quizartinib AUCss following 40 mg QD in the Induction Phase. The steepness of the ER relationship was modest and relatively uncertain. No ER relationship was identified for remission rate and EFS based on

the definition of Induction treatment failure as failure to achieve CR within 42 days from the start of the last cycle of Induction chemotherapy.

**Figure 7. Univariate forest plot of hazard ratios based on the final overall survival**




AUCss = steady state AUC in the 24-hour dosing interval; y = years
Note: The dots and the whiskers represent the median and the 95% CI of the hazard ratio, respectively, displayed numerically as median (95% CI) on the right side of the panel. The vertical black line represents the hazard ratio for a typical patient in placebo arm in the analysis data set, aged 56 years.

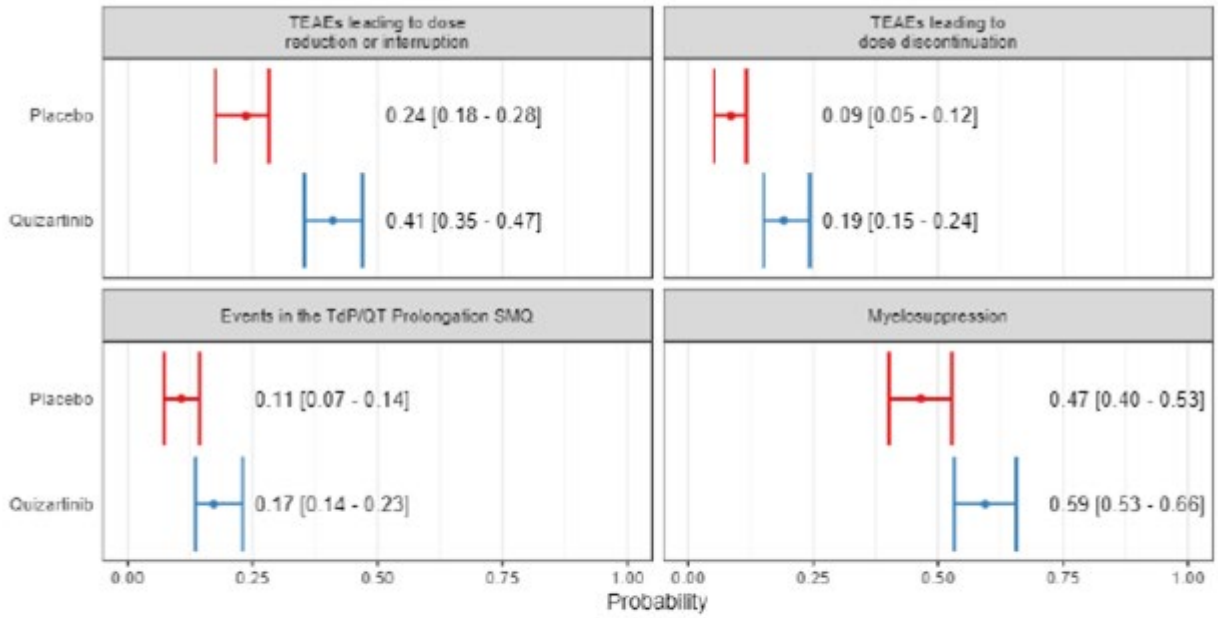
*Exposure-response Relationships: Safety*

Exposure-first occurrence TEAEs in Study AC220-A-U302

Logistic regression modelling was carried out to assess the relationship between exposure and the first occurrence of the following AEs: TEAEs of any grade, TEAEs of Grade ≥3, serious TEAEs (TESAEs), TEAEs leading to dose reduction/interruption, TEAEs leading to dose discontinuation, events in the Torsades de Pointes (TdP)/QT prolongation SMQ, infection, haemorrhages, hepatotoxicity, and myelosuppression.

No covariate was found to have an impact on the probability of the different AEs analysed. No ER relationship was identified for the probability of first occurrence of TEAEs of any Grade, Grade ≥3 TEAEs, TESAEs, TEAEs associated with study drug dose reduction/interruption, TEAEs associated with study drug discontinuation, events in the TdP/QT prolongation SMQ, infection, haemorrhages, hepatotoxicity, or myelosuppression. A quizartinib treatment effect was found for TEAEs associated with study drug dose reduction/interruption, TEAEs associated with study drug discontinuation, events in the TdP/QT prolongation SMQ search, and myelosuppression (Figure 8).

**Figure 8. Forest plot of probabilities for different adverse events**




CI = confidence interval; TdP/QT Prolongation SMQ = Torsades de Pointes/ QT prolongation Standardized MedDRA Query; TEAEs = treatment emergent adverse events
Note: The dots and whiskers represent the median and the 95% CI of the probability, respectively, displayed numerically as median (95% CI) on the right of each panel.

## 2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

*In vitro* and clinical studies were conducted with quizartinib. Furthermore, *in vitro* studies were conducted with AC886 and the PK was investigated in clinical studies. PopPK modelling was used to investigate the effect of different intrinsic and extrinsic factors on the clearance of quizartinib and AC886. In addition, PBPK modelling was used to predict the DDI of quizartinib as perpetrator in combination with a UGT1A1 substrate and the effect of a strong CYP3A4 inhibitor in CYP3A5 normal and poor metabolisers.

Absorption, distribution, metabolism and excretion of quizartinib and its main metabolite AC886 have been sufficiently investigated and showed an acceptable PK profile. The PK is dose proportional for quizartinib and AC886 over the dose range of 26.5 mg to 79.5 mg quizartinib, the PK for the clinical dose can be calculated. Food did not significantly impact the exposure to quizartinib and AC886 and changes seen are considered not clinically relevant. In the pivotal phase 3 study no food restrictions were given, neither are there recommendations in the SmPC. This is supported based on the food-effect study results. Based on the provided data quizartinib is most likely mainly metabolised to AC886. Elimination occurs mainly via faeces. Mild and moderate renal and hepatic impairment seems not to have a clinically relevant impact the PK of quizartinib and AC886. Patients with severe renal impairment (CLcr < 30 mL/min) were not included in the clinical studies; therefore, Vanflyta is not recommended for use in these patients. Body weight was also not found to have a clinically relevant impact on the PK and the safety profile of quizartinib and AC886.

Results of metabolism through CYP3A5, indicate that CYP3A5 contributes to the overall metabolism of quizartinib and seems to lead to a lower Cmax and AUC for quizartinib + AC886 due to metabolism.

However, the sum of quizartinib+AC886 exposures lies entirely within the 80% to 125% bound and the impact of metabolism is therefore not considered clinically relevant.

Studies with strong CYP3A/P-gp inhibitor increased quizartinib and decreased AC886 exposure which may increase the risk of toxicity. Dose adjustments by phase for adverse reactions and/or concomitant use with strong CYP3A inhibitors are therefore recommended during treatment with Vanflyta.

The clinical DDI study with a strong CYP3A4 inhibitor was most likely conducted mainly in CYP3A5 poor metabolisers which results in the highest increase in exposure (worst-case scenario) and the proposed dose reduction in section 4.5 of the SmPC is based on these data. Therefore, concomitant administration with strong CYP3A inhibitors is only recommended when reducing the administered starting dose to 17.7 mg and the continuation dose to 26.5 mg. This interaction is also identified as important identified risk in the RMP (see also safety discussion).

It remains currently unknown if the proposed dose reduction based on the worst-case scenario in CYP3A5 poor metabolisers is also suitable for CYP3A5 normal metabolisers in which the increase in exposure due to CYP3A4 inhibition may be less pronounced. The dose reduction may be too high in CYP3A5 normal metabolisers, however since this does not lead to an increase in safety issues this issue is not further pursued.

The applicant submitted a population pharmacokinetic model that was developed using observations of healthy volunteers and patients. Based on the prediction-corrected Visual Predictive Checks (pcVPCs), the PopPK model seems to be able to predict the PK of quizartinib and AC886 in healthy volunteers and patients. Furthermore, blood concentrations varied across AC886 plasma concentrations and haematocrit values. Therefore, an additional model describing Kb/p values of AC886 versus AC886 plasma concentrations was developed. The model includes a breakpoint at a plasma concentration of 88.2 ng/mL, which is quite an empirical model as it does not have a physiological basis. Nevertheless, it could be shown that this model showed superior predictive performance compared to potential other models (e.g. Emax or exponential). Simulations with the selected model showed that the predictions of individual concentration-time courses were quite well described even if the model overpredicted the observed concentrations between Cmax and around 10 hours.

Furthermore, PBPK modelling was used to predict the DDI of quizartinib as perpetrator in combination with a UGT1A1 substrate. It is unclear how much UGT1A1 activity is present in the intestine in the SimCYP model. The PBPK model appears to be able to predict the exposure after a single dose in healthy volunteers and following multiple dosing in patients. The worst-case results from the prediction can be used to waive a clinical DDI study for quizartinib with a medicinal product that is metabolised by UGT1A1 in the intestine. Based on the provided data it is unlikely that quizartinib is a clinically significant inhibitor of UGT1A1 (see also SmPC section 5.2). Furthermore, PBPK modelling was used to predict the effect of a strong CYP3A4 inhibitor on the PK of quizartinib and AC886 in CYP3A5 normal and poor metabolisers. However, the PBPK model was not qualified for its ability to identify differences in effect of CYP3A4 inhibitors on the PK in CYP3A5 normal and poor metabolisers, e.g. effect of itraconazole on the PK of venetoclax. It is therefore unknown if the model is able to capture the effect of CYP3A5 status.

The applicant used the plasma concentrations of quizartinib and AC886 taking the different binding affinity for FLT3 into account for the exposure-response modelling. No exposure (Cmax) -safety relationship was observed. Only placebo versus treatment was shown with an increase in TEAEs leading to dose reduction or discontinuation, events in the TdP/QT or myelosuppression.

Pharmacodynamics

The FLT3-ITD threshold for positivity was studied in Study AC220-002, analysis of ITD negative subjects from this Study showed that those subjects with a low level (≤10%) of the ITD mutation had similar response rates as the positive (>10%) subjects, while those with no detectable ITD mutation (<0.3%) had lower response rates. Therefore, the cutoff was reduced to ≥3% in Studies AC220-007 and AC220-A-U302 to detect ITD mutations at that low percentage and to allow for subjects with lower levels of FLT3 ITD to be enrolled and potentially benefit from quizartinib therapy. In study 007 quizartinib reduced phosphorylation of its intended target, FLT3, as well as the downstream signalling protein STAT5 in the peripheral blood of the AML patients. The applicant concluded that due to higher phospho- and total FLT3 signals for ITD+ subjects before treatment there were significantly greater reductions in p/tFLT3 signal ratios at day 2, as well as greater reductions in tFLT3 levels at day 8. Similarly, there were significantly greater reductions in p/tSTAT5 signal ratios at both days 2 and 8 after treatment for ITD+ subjects vs. ITD- subjects.

In Study 2686-CL-2004, a Phase 2 study in FLT3-ITD-positive Relapsed or Refractory AML patients, quizartinib inhibited FLT3 phosphorylation in the PIA assay with ITD(+) cells to medians of 98.6% and 99.2% for 30 and 60 mg, respectively, with undiluted plasma sampled on days 8 or 15. The $IC_{90}$ (plasma concentration of quizartinib + AC886 that resulted in a 90% inhibition of kinase activity) were evaluated with 182 nM in FLT3-ITD cells, 1160 nM in FLT3-WT cells, and 3977 nM in KIT cells. On basis of these $IC_{90}$s, the current plasma levels of Cmaxss of quizartinib+AC886 in all treatment phases (as derived from popPK model), i.e. >30mg, are obviously sufficient to inhibit >90% of FLT3-ITD activity, and the 60mg dose with 1.41µM would be able to also inhibit wt-FLT3 to >90%.

With regard to the study U308 it was explained that the higher cut-offs for FLT 3 used in subgroup analyses for OS were related to those of ELN guidelines, which seems overall acceptable. Though, it remains unclear whether the ELN-subgroup cut-offs are comparably justified with regard to FLT3-ITD basepair length. However, no discussion about the VAF% cut-off-groups and their potential predictivity for differing response to quizartinib treatment was provided. The study population was a preselected FLT3-positive population and only for the VAF >50% subgroup a clinically significant benefit on the primary endpoint OS could be observed whereas the OS results for both the lower VAF groups are not significant. Also the newly submitted analysis for response rates and EFS demonstrated a relation to NPM1wt/mut status while not significantly different for quizartinib treatment or placebo.

As already assessed previously it is more the NPM1 mutation status than the quizartinib treatment that results in clinically relevant differences in EFS and response rates between subgroups, and especially for Overall Survival the HR for NPM1-wt is above 1. Therefore, the applicant is requested to provide further subgroup analysis for FLT3-ITD %VAF subgroups plus NPM1-status to confirm that there is a benefit and no clinically relevant negative (detrimental) effect on the primary endpoint OS in all subgroups and especially those such as FLT3-ITD low plus NPM1wt, including also sub-grouping for length of FLT3-ITD basepairs.

Several AML mutation data analyses listed in pivotal study endpoints as well as further PD/biomarker questions will be included in a biomarker report for which submission is to be expected post approval . Herein also analyses and discussion on the relevance of presence and %VAFs at baseline of observed other mutations (e.g. NPM1, IDH1/2, …) both for response and relapse as well as potential PD response differences from quizartinib treatment between longer and shorter ITD-bp length of FLT3 is expected.

*Genetic differences in PD response*

NPM1 mutation was found to be associated with significantly higher rates of CR and CRc, irrespective of quizartinib treatment. From the Forrest Plot for OS of the phase 3 study it seems that the higher

%VAF of FLT3-ITD the lower the Hazard ratio. Therefore it is requested to provide further subgroup analysis for FLT3-ITD subgroups plus NPM1-status to confirm that there is a benefit and no clinically relevant negative effect in subgoups such as FLT2-ITD low plus NPM1wt.

Plasma inhibitory activity data from the Phase 2b study in subjects with R/R AML, Study 2689-CL-2004, demonstrated that 30 mg is the minimum dose for complete and rapid inhibition of FLT3-ITD signalling (Nepomuceno, 2014). To account for potential compensatory mechanisms at the initiation of quizartinib therapy, such as increases in FLT3 ligand and direct cell to cell contact between blast cells and stromal cells that can protect leukaemic blasts from apoptosis (Sato, 2011; Yang, 2014), and to reduce the effect of quizartinib, the dose of 40 mg was chosen in combination with chemotherapy together with the safety data from the previous Phase 1 studies.

With respect to the exposure response relation it was observed that age was a statistically significant covariate on the baseline hazard for OS, with older subjects being at higher risk. OS was found to be related to quizartinib exposure, defined by predicted quizartinib AUCss following 40 mg QD in the Induction Phase. The steepness of the ER relationship was modest and relatively uncertain. No ER relationship was identified for remission rate and EFS based on the definition of Induction treatment failure as failure to achieve CR within 42 days from the start of the last cycle of Induction chemotherapy.

Dose-dependent QTc interval prolongation has been observed in clinical trials with quizartinib. The median model-predicted change from baseline of QTcF at Cmax,ss during the Continuation Phase at 30 mg and 60 mg were 18.4 ms and 24.1 ms, respectively and this is reflected in section 5.1 of the SmPC. With ER-safety analysis, a quizartinib treatment effect was indeed found for events in the TdP/QT prolongation SMQ search, but also for TEAEs associated with study drug dose reduction/interruption, TEAEs associated with study drug discontinuation, and myelosuppression.

## 2.6.4. Conclusions on clinical pharmacology

The PK of quizartinib and its pharmacologically active metabolite AC886 were sufficiently investigated *in vitro* and *in vivo*.

## 2.6.5. Clinical efficacy

The quizartinib clinical development programme for newly diagnosed FLT3-ITD (+) AML comprises a pivotal Phase 3 study, AC220-A-U302 (N = 539) and 2 completed Phase 1 studies in subjects with newly diagnosed AML, Studies 2689-CL-0005 (N = 18) and AC220-A-J102 (N = 7). In addition, 1 Phase 1 study, 2689-CL-0011 (N = 13), in subjects who received quizartinib as maintenance following allo-HSCT, has been completed.

### *2.6.5.1. Dose response studies*

**Study 2689-CL-2004**

This was an open-label, randomised, multiple-dose, Phase 2b study in 76 FLT3-ITD(+) AML subjects who were refractory to or had relapsed after second-line AML therapy with or without consolidating HSCT. Subjects were randomly assigned to 28-day cycles of 30 or 60 mg/day quizartinib. 74 patients were treated. Quizartinib was to be taken as a once daily oral solution for continuous 28-day cycles.

To be eligible to participate in this study, subjects must have had morphologically documented primary AML or AML secondary to myelodysplastic syndrome (MDS) and had relapsed or was refractory after 1

second-line (salvage) regimen or after HSCT. Subject had to be positive for FLT3-ITD activating mutation in bone marrow or peripheral blood (>10% allelic ratio).

*Efficacy Results:*

• Twenty-four (63.2%) subjects in the 30 mg dose group and 7 (19.4%) subjects in the 60 mg dose group had their dose escalated during the study.

• In subjects with relapsed or refractory AML, and response as assessed by local morphology for the ITT Analysis Set, the primary endpoint of composite complete remission (CRc) rate was achieved by 47.4% (90% CI: 33.3, 61.8) of subjects overall and in both the 30 mg and 60 mg dose groups following treatment with quizartinib, showing that there was no difference in response between the 2 doses.

• Overall, the median time to CRc was 4.5 weeks, 4.4 weeks in the 30 mg dose group and 4.6 weeks in the 60 mg dose group.

• More than 50% of all subjects achieved some level of response at the end of Cycle 2: complete remission with incomplete neutrophil or platelet recovery(Cri) in 28 (36.8%) subjects, partial remission (PR) in 16 (21.1%) subjects, CR in 2 (2.6%) subjects, and CRp in 1 (1.3%) subject. Similarly, more than 50% of all subjects achieved some level of response at the end of study timepoint: CRi in 31 (40.8%) subjects, PR in 14 (18.4%) subjects, CR in 3 (3.9%) subjects, and CRp in 2 (2.6%) subjects. The overall response (CRc + PR) at the end of Cycle 2 and the end of study was 55% and 60%, respectively, in the 30 mg dose group and 68% and 71%, respectively, in the 60 mg dose group.

- In the 30 mg dose group, the best response achieved at the end of Cycle 2 was: CRi in 14 (36.8%) subjects, PR in 5 (13.2%) subjects, and CR in 2 (5.3%) subjects. At the end of the study the best response achieved was: CRi in 16 (42.1%) subjects, PR in 5 (13.2%) subjects, and CR in 2 (5.3%) subjects.
- In the 60 mg dose group, the best response achieved at the end of Cycle 2 was: CRi in 14 (36.8%) subjects, PR in 11 (28.9%) subjects, and CRp in 1 (2.6%) subject. At the end of the study the best response achieved was: CRi in 15 (39.5%) subjects, PR in 9 (23.7%) subjects, CRp in 2 (5.3%) subjects, and CR in 1 (2.6%) subject.

• Analysis of a subject's ability to respond to quizartinib treatment based on whether the subject responded to their last AML therapy showed that 14 of 26 (54%) non-responders to the last line of treatment, achieved a CRc and at the end of the study.

• The median duration of CRc was 5.4 weeks. Median duration of CRc was 4.2 weeks in the 30 mg dose group and 9.1 weeks in the 60 mg dose group. Median duration of overall response (CRc + PR) for all subjects was 8.1 weeks. Median duration of overall response was 7.3 weeks in the 30 mg dose group and 9.1 weeks in the 60 mg dose group.

• Median OS for subjects in this study was 22.6 weeks (95% CI: 19.9, 28.3), with a long-term survival (OS ≥52 weeks, ie, ≥ 365 days) rate of 7.9% (6 subjects). Median OS was 20.9 weeks in the 30 mg dose group and 27.3 weeks in the 60 mg dose group. The long-term survival rate was 2.6% (1 subject) in the 30 mg dose group and 13.2% (5 subjects) in the 60 mg dose group.

- Median EFS was 12.3 weeks (95% CI: 9.7, 16.1) overall. In the 30 mg and 60 mg dose groups, median EFS was 12.0 weeks (95% CI: 8.3, 16.1) and 13.7 weeks (95% CI: 9.7, 26.1), respectively.
- Thirty-six subjects in the ITT population were included in the analysis for LFS. Of these, 20 (55.6%) subjects had an LFS event observed. Median LFS was 5.3 weeks (95% CI: 4.1,

11.9) overall. Median LFS was 4.1 weeks (95% CI: 2.1, 9.7) in the 30 mg dose group and 9.1 weeks (95% CI: 4.0, 22.3) in the 60 mg dose group.

- Twelve of 38 (31.6%) subjects in the 30 mg dose group and 16 of 38 (42.1%) in the 60 mg dose group underwent HSCT after treatment with quizartinib.

In summary, the two quizartinib dosing regimens, starting dose of 30 mg/day or 60 mg/day with escalations to 60 mg/day or 90 mg/day, respectively, were similar with regard to the primary efficacy endpoint of CRc rate. Dose escalation was more frequent in the 30 mg dose group than in the 60 mg dose group. Duration of CRc, overall survival, and transplantation rate were higher in the 60 mg/day dose group.

**Study 2689-CL-0005:** A 2-part, Phase 1, multicentre, open-label, sequential group, dose-escalation trial using a modified 3+3 design. In Part 1, subjects were to be enrolled into successive cohorts of 5 or 6 subjects to determine the maximum tolerated dose (MTD). Dose escalation decisions were made based on does limiting toxicities (DLTs) that occurred during remission induction. The following dose levels of quizartinib were evaluated: 60 mg once daily (QD) × 7 days; 60 mg QD × 14 days; 40 mg QD × 14 days. The MTD was defined as the dose level at which ≤ 1 out of 6 or 0 out of 5 subjects experienced a DLT and 1 dose level below the lowest dose level at which ≥ 2 out of 2 to 6 subjects experienced a DLT. Male or female subjects aged ≥ 18 years and ≤ 60 years with a diagnosis of previously-untreated de novo AML according to WHO classification (2008). Subjects with both positive and negative FLT3 – internal tandem duplication (ITD) mutation status were eligible.

A total of 3 subjects had reports of DLTs: 0 in the 60 mg/7-Day cohort; 2 in the 60 mg/14-Day cohort; and 1 in the 40 mg/14-Day cohort. In the 60 mg/14-Day cohort, 1 subject had a DLT of pericardial effusion; and 1 subject had DLTs of febrile neutropenia, platelet count decreased, and ECG QT prolonged. In the 40 mg/14-Day cohort, 1 subject had a DLT of pericarditis. The 40 mg/14-Day dose regimen was determined to be the MTD as this was the lowest dose level at which ≤ 1 out of 6 subjects experienced a DLT.

**Study 2689-CL-0011**: A 2-part, Phase 1, multi-centre, open-label, sequential group dose escalation study. Subjects were treated with quizartinib between 30 to 60 days after receiving allogeneic HSCT. Quizartinib 40 mg or 60 mg was taken QD, with 28 consecutive days defining a treatment cycle. Subjects could receive up to 24 continuous 28-day treatment cycles. In Part 1, subjects were enrolled into successive cohorts to determine the MTD. In Part 2 subjects were to be enrolled into an expanded cohort at the MTD to further evaluate safety, efficacy, PK, and PD of quizartinib; however the study was terminated before Part 2 could begin. Of 13 subjects enrolled, 10 subjects received treatment for more than 1 year, and 6 of these received treatment for almost 2 years. DLTs were observed in 2 subjects, 1 at each dose; however an MTD was not identified.

Based on data from the Phase 2b of 76 subjects with relapsed/refractory FLT3-ITD AML (2689-CL-2004), which evaluated a starting dose of either 30 mg/day or 60 mg/day with escalation permitted to 60 mg/day or 90 mg/day, it was decided that 60 mg daily was the maximum dose to be taken forward into Phase 3 studies and therefore dose escalation above 60 mg daily was not explored. The recommended dose regimen for the pivotal phase 3 study for the combination with standard chemotherapy was at a dose of 40 mg QD and quizartinib continuation monotherapy at 30 mg QD.

#### *2.6.5.2. Main study*

***AC220-A-U302 (Quantum-First)***

## Title of study

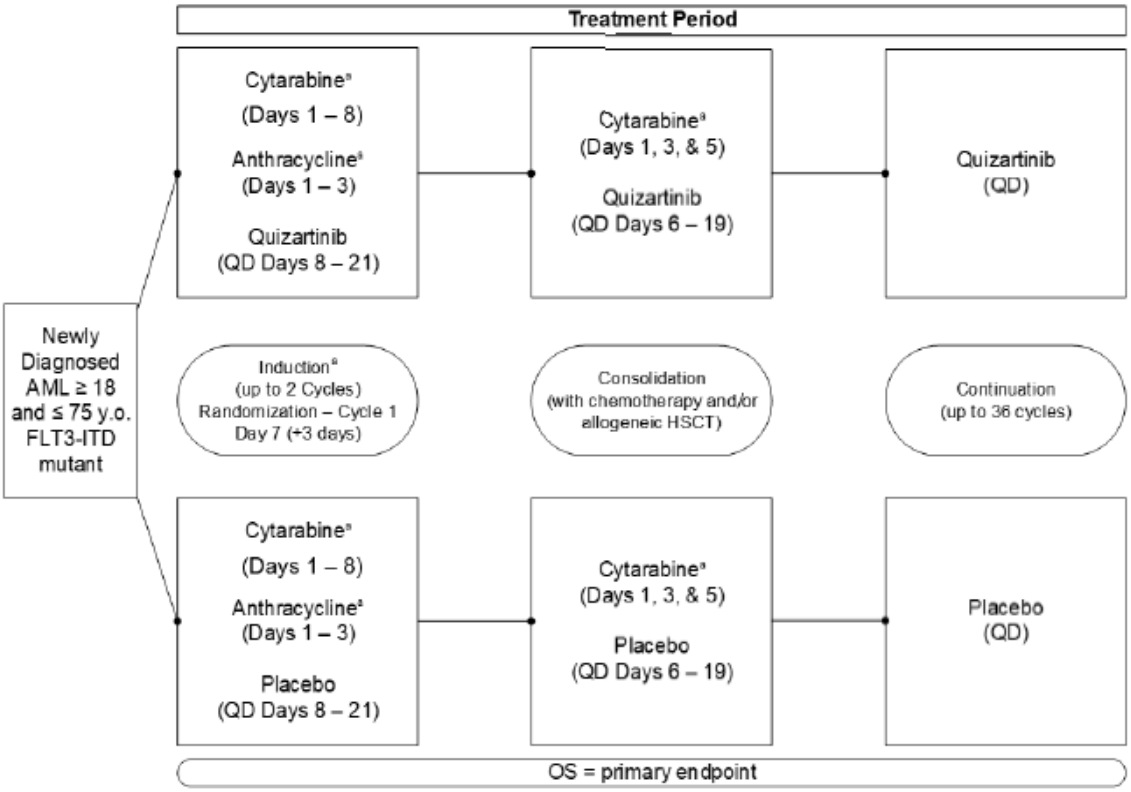
*A Phase 3, Double-Blind, Placebo-controlled Study of Quizartinib Administered in Combination with Induction and Consolidation Chemotherapy, and Administered as Continuation Therapy in Subjects 18 to 75 Years Old with Newly Diagnosed FLT3-ITD (+) Acute Myeloid Leukemia (QuANTUM First)*

***Methods***

A Phase 3, randomised, double-blind, placebo-controlled, global study to compare the effect of quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles) on the primary endpoint of OS in subjects with newly diagnosed FLT3-ITD (+) AML. Worldwide (at data cut off (DCO)) 193 sites had enrolled a subject. The target sample size was approximately 536 subjects. Randomisation was done in a 1:1 ratio into the two treatment arms (quizartinib or placebo) and occurred at cycle 1 day 7, this allowed subjects to start induction treatment while awaiting results of the FLT3 testing, after which randomisation and start quizartinib/placebo commenced.

The study design consisted of 4 consecutive phases (Induction, Consolidation, Continuation, and Long-term Follow-up). The study design from Screening through the treatment period is outlined below. The Long-term Follow-up Phase begins upon completion of 36 cycles of study drug (quizartinib/placebo) in the Continuation Phase or permanent discontinuation of study drug in any phase.
Induction/consolidation and maintenance/continuation are tested together and the study design does not allow to isolate the effect in the two phases and question the duration.

**Figure 9. Outline of pivotal study AC220-A-U302**




AML = acute myeloid leukemia; *FLT3*-ITD = FMS-like tyrosine kinase 3 internal tandem duplication; HSCT = hematopoietic stem cell transplantation; OS = overall survival; QD = once a day; y.o. = years old

[a] During Induction Cycle 2, investigators may have chosen to administer the "7 + 3" chemotherapy regimen or the "5 + 2" chemotherapy regimen, and study drug would therefore have started on Day 8 or Day 6, respectively.

- **Study Participants**

**Key Inclusion Criteria**

Subjects had to have satisfied all of the following criteria to be randomised:

1. Must have been competent and able to comprehend, sign, and date an Ethics Committee (EC)- or IRB-approved ICF before performance of any study-specific procedures or tests

2. ≥18 years or the minimum legal adult age (whichever was greater) and ≤75 years (at Screening)

3. Newly diagnosed, morphologically documented primary AML or AML secondary to myelodysplastic syndrome (MDS) or a myeloproliferative neoplasm (MPN), based on the World Health Organization (WHO) 2008 classification (at Screening)

4. ECOG PS 0-2

5. Presence of FLT3-ITD activating mutation in bone marrow (≥3 % FLT3-ITD/total FLT3) as determined prospectively by a clinical study assay

6. Adequate renal and hepatic function

7. Serum electrolytes within institution's normal limits

8. Subject must have been either sterile or using an acceptable contraceptive method as specified in Appendix 17.2 of the study protocol

**Inclusion Criteria – Consolidation Phase**

Subjects must have satisfied all of the following criteria to start the Consolidation Phase and receive consolidation therapy:

1. Achieved CR or CRi based on local laboratory results, at the end of the Induction Phase

2. Able to begin Consolidation Phase within 60 days of Day 1 of the last induction cycle

**Inclusion Criteria – Continuation Phase**

Subjects must have satisfied all of the following criteria to start the Continuation Phase and receive continuation therapy:

1. Subject did not have active acute or ≥Grade 3 graft-versus-host disease (GVHD)

2. Subject had not initiated therapy for active GVHD (prophylaxis was allowed) within 21 days

3. Confirmed <5% of blasts based on the most recent bone marrow aspirate, based on the local laboratory results, performed within 28 days prior to Cycle 1 Day 1 of continuation therapy

4. Absolute neutrophil count (ANC) >500/mm3 and platelet count >50,000/mm3 without platelet transfusion support within 24 hours prior to Cycle 1 Day 1 of continuation therapy

5. Subject was able to begin Continuation Phase within 60 days of Day 1 of the last consolidation cycle

**Key Exclusion Criteria**

Subjects who met any of the following criteria were not eligible to be randomised:

1. Diagnosis of acute promyelocytic leukaemia (APL), French-American-British classification M3 or WHO classification of APL with translocation, t(15;17)(q22;q12), or BCR-ABL positive leukaemia (ie, chronic myelogenous leukaemia in blast crisis) (subjects who underwent diagnostic workup for APL and treatment with all-trans retinoic acid [ATRA], but who were found not to have APL, were eligible [treatment with ATRA must have been discontinued before starting induction chemotherapy])

2. Diagnosis of AML secondary to prior chemotherapy or radiotherapy for other neoplasms

3. Prior treatment for AML

4. History of known central nervous system (CNS) leukaemia, including cerebrospinal fluid positive for AML blasts; lumbar puncture was recommended for subjects with symptoms of CNS leukaemia to rule out extramedullary CNS involvement

5. History of other malignancies, except adequately treated nonmelanoma skin cancer, curatively treated in-situ disease, or other solid tumours curatively treated with no evidence of disease for at least 2 years

6. Uncontrolled or significant cardiovascular disease

7. Active acute or chronic systemic fungal, bacterial, or viral infection not well controlled by antifungal, antibacterial, or antiviral therapy

8. Were considered otherwise inappropriate for the study by the investigator

- **Treatments**

*Induction Phase (Up to 2 Cycles)*
Subjects were permitted to receive up to 2 cycles of induction chemotherapy.

Cycle 1: Cycle 1 Day 1 was defined as the start date of the chemotherapy infusions. Subjects have been randomised on Day 7. If necessary, Randomisation may be performed later (eg, Days 8 to 10) to allow time for addressing electrolyte abnormalities, QTcF prolongation, etc.

Cytarabine (cytosine arabinoside) 100 mg/m2/day (200 mg/m2/day allowed if this is the institutional or local standard) was to be administered by continuous intravenous (IV) infusion for a total of 7 days (Day 1 through Day 8).

One of the following anthracycline regimens (investigator's choice) was to be administered: Daunorubicin 60 mg/m2/day IV infusion on Days 1, 2, and 3; or Idarubicin 12 mg/m2/day IV infusion on Days 1, 2, and 3.

Quizartinib (40mg)/placebo was to be administered orally once daily for 14 days. For subjects concomitantly receiving a strong cytochrome P450 (CYP) 3A4 inhibitor, the dose was to be reduced to 20 mg/day. Dosing should have started following the end of the cytarabine infusion, normally on Day 8. If quizartinib/placebo administration could not begin as scheduled, the start of dosing should have been delayed, but best efforts should have been made to start within 3 days of Randomisation if possible. If quizartinib/placebo was interrupted, missed doses have not been made up.

On Day 21 (window Day 21 to Day 28), a bone marrow aspirate specimen (or a core biopsy specimen if aspirate could not be obtained) has been collected for local and central pathology for response assessment. At the investigator's discretion, to allow for blood counts to recover or other reasons, the second Induction cycle might have started up to 60 days after Day 1 of the first Induction cycle.

Cycle 2: Subjects began the cytarabine and anthracycline regimen on Day 1. It was recommended to wait at least 7 days after the last dose of quizartinib/placebo in Cycle 1 of Induction before starting Cycle 2 of induction, since quizartinib has a long elimination half-life and there are no data on the safety of administering anthracycline within 7 days following quizartinib administration. For Cycle 2 of induction, investigators could have chosen to administer one of the following:

"7 + 3" chemotherapy regimen, defined as 7 days of continuous IV infusion of standard dose cytarabine plus 3 days of anthracycline (the same anthracycline must have been used throughout the Induction Phase)

"5 + 2" chemotherapy regimen, defined as 5 days of continuous IV infusion of standard dose cytarabine plus 2 days of anthracycline (the same anthracycline must have been used throughout the Induction Phase)

Quizartinib 40 mg or placebo dosing was to start following the end of the cytarabine infusion, normally on Cycle 2 Day 8 or Cycle 2 Day 6, depending on the chemotherapy regimen selected by the investigator (ie, "7 + 3" or "5 + 2", respectively). Study drug was to be administered orally once daily for 14 days. For subjects concomitantly receiving a strong CYP3A4 inhibitor, the dose was to be reduced to 20 mg/day.

*Consolidation Phase*
Subjects who achieve a CR or CRi at the end of the Induction Phase were to enter the consolidation Phase.

During consolidation, there were three options for treatment:

1) consolidation chemotherapy followed by quizartinib for 14 days,

2) allo-HSCT, or

3) consolidation chemotherapy followed by quizartinib for 14 days followed by allo-HSCT.

For regimens including consolidation chemotherapy, cytarabine was to be given on Days 1, 3, and 5. The cytarabine regimen was as follows:

- For subjects <60 years: cytarabine 3.0 g/m2 by IV infusion, every 12 hours for a total of 6 doses. For subjects ≥60 years: cytarabine 1.5 g/m2 by IV infusion, every 12 hours for a total of 6 doses.
- Subjects could have received up to 4 cycles of consolidation chemotherapy. Subjects were not required to complete a full cycle if they were unable to tolerate any cycle during the Consolidation Phase.
- Quizartinib (40 mg) or placebo was to be administered orally once daily for 14 days starting on Day 6. For subjects concomitantly receiving a strong CYP3A4 inhibitor, the dose was to be reduced to 20 mg/day.

*Continuation Phase (Up to 36 Cycles)*
Quizartinib/placebo continuation therapy was to begin after induction and consolidation therapy (including allo-HSCT) upon blood count recovery (ANC >500/mm3 and platelet count >50,000/mm3 without a platelet transfusion within 24 hours of drawing blood samples). For subjects who underwent allo-HSCT, continuation therapy was to begin any time between 30 and 180 days after the transplant. Study drug was to be administered orally once daily starting on Day 1, with no breaks in dosing between cycles. If study drug was interrupted, missed doses were not to be made up. Study drug continuation therapy was to continue for up to 36 cycles after induction or consolidation until relapse, start of non-protocol specified AML treatment, death, unacceptable toxicity, study closure, or completion of study drug, whichever occurred first.

The dose of study drug on Cycle 1 Days 1 to 15 was to be 30 mg orally once daily. On Cycle 1 Day 16, the dose was to be increased to 60 mg/day if the average QTcF of the triplicate electrocardiogram (ECG) was ≤450 ms on Cycle 1 Day 15. Once the dose was increased to 60 mg/day, the subject was allowed to continue on this dose as long as dose reduction was not needed.

For subjects concomitantly receiving a strong CYP3A4 inhibitor, the dose of study drug on Cycle 1 Days 1 to 15 was to be 20 mg/day. On Cycle 1 Day 16, the dose was to be increased to 30 mg/day if the average QTcF of the triplicate ECG was ≤450 ms on Cycle 1 Day 15. If the dose of study drug was not able to be increased on Cycle 1 Day 16, the dose could have been increased on Cycle 2 Day 2 if the average QTcF of the triplicate ECG was ≤450 ms on Cycle 2 Day 1.

Subjects had their blood counts monitored at least every 4 weeks and had a bone marrow exam every 12 weeks for 48 weeks and then every 24 weeks until week 96.

*Allogeneic Hematopoietic Stem Cell Transplantation*
Subjects were permitted to undergo allo-HSCT after CR or CRi was achieved. Allogeneic HSCT for consolidation was able to be performed after the Induction Phase, anytime during the Consolidation Phase, or, if certain criteria were met, within the first 3 months of the Continuation Phase. Study drug was to be discontinued at least 7 days before the start of a conditioning regimen. Any hematopoietic stem cell transplantation (HSCT) performed for other reasons (eg, molecular relapse) was to be considered non-protocol-specified AML therapy, and the subject was to be discontinued from study drug but continued to be followed for outcome data. Subjects were not permitted to undergo autologous HSCT at any time during the study. Subjects who had autologous HSCT were to be discontinued from study drug but continued to be followed for outcome data.

For subjects who undergo allogeneic HSCT, treatment with quizartinib/placebo should be discontinued 7 days before the start of a conditioning regimen. Subjects may begin continuation therapy anytime between 30 to 180 days after the allogeneic HSCT.

- **Objectives**

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

The secondary objectives of this study were the following:

• To compare the following in subjects treated with quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles):

- Event-free survival (EFS)
- CRc rate (CRc = CR + CR with incomplete neutrophil or platelet recovery [CRi]) after induction
- Percentage of subjects achieving CRc with FLT3-ITD minimal or measurable residual disease (MRD) negativity after induction
- CR rate after induction
- Percentage of subjects achieving CR with FLT3-ITD MRD negativity after induction

• To further characterise the safety profile of quizartinib administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles

• To assess the PK of quizartinib and its metabolite (AC886)

- **Outcomes/endpoints**

The total duration of treatment with study drug was to have been up to 42 cycles (inclusive of Induction, Consolidation, and Continuation Phases). The total duration of subject participation was to be until death, withdrawal of consent, lost to follow-up, or study closure, whichever occurred first.

Primary Efficacy Endpoint: OS, defined as the time from Randomisation until death from any cause. Subjects alive or lost to follow-up at the time of analysis were to be censored at the date when they were last known to be alive.

Secondary Efficacy Endpoints:

• EFS (based on IRC assessment), defined as the time from Randomisation until the date of the earliest of any of the following:

- Refractory disease (or treatment failure) as determined at the end of the Induction Phase and defined as CR or CRi never achieved in the Induction Phase; or Blasts <5% if Auer-rod positive; or appearance of new or worsening extramedullary disease.
- Relapse after CR or CRi, defined as ≥5% blasts in the bone marrow aspirate[1] and/or biopsy not attributable to any other cause; or reappearance of leukemic blasts in the peripheral blood; and/or new appearance of extramedullary leukaemia; or presence of Auer rods
- Death from any cause at any time during the study
- CRc rate, defined as the percentage of subjects achieving CR or CRi after induction.

[1] As per the study protocol, a bone marrow aspirate was to be collected at the planned time points until 24 months after the start of continuation therapy, and at any time during the study treatment or the long-term follow-up in case of suspicion of relapse based on abnormal peripheral smears or when subjects developed cytopenia.

- Percentage of subjects achieving CRc with FLT3-ITD MRD negativity.
- CR rate, defined as the percentage of subjects achieving CR after induction.
- Percentage of subjects achieving CR with FLT3-ITD MRD negativity following induction therapy.

- **Sample size**

Simulations indicated that about 84% power and 287 events would need to be obtained to achieve a statistically significant difference in OS distribution with approximately 536 subjects by a 2-sided log-rank test at the 0.05 significance level when OS was analysed at 24 months after the last subject was randomised. No interim analysis was performed.

- **Randomisation and Blinding (masking)**

Randomisation was done in a 1:1 ratio into 2 treatment groups (quizartinib or placebo). Randomisation was to be stratified based on: Region (North America, Europe, Asia/Other Regions); Age (<60, ≥ 60 years old); White blood cell (WBC) count at the time of diagnosis of AML ($<40\times10^9$/L, $\geq40\times10^9$/L). In total, there are 12 strata (=3 × 2 × 2). Within each stratum, a permuted-block randomisation is used to randomise subjects.

This study had a double-blind design. Neither the subjects nor any of the Investigators, Sponsor, or contract research organisations (CROs) have been aware of the treatments received prior to database lock.

In the case of an emergency where, in the opinion of the investigator, the study treatment assignment must be unblinded in order to evaluate further a course of medical treatment, it was required that the investigator discuss the case with the Medical Monitor, but the discussion may occur after unblinding if the subject requires emergency treatment.

- **Statistical methods**

The current version of the SAP is version 2.0, dated 11 October 2021. This version of the SAP is intended to follow Protocol version 7.0.

*Analysis sets*

Intent-to-treat analysis set: The ITT Analysis Set includes all subjects who are randomised.

Per-Protocol Analysis Set: The Per-protocol Analysis Set (PPS) includes all subjects in the ITT Analysis Set who have no major protocol deviations that would affect assessment of efficacy endpoints. In addition, subjects who are randomised but not treated have been excluded from PPS. Efficacy analysis based on PPS Major protocol deviations have been defined and documented prior to data base lock.

*Interim analyses*

No formal interim analysis of efficacy has been performed.

*Multiple Comparisons/Multiplicity*

To control for the family-wise type I error rate for primary and secondary efficacy endpoints, serial hierarchically ordered gatekeeping strategy has been employed. The primary assessment of OS in the ITT Analysis Set has been evaluated first, and if significant at a 2-sided alpha of 0.05, a statistical evaluation of EFS by IRC based on the AML guidances (FDA, 2020; European Medicines Agency [EMA], 2019) in the ITT Analysis Set has been performed. After EFS evaluation, order of other secondary endpoints to be tested has been CR rate, rate of subjects achieving CR with FLT3-ITD MRD negativity, CRc rate, and rate of subjects achieving CRc with FLT3-ITD MRD negativity. Testing has stopped once one test in the sequence failed to be statistically significant.

*Primary endpoint*

The primary efficacy endpoint for this study is Overall survival (OS). OS is defined as the time from the date of randomisation to the date of death due to any cause. Subjects without an OS event are censored at the last known alive date. No other censoring rules were specified for the primary OS analysis.

The primary analytic method for OS is a stratified log-rank test performed at the overall 2.5 level, with 3 stratification factors used for randomisation (Region [North America, Europe, Asia/Other Regions], Age [<60 60 years old], White blood cell count at the time of diagnosis of AML [<40×109 9/L]) per IXRS.

The distribution of OS has been summarised using the Kaplan-Meier method. Median OS has been estimated for each treatment group from the 50th percentile of the corresponding Kaplan-Meier estimates, and the 2-sided 95% CI for the median of each treatment group has been calculated using the method of Brookmeyer and Crowley. The corresponding Kaplan-Meier curves has also been presented.

The hazard ratio with 95% CI for treatment group has been estimated using stratified Cox proportional hazards models, with the 3 stratification factors used for randomisation per IXRS.

Sensitivity and supplementary analyses to examine the robustness of the OS results has been conducted. The same analysis methods and testing used for the primary OS analysis has been applied to the following analyses:

1. OS analysis unstratified.

2. OS censored at the start of the conditioning regimen for HSCT. The censoring rule is the same as that of the primary analysis, except that subjects who undergo HSCT on or before cut-off date have been censored at the start of the conditioning regimen for HSCT.

3. OS analysis (performed using PPS).

In addition, sensitivity analysis of OS based on the pre-specified number of OS events (N=287) may have bene performed.

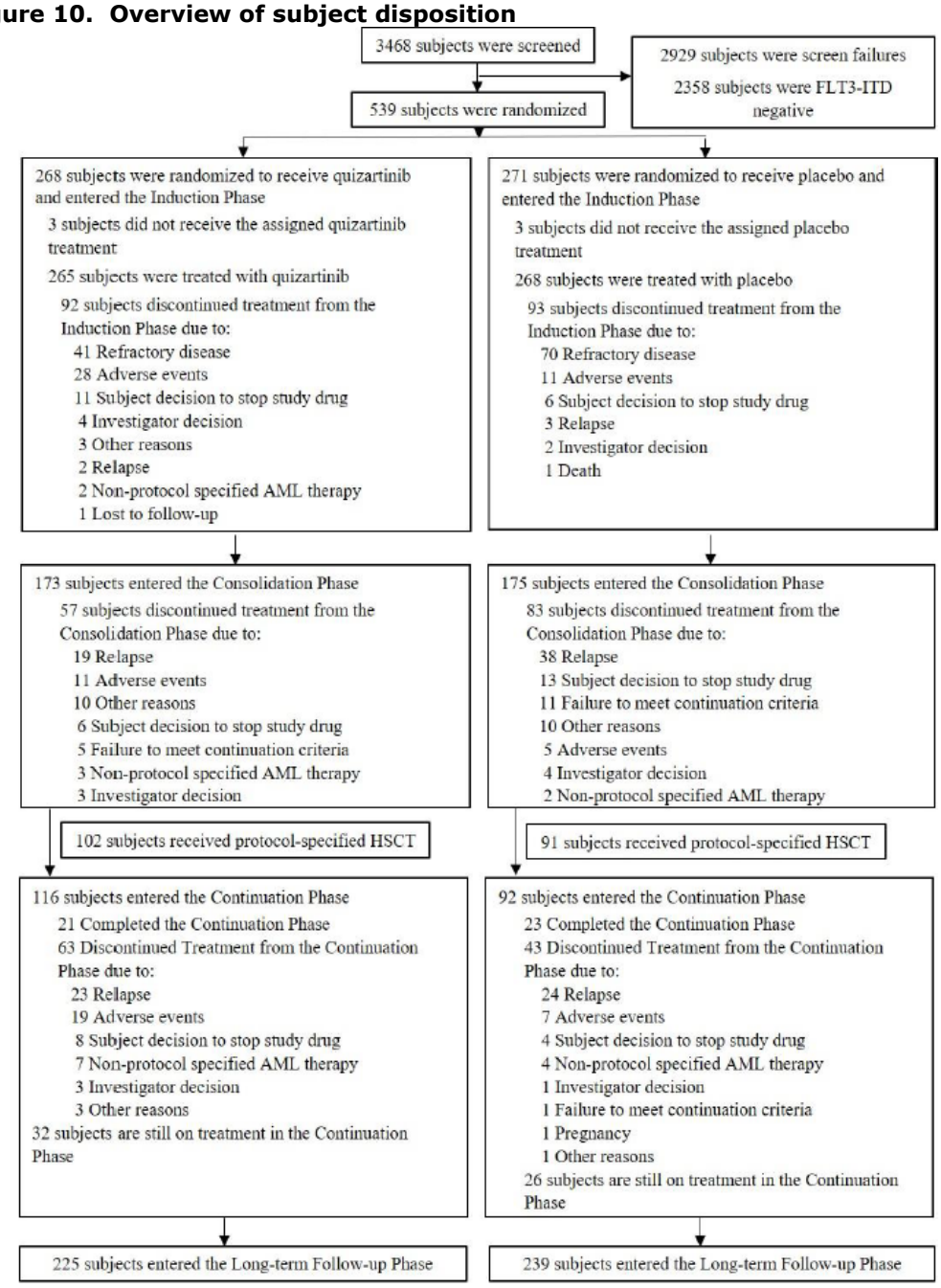
*RMST Analysis*

To account for a possible plateau effect in OS, the restricted mean survival time (RMST) method has been applied as a sensitivity analysis to explore the robustness of the primary OS analysis result. The RMST up to a time point (tau) is interpreted as the expected survival time restricted to the common follow- in each treatment arm. clinical relevance (that is, it represents a clinically meaningful follow-up duration) for the hypothesis being tested. The default of tau is set as the minimum of the largest observed survival time in each treatment arm. Other time points may have been considered if it is deemed to be clinical relevant. The treatment effect between the two treatment arms has been assessed based on the difference in RMST. The associated s for the differences in means and 2-sided p-value has been generated.

***Results***

- **Participant flow**

**Figure 10. Overview of subject disposition**




AML = acute myeloid leukemia; *FLT3*-ITD = FMS-like tyrosine kinase 3-internal tandem duplication; HSCT = hematopoietic stem cell transplantation
Data cutoff date: 13 Aug 2021.
Source: Figure 14.1.1

The participant flow is presented in Figure 10. On top of negativity to FLT3 testing shown in the figure above, additional reasons for screen failure included: withdrawal by subject (68 [2.3%] subjects), death (41 [1.4%] subjects), other (21 [0.7%] subjects), and adverse event (12 [0.4%] subjects). During the induction phase of the study 34.7% discontinued the study drug, equal in both arms but differentially distributed. The main reason was refractory disease (43% in quizartinib versus 75% in

placebo) or adverse events (30% vs 12%). Subsequently, 65.3% of subjects entered the consolidation phase in both arms of which 21.5% (quizartinib) and 31.0% (placebo) discontinued.

**Table 1. Subject disposition (All screened subjects)**

| | Quizartinib (N = 268) n (%) | Placebo (N = 271) n (%) | Total (N = 539) n (%) |
|---|---|---|---|
| Screened | — | — | 3468 |
| Screen failures | — | — | 2929 |
| Randomized | 268 (100.0) | 271 (100.0) | 539 (100.0) |
| Randomized but not treated | 3 (1.1) | 3 (1.1) | 6 (1.1) |
| Subject status[a] | | | |
| Entered Induction Phase | 265 (100.0) | 268 (100.0) | 533 (100.0) |
| Received a second cycle of induction therapy | 54 (20.4) | 56 (20.9) | 110 (20.6) |
| Discontinued study drug during Induction Phase | 92 (34.7) | 93 (34.7) | 185 (34.7) |
| Entered Consolidation Phase | 173 (65.3) | 175 (65.3) | 348 (65.3) |
| Study drug plus chemotherapy | 75 (28.3) | 86 (32.1) | 161 (30.2) |
| HSCT only | 6 (2.3) | 6 (2.2) | 12 (2.3) |
| Study drug plus chemotherapy followed by HSCT | 92 (34.7) | 83 (31.0) | 175 (32.8) |
| Discontinued study drug during Consolidation Phase | 57 (21.5) | 83 (31.0) | 140 (26.3) |
| Entered Continuation Phase | 116 (43.8) | 92 (34.3) | 208 (39.0) |
| Completed Continuation Phase | 21 (7.9) | 23 (8.6) | 44 (8.3) |
| Discontinued study drug during Continuation Phase | 63 (23.8) | 43 (16.0) | 106 (19.9) |
| Ongoing in Continuation Phase | 32 (12.1) | 26 (9.7) | 58 (10.9) |
| Entered Long-term Follow-up Phase | 225 (84.9) | 239 (89.2) | 464 (87.1) |
| Discontinued from study drug during any phase | 212 (80.0) | 219 (81.7) | 431 (80.9) |
| Primary reason for discontinuation of study drug[b] | | | |
| Refractory disease | 41 (15.5) | 70 (26.1) | 111 (20.8) |
| Relapse | 44 (16.6) | 65 (24.3) | 109 (20.5) |
| Adverse event | 58 (21.9) | 23 (8.6) | 81 (15.2) |
| Subject decision to stop study drug | 25 (9.4) | 23 (8.6) | 48 (9.0) |
| Other[c] | 16 (6.0) | 11 (4.1) | 27 (5.1) |

| | Quizartinib (N = 268) n (%) | Placebo (N = 271) n (%) | Total (N = 539) n (%) |
|---|---|---|---|
| Non-protocol-specified AML therapy | 12 (4.5) | 6 (2.2) | 18 (3.4) |
| Investigator decision | 10 (3.8) | 7 (2.6) | 17 (3.2) |
| Failure to meet continuation criteria | 5 (1.9) | 12 (4.5) | 17 (3.2) |
| Lost to follow-up | 1 (0.4) | 0 | 1 (0.2) |
| Pregnancy | 0 | 1 (0.4) | 1 (0.2) |
| Death | 0 | 1 (0.4) | 1 (0.2) |
| Subjects having protocol-specified HSCT | 102 (38.5) | 91 (34.0) | 193 (36.2) |
| Received protocol-specified HSCT in Consolidation Phase | 98 (37.0) | 89 (33.2) | 187 (35.1) |
| Received protocol-specified HSCT in Continuation Phase | 4 (1.5) | 2 (0.7) | 6 (1.1) |
| Study status[d] | | | |
| Ongoing with study drug | 32 (11.9) | 26 (9.6) | 58 (10.8) |
| Alive, continuing in long-term follow-up | 88 (32.8) | 77 (28.4) | 165 (30.6) |
| Discontinued from study | 148 (55.2) | 168 (62.0) | 316 (58.6) |
| Primary reason for study discontinuation | | | |
| Death | 133 (49.6) | 158 (58.3) | 291 (54.0) |
| Lost to follow-up | 2 (0.7) | 1 (0.4) | 3 (0.6) |
| Withdrawal of consent | 13 (4.9) | 9 (3.3) | 22 (4.1) |

AML = acute myeloid leukemia; DCO = data cutoff; HSCT = hematopoietic stem cell transplantation; ITT = intent-to-treat

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

[b] The primary reasons for discontinuation from study drug are as follows: adverse events, death, refractory disease, relapse, nonprotocol-specified AML therapy, pregnancy, subject decision to stop study drug, study terminated by Sponsor, protocol violation, lost to follow-up, investigator decision, subject does not meet one or more of the eligibility criteria for the Continuation Phase, and other. If the number of subjects who discontinued study drug due to a reason is greater than 0, the reason and the corresponding number are presented in the table.

[c] Investigator-provided reasons for discontinuation of study drug are available in Listing 16.2.1.1.

[d] Percentages are based on the number of subjects in the ITT Analysis Set at the time of the DCO date.

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

Data cutoff date: 13 Aug 2021.

Even though the number of discontinuations during the induction phase was very similar between the study arms (34.7%), there was an imbalance between in reason for discontinuation of treatment with more patients in the quizartinib arm discontinuing due to an AE, or following a decision by the subject or investigator.

- **Recruitment**

First subject first visit date: 18 Aug 2016

Data cutoff (DCO) date: 13 Aug 2021

- **Conduct of the study**

Amendments and protocol violations to the study are listed in Table 4 and Table 5. Of importance, in Protocol Amendment 5, the primary endpoint was changed from EFS to dual primary endpoints of EFS and OS. Subsequently, based on FDA feedback EFS was then changed to a secondary endpoint in Protocol Amendment 6, and the definition of EFS was changed in Protocol Amendment 7.

**Table 4. Substantial changes in the conduct of the study**

| Version No., Date | Substantial Change(s) |
|---|---|
| 2.0, 06 Apr 2017 | • Updated CMC information for quizartinib and updated quizartinib dosing instructions to allow dose to be taken without regard to meals.<br>• Modified the cytarabine regimen in induction to allow a dose of 200 mg/m$^2$/day.<br>• Added clarification that subjects with ≥5% blasts at the end of the first cycle of induction will receive a second cycle of induction, if appropriate.<br>• Increased the maximum length of each induction and consolidation cycle to 60 days, if needed for recovery.<br>• Changed the schedule for collecting bone marrow aspirate specimens in induction and increased the window for the bone marrow procedures in consolidation to allow additional time for count recovery.<br>• Updated eligibility criteria to allow enrollment of subjects with AML secondary to MPN and of subjects without APL who had undergone diagnostic workup for APL and had received treatment with ATRA.<br>• Updated language surrounding contraception, pregnancy, and childbearing potential.<br>• Added language allowing dose adjustment for chemotherapy for renal and hepatic function. |

| Version No., Date | Substantial Change(s) |
|---|---|
| | and the reference for the cytogenetic risk classification being used in the study.<br>• Added text indicating that for the triplicate 12-lead ECG, if the QTcF from the local ECG machine is >450 ms but the QTcF measured by the ECG central laboratory is ≤450 ms, there is no need to repeat the pre-Randomization triplicate ECG at -0.5 to 0 hours predose.<br>• Added text for activities to be performed from Day 21 up to Day 56 ± 3 days in Cycles 1 and 2 of the Induction Phase for subjects for whom there is a plan to perform a repeat bone marrow aspirate upon count recovery or at Day 56 ± 3 days: review and document all concomitant medications transfusions received, record all AEs, and collect and send blood samples for hematology (starting on Day 21 and weekly thereafter until count recovery). Added chemistry where missing.<br>• Added procedures to be done if this is the last consolidation cycle.<br>• Added statement that subjects who permanently discontinued study drug because they completed 12 cycles under protocol Version 1.0 or 2.0, then restarted on study drug, and completed 36 cycles will need an additional end-of-treatment visit upon final permanent discontinuation of study drug.<br>• Revised text to indicate that the investigator should use the automated QTcF values from the study-supplied ECG machine to guide decisions regarding dose reduction, escalation, or interruption until the average QTcF value from the central ECG laboratory is available. Once the QTcF value from the central ECG laboratory has been received, it should be used to guide dosing decisions.<br>• Added formula for correcting serum calcium for hypoalbuminemia. |
| 5.0, 07 Apr 2020 | • Changed primary objective/endpoint from EFS to dual primary endpoints of EFS and OS. Clarified that EFS and OS will be stratified with the 3 stratification factors (region, age, and WBC count at the time of diagnosis of AML) used at Randomization.<br>• Clarified that if either EFS or OS analysis is statistically significant, the study will be considered positive.<br>• Changed leukemia-free survival to RFS.<br>• Removed "Duration of CRc".<br>• Added "RFS in subjects who enter the Continuation Phase, after achieving CRc in induction", which will be analyzed similarly as RFS.<br>• Revised the study duration to indicate that after the last subject is randomized, there will be a minimum follow-up of 24 months to a maximum follow-up of 30 months.<br>• Added that the primary completion date is when the final OS analysis is completed.<br>• Increased target number of EFS events required, from "331" to "410".<br>• Added that the OS analysis will be performed when 287 OS events are observed.<br>• Changed log-rank test from "1-sided" to "2-sided" and modified the associated language.<br>• Corrected bone marrow exam every 12 weeks for 48 weeks and then every 24 weeks until Week 96.<br>• Clarified that "withdrawal by subject" in protocol Section 5.9.1 refers only to a subject's decision to stop study drug.<br>• Added the collection of Karnofsky performance status prior to the start of the conditioning regimen was added. |

| Version No., Date | Substantial Change(s) |
|---|---|
| | • Added directions to avoid excessive exposure to sunlight and other sources of ultraviolet light.<br>• Removed prohibition of concomitant use of proton pump inhibitors and P-gp inhibitors or inducers.<br>• Added requirement that predose QTcF (average of triplicate) must be ≤450 ms in order to proceed with the administration of the first dose of study drug.<br>• Added the 3-month timepoint to the schedule of MRD assessments in the Maintenance Phase and defined the time points for assessment of mutations.<br>• Added a clarification that EFS analysis would be based on the adjudicated response assessment by CEC using local morphology results and that a sensitivity analysis of EFS would be performed based on the investigator's response assessment.<br>• Removed CRp and updated the definition of other response criteria. |
| 3.0, 20 Nov 2018 | • Changed the duration of double-blind therapy in the Continuation Phase (formerly the Maintenance Phase) from up to 12 cycles to up to 36 cycles.<br>• Added a sentence allowing subjects who have completed 12 cycles of continuation therapy and therefore discontinued study drug (as required in protocol Versions 1.0 and 2.0) to restart continuation therapy at the discretion of the investigator after discussion with the Medical Monitor.<br>• Collected of Health Economic and Outcome Research data every 3 cycles until the end of the Continuation Phase (Cycle 36). |
| 4.0, 26 June 2019 | • Specified examples of mutations to be assessed.<br>• For IRC assessment only, added additional exploratory objectives of rates CRh and MLFS after induction and corresponding endpoints.<br>• To allow under certain circumstances HSCT for consolidation to be performed within the first 3 months of the Continuation Phase.<br>• Modified the inclusion criterion for TBL to allow enrollment of subjects in whom the increased TBL is related to documented Gilbert's syndrome or increased unconjugated (indirect) bilirubin due to hemolysis.<br>• Clarified that the normal range for serum electrolytes referred to in the inclusion criteria is the institution's normal range.<br>• An echocardiogram or multi-gated acquisition scan is to be performed for all subjects during Screening to assess LVEF, even if testing is not routinely done at an institution.<br>• Clarified that subjects who discontinued continuation therapy because they completed 12 cycles under protocol Version 1.0 or 2.0 and then restarted continuation therapy under protocol Version 3.0 or a subsequent version, will receive double-blind therapy in the same treatment arm (quizartinib or placebo) to which they were randomized.<br>• Added text requiring permanent discontinuation of study drug for recurrent QTcF >500 ms.<br>• Added text regarding management of electrolyte abnormalities, monitoring of serum potassium at least 3 times per week in the Induction and Consolidation Phases, and monitoring of serum magnesium and calcium.<br>• Modified the instructions for study drug dose reduction in case of myelosuppression to provide separate instructions for subjects who enter the Continuation Phase with hematologic recovery and those who enter without hematologic recovery.<br>• Changed "target" to "AML" for disease history; added cytogenetic risk classification |

| Version No., Date | Substantial Change(s) |
|---|---|
| | • Added additional timepoints for the collection of GVHD information, in addition to the collection that must be done every 4 weeks during the transplant period, were added.<br>• Corrected Per-protocol Analysis Set as all subjects in the ITT Analysis Set who have no major protocol deviations that would affect assessment of efficacy endpoints.<br>• Added AESI to the type of safety data that is to be listed. |
| 6.0, 28 Oct 2020 | • Moved EFS to secondary objectives/endpoints, including for subgroup analyses, resulting in OS being the sole primary objective/endpoint.<br>• Added that serial hierarchically ordered gatekeeping strategy will be employed to control for the family-wise type I error rate for the primary and secondary efficacy endpoints.<br>• Updated the definition of RFS to start from the time of Randomization, for subjects who achieve CR or CRi in the Induction Phase and added "whichever comes first".<br>• Updated duration of CR to include "or death from any cause".<br>• Added that local pathology reports from the bone marrow aspirate/biopsy will be de identified and collected for submission to the IRC.<br>• Updated GVHD data collection requirements at 100 days, and 6, 12, 18, and 24 months post allo-HSCT.<br>• Added that outcomes and remission status after subsequent antileukemic treatments will be recorded if available.<br>• Clarified that the IRC will assess response for each bone marrow aspirate (or biopsy, if applicable sample collected during the Induction Phase).<br>• Added that EFS based on investigator's response assessment will also be analyzed.<br>• Added the definition of CR that will be used by the IRC for assessment of response.<br>• Added a new section and tables for acute GVHD grading and staging, percent body surfaces, and chronic GVHD organ scoring. |
| 7.0, 26 May 2021 | • Changed the statistical testing order of the secondary endpoints and clarified that the EFS analysis which uses the IRC assessment will be based on the EFS definition in recent HA AML Guidance documents. |

AE = adverse event; AESI = adverse event of special interest; allo-HSCT = allogeneic hematopoietic stem cell transplantation; AML = acute myeloid leukemia; APL = acute promyelocytic leukemia; ATRA = all-trans retinoic acid; CEC = Clinical Events Committee; CMC = Chemistry, Manufacturing, and Controls; CR = complete remission; CRc = composite complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with either incomplete neutrophil or platelet recovery; CRp = complete remission with incomplete platelet recovery; ECG = electrocardiogram; EFS = event-free survival; GVHD = graft-versus-host disease; HA = health authority; IRC = Independent Review Committee; ITT = intent-to-treat; LVEF = left ventricular ejection fraction; MLFS = morphologic leukemia-free state; MPN = myeloproliferative neoplasm; MRD = minimal or measurable residual disease; No. = number; OS = overall survival; P-gp = P glycoprotein; QT = interval between the start of the Q wave and the end of the T wave; QTcF = QT interval corrected with Fridericia's formula; RFS = relapse free survival; TBL = total bilirubin; WBC

**Table 2. Protocol violations in ITT**

| | Quizartinib (N=268) n (%) | Placebo (N=271) n (%) | Total (N=539) n (%) |
|---|---|---|---|
| Subjects with Any Major Protocol Deviations | 141 ( 52.6) | 136 ( 50.2) | 277 ( 51.4) |
| Informed Consent | 17 ( 6.3) | 11 ( 4.1) | 28 ( 5.2) |
| 1A. Study-specific procedure(s) performed before informed consent obtained. | 4 ( 1.5) | 2 ( 0.7) | 6 ( 1.1) |
| 1C. Consent process not executed by adequately qualified staff | 2 ( 0.7) | 1 ( 0.4) | 3 ( 0.6) |
| 1D. Administered consent does not include updates or information required and approved by IRB/EC | 7 ( 2.6) | 7 ( 2.6) | 14 ( 2.6) |
| 1E. Failure to obtain informed consent | 3 ( 1.1) | 2 ( 0.7) | 5 ( 0.9) |
| 1G. Incomplete consent or consent not executed properly | 2 ( 0.7) | 0 | 2 ( 0.4) |
| Investigational Product | 47 ( 17.5) | 36 ( 13.3) | 83 ( 15.4) |
| 2B IP (Starting the incorrect dose as per protocol in any phase) MAJOR | 7 ( 2.6) | 5 ( 1.8) | 12 ( 2.2) |
| 2E Co-administration of a strong CYP3A4 inhibitor and IP without IP dose reduction for >2 days | 13 ( 4.9) | 13 ( 4.8) | 26 ( 4.8) |
| 2F IP was not dose adjusted with QTcF prolongation per protocol | 4 ( 1.5) | 3 ( 1.1) | 7 ( 1.3) |
| 2G IP was not dose reduced per protocol requirements | 5 ( 1.9) | 4 ( 1.5) | 9 ( 1.7) |
| 2I IP was not dose escalated pre protocol requirements | 2 ( 0.7) | 1 ( 0.4) | 3 ( 0.6) |
| 2J IP was not dispensed or administered per protocol (MAJOR) | 9 ( 3.4) | 7 ( 2.6) | 16 ( 3.0) |
| 2K Chemotherapy was not administered per protocol | 9 ( 3.4) | 7 ( 2.6) | 16 ( 3.0) |
| 2M Subject Non-Compliance with IP | 2 ( 0.7) | 1 ( 0.4) | 3 ( 0.6) |
| 8. COVID Impact Deviation - 2J | 1 ( 0.4) | 0 | 1 ( 0.2) |
| Safety | 35 ( 13.1) | 41 ( 15.1) | 76 ( 14.1) |
| 3A SAE not reported within 24 hour timeline | 35 ( 13.1) | 41 ( 15.1) | 76 ( 14.1) |
| Study Conduct/Procedures | 91 ( 34.0) | 82 ( 30.3) | 173 ( 32.1) |
| 4A Subject did not meet inclusion criteria but was enrolled in the study | 29 ( 10.8) | 23 ( 8.5) | 52 ( 9.6) |
| 4B Subject met exclusion criteria and enrolled in the study | 5 ( 1.9) | 4 ( 1.5) | 9 ( 1.7) |
| 4C Subject did not achieve CR, CRp, Cri after the Induction phase but entered consolidation phase | 5 ( 1.9) | 4 ( 1.5) | 9 ( 1.7) |
| 4E (Continuation Phase) Subject Failed to Meet inclusion criteria but was enrolled in the Continuation phase | 4 ( 1.5) | 2 ( 0.7) | 6 ( 1.1) |

The number of subjects with a major protocol violation was high (52.6% quiz vs 50.2%) and could mainly be attributed to starting of the incorrect dose as per protocol in any phase (17.5% vs 13.3%) and late reporting of SAEs (13.1% vs 15.1%). As well as visits, assessment or procedures not

performed per protocol (22.8% vs 19.2%). The applicant states that there was no impact on the study conduct that would affect assessment of efficacy endpoints and the interpretation of results.

- **Baseline data**

Key demographic and baseline characteristics for all enrolled subjects are displayed below. In general, demographic and baseline characteristics for subjects in the ITT Analysis Set were consistent with an FLT3-ITD (+) newly diagnosed AML population. Baseline AML disease characteristics for the ITT Analysis Set are presented in Table **7.**6. Baseline AML characteristics were generally comparable between the 2 treatment arms. The majority of subjects in both the quizartinib and placebo arms had an intermediate or unfavourable cytogenetic risk (216 [80.6%] and 220 [81.2%] subjects, respectively).

**Table 6. Demographic and baseline characteristics (ITT analysis set)**

| | Quizartinib (N = 268) | Placebo (N = 271) | Total (N = 539) |
|---|---|---|---|
| **Age (years)[a]** | | | |
| n | 268 | 271 | 539 |
| Mean (SD) | 53.6 (13.07) | 54.3 (12.81) | 54.0 (12.93) |
| Median | 56.0 | 56.0 | 56.0 |
| Min, max | 23, 75 | 20, 75 | 20, 75 |
| **Age, n (%)** | | | |
| <60 years | 161 (60.1) | 162 (59.8) | 323 (59.9) |
| ≥60 years | 107 (39.9) | 109 (40.2) | 216 (40.1) |
| ≥60, <65 years | 37 (13.8) | 44 (16.2) | 81 (15.0) |
| ≥65 years | 70 (26.1) | 65 (24.0) | 135 (25.0) |
| **Sex, n (%)** | | | |
| Male | 124 (46.3) | 121 (44.6) | 245 (45.5) |
| Female | 144 (53.7) | 150 (55.4) | 294 (54.5) |
| **Race, n (%)** | | | |
| Asian | 80 (29.9) | 78 (28.8) | 158 (29.3) |
| Black or African American | 2 (0.7) | 5 (1.8) | 7 (1.3) |
| American Indian or Alaska Native | 0 | 1 (0.4) | 1 (0.2) |
| Native Hawaiian/Pacific Islander | 0 | 0 | 0 |
| White | 159 (59.3) | 163 (60.1) | 322 (59.7) |
| Other | 27 (10.1) | 24 (8.9) | 51 (9.5) |
| **Ethnicity, n (%)** | | | |
| Hispanic/Latino | 7 (2.6) | 15 (5.5) | 22 (4.1) |
| Non-Hispanic/Non-Latino | 236 (88.1) | 234 (86.3) | 470 (87.2) |
| Not reported | 25 (9.3) | 22 (8.1) | 47 (8.7) |
| **Region, n (%)** | | | |
| North America | 16 (6.0) | 18 (6.6) | 34 (6.3) |
| Europe | 163 (60.8) | 163 (60.1) | 326 (60.5) |
| Asia/Other Regions | 89 (33.2) | 90 (33.2) | 179 (33.2) |
| **ECOG score, n (%)** | | | |
| 0 | 87 (32.5) | 98 (36.2) | 185 (34.3) |
| 1 | 134 (50.0) | 136 (50.2) | 270 (50.1) |
| 2 | 47 (17.5) | 36 (13.3) | 83 (15.4) |
| Missing | 0 | 1 (0.4) | 1 (0.2) |

CSR = clinical study report; ECOG = Eastern Cooperative Oncology Group; ITT = Intent-to-Treat; max = maximum; min = minimum; SD = standard deviation

[a] Age in years is calculated using the birth date and informed consent date.

Notes: The baseline value is defined as the last nonmissing value before initial administration of study drug.

Data cutoff date: 13 Aug 2021.

Source: AC220-A-U302 CSR Table 14.1.2.1

**Table 7. AML disease history (ITT analysis set)**

| | Quizartinib (N = 268) | Placebo (N = 271) | Total (N = 539) |
|---|---|---|---|
| **Time from diagnosis to Randomization (weeks)[a]** | | | |
| n | 268 | 271 | 539 |
| Mean (SD) | 1.98 (0.790) | 1.96 (0.926) | 1.97 (0.860) |
| Median | 1.86 | 1.71 | 1.71 |
| Min, max | 0.9, 5.3 | 1.0, 9.1 | 0.9, 9.1 |
| **Antecedent hematological disorder, n (%)** | | | |
| Yes | 25 (9.3) | 16 (5.9) | 41 (7.6) |
| MDS | 18 (6.7) | 9 (3.3) | 27 (5.0) |
| Other | 7 (2.6) | 7 (2.6) | 14 (2.6) |
| No | 243 (90.7) | 255 (94.1) | 498 (92.4) |

| | Quizartinib (N = 268) | Placebo (N = 271) | Total (N = 539) |
|---|---|---|---|
| **WHO classification[b], n (%)** | | | |
| AML with recurrent genetic abnormalities | | | |
| AML with t(8;21)(q22;q22); RUNX1-RUNX1T1 | 8 (3.0) | 9 (3.3) | 17 (3.2) |
| AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBEB-MYH11 | 1 (0.4) | 3 (1.1) | 4 (0.7) |
| AML with t(9;11)(p22;q23); MLLT3-MLL | 0 | 4 (1.5) | 4 (0.7) |
| AML with t(6;9)(p23;q34);DEK-NUP214 | 3 (1.1) | 1 (0.4) | 4 (0.7) |
| AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1 | 1 (0.4) | 0 | 1 (0.2) |
| AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1 | 0 | 0 | 0 |
| AML with mutated *NPM1*[c] | 142 (53.0) | 140 (51.7) | 282 (52.3) |
| AML with mutated *CEBPA*[c, d] | 61 (22.8) | 65 (24.0) | 126 (23.4) |
| AML with myelodysplasia-related changes | 23 (8.6) | 16 (5.9) | 39 (7.2) |
| Therapy-related myeloid neoplasms | 0 | 0 | 0 |
| AML not otherwise categorized | | | |
| AML minimally differentiated | 24 (9.0) | 23 (8.5) | 47 (8.7) |
| AML without maturation | 47 (17.5) | 41 (15.1) | 88 (16.3) |
| AML with maturation | 37 (13.8) | 48 (17.7) | 85 (15.8) |
| Acute myelomonocytic leukemia | 40 (14.9) | 59 (21.8) | 99 (18.4) |
| Acute monoblastic/monocytic leukemia | 38 (14.2) | 31 (11.4) | 69 (12.8) |
| Acute erythroid leukemia | | | |
| Pure erythroid leukemia | 0 | 2 (0.7) | 2 (0.4) |
| Erythroleukemia, erythroid/myeloid | 0 | 0 | 0 |
| Acute megakaryoblastic leukemia | 0 | 0 | 0 |
| Acute basophilic leukemia | 0 | 0 | 0 |
| Acute panmyelosis with myelofibrosis | 1 (0.4) | 0 | 1 (0.2) |
| Myeloid sarcoma | 0 | 1 (0.4) | 1 (0.2) |
| **Risk status with specific cytogenetic patterns[e], n (%)** | | | |
| Favorable | 14 (5.2) | 19 (7.0) | 33 (6.1) |
| Intermediate | 197 (73.5) | 193 (71.2) | 390 (72.4) |
| Unfavorable | 19 (7.1) | 27 (10.0) | 46 (8.5) |
| Unknown | 38 (14.2) | 31 (11.4) | 69 (12.8) |
| Missing | 0 | 1 (0.4) | 1 (0.2) |

| | Quizartinib (N = 268) | Placebo (N = 271) | Total (N = 539) |
|---|---|---|---|
| ***FLT3*-ITD mutation status by central laboratory testing, n (%)** | | | |
| Positive | 267 (99.6) | 271 (100) | 538 (99.8) |
| Negative | 0 | 0 | 0 |
| Unknown | 1 (0.4) | 0 | 1 (0.2) |
| ***FLT3*-ITD VAF by central laboratory testing[f] (*FLT3*-ITD/total *FLT3*), n (%)** | | | |
| 0 to <3% | 0 | 0 | 0 |
| ≥3% to ≤25% | 94 (35.1) | 98 (36.2) | 192 (35.6) |
| >25% to ≤50% | 143 (53.4) | 138 (50.9) | 281 (52.1) |
| >50% | 30 (11.2) | 35 (12.9) | 65 (12.1) |
| >25% | 173 (64.6) | 173 (63.8) | 346 (64.2) |
| Unknown | 1 (0.4) | 0 | 1 (0.2) |
| **WBC count at diagnosis of AML, n (%)** | | | |
| <40 × $10^9$/L | 135 (50.4) | 137 (50.6) | 272 (50.5) |
| ≥40 × $10^9$/L | 133 (49.6) | 134 (49.4) | 267 (49.5) |

AML = acute myeloid leukemia; *CEBPA* = CCAAT enhancer-binding protein alpha; CSR = clinical study report; *FLT3* = FMS-like tyrosine kinase 3; ITD = internal tandem duplication; ITT = Intent-to-Treat; MDS = myelodysplastic syndrome; max = maximum; min = minimum; MPN = myeloproliferative neoplasm; *NPM1* = nucleophosmin 1; SD = standard deviation; VAF = variant allele frequency; WBC = white blood cell; WHO = World Health Organization

[a] Duration of disease is defined as (Randomization date − disease diagnosis date + 1)/7.

[b] Some subjects were reported in more than 1 category.

[c] *NPM1* and *CEBPA* data are based on the Navigate central data.

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

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

[f] *FLT3*-ITD VAF refers to *FLT3*-ITD/Total *FLT3*.

Note: Data cutoff date: 13 Aug 2021.

Source: AC220-A-U302 CSR Table 14.1.3.1.1

- **Numbers analysed**

**Table 3. Data sets analysed**

| Analysis Set | Quizartinib (N = 268) n (%) | Placebo (N = 271) n (%) | Total (N = 539) n (%) |
|---|---|---|---|
| ITT | 268 (100.0) | 271 (100.0) | 539 (100.0) |
| Safety | 265 (98.9) | 268 (98.9) | 533 (98.9) |
| Per-protocol | 265 (98.9) | 266 (98.2) | 531 (98.5) |

ITT = intent-to-treat

Data cutoff date: 13 Aug 2021.

Source: Table 14.1.1.1.1

- **Outcomes and estimation**

The results of the primary endpoint, OS are presented in figure 11 and Table 9.

**Figure 21. Kaplan-Meier Plot of Overall Survival (ITT Analysis Set)**

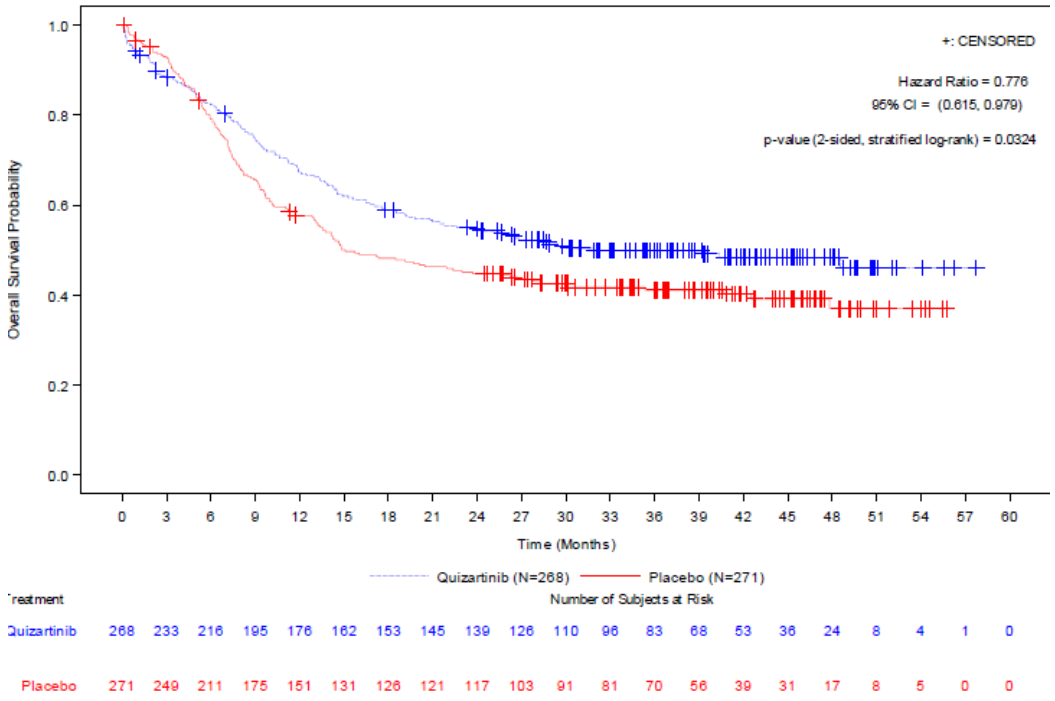



**Table 4 Primary analysis of overall survival (ITT analysis set)**

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

AML = acute myeloid leukemia; CI = confidence interval; CSR = clinical study report; ITT = Intent-to-Treat; NE = not estimable; OS = overall survival; WBC = white blood cell

[a] Stratification factors include region (North America, Europe, and Asia/Other Regions), age (<60 and ≥60 years old), and WBC count at the time of diagnosis of AML (<40 × $10^9$/L and ≥40 × $10^9$/L).

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

[c] Estimated using the Kaplan-Meier method.

Notes: Denominator for percentages is the number of subjects in the ITT Analysis Set.
OS is defined as the time from the date of Randomization to the date of death from any cause.
Data cutoff date: 13 Aug 2021.

The study met its primary endpoint of OS with a HR of 0.776 (0.615- 0.979) and a 2-sided p value: 0.03. At the time of data cut off (DCO), there were 133 (49.6%) and 158 (58.3%) deaths in the

quizartinib and placebo arms, respectively. The median follow-up time was 39.2 months (95% CI of 37.2 to 41.5 months) in the quizartinib arm. The quizartinib arm had a higher plateau, with 49.9% (95%CI: 43.7-55.9) of the patients surviving at the 3-year time point, versus 41.1% (95%CI: 35.0-47.0) of the patients in the placebo arm. In the beginning of the OS curve (up to app. 5 months) there is a crossing of the curves in favour of placebo treatment which resolves after 6 months. More early deaths (ie, deaths within 30/60 days of initiation of study drug) occurred with quizartinib compared with placebo. In total, of the treated subjects, 20 (7.5%) and 13 (4.9%) subjects, respectively, died within 60 days of study drug initiation, of which 15 (5.7%) and 9 (3.4%) subjects, respectively, died within 30 days of study drug initiation. The applicant has provided the causes of the early death which are discussed in the safety section of this assessment report.

In line with the treatment policy estimand strategy, survival data was sufficiently complete with a follow up >96% of subjects in both arms including the discontinued patients. In total, 22 subjects withdrew their consent (13 [4.9%] and 9 [3.3%] subjects in the quizartinib and placebo groups, respectively), and 3 (0.6%) subjects were lost to follow up (2 [0.7%] and 1 [0.4%] subjects in the quizartinib and placebo groups.

- **Sensitivity analysis for OS**

The applicant performed several sensitivity analysis (Table 10; Table 11) for OS. The restricted mean survival time (RMST) method was conducted using survival cutoff time points at 36, 42, 48, and 55.8 months.

**Table 10. Overall survival using sensitivity and supplementary analyses (ITT analysis set)**

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

AML = acute myeloid leukemia; CI = confidence interval; CSR = clinical study report; HSCT = hematopoietic stem cell transplantation; ITT = Intent-to-Treat; OS = overall survival; NE = not estimable; WBC = white blood cell
[a] Median OS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.
[b] Log-rank test and Cox proportional hazards model are not adjusted for stratification factors.
[c] Stratification factors include region (North America, Europe, and Asia/Other Regions), age (<60 and ≥60 years), and WBC count at the time of diagnosis of AML (<40 × $10^9$/L and ≥40 × $10^9$/L).
Notes: OS is defined as the time from the date of Randomization to the date of death from any cause.
Data cutoff date: 13 Aug 2021.

**Table 5. Sensitivity analysis of overall survival – RMST analysis at 36, 42, and 48 months (study AC220-A-U302, intent-to-treat analysis)**

| | **Quizartinib (N = 268)** | **Placebo (N = 271)** | **Analysis (Quizartinib vs. Placebo)** |
|---|---|---|---|
| Subjects (%) with events (deaths) | 133 (49.6) | 158 (58.3) | |
| Subjects (%) without Events (Censored) | 135 (50.4) | 113 (41.7) | |

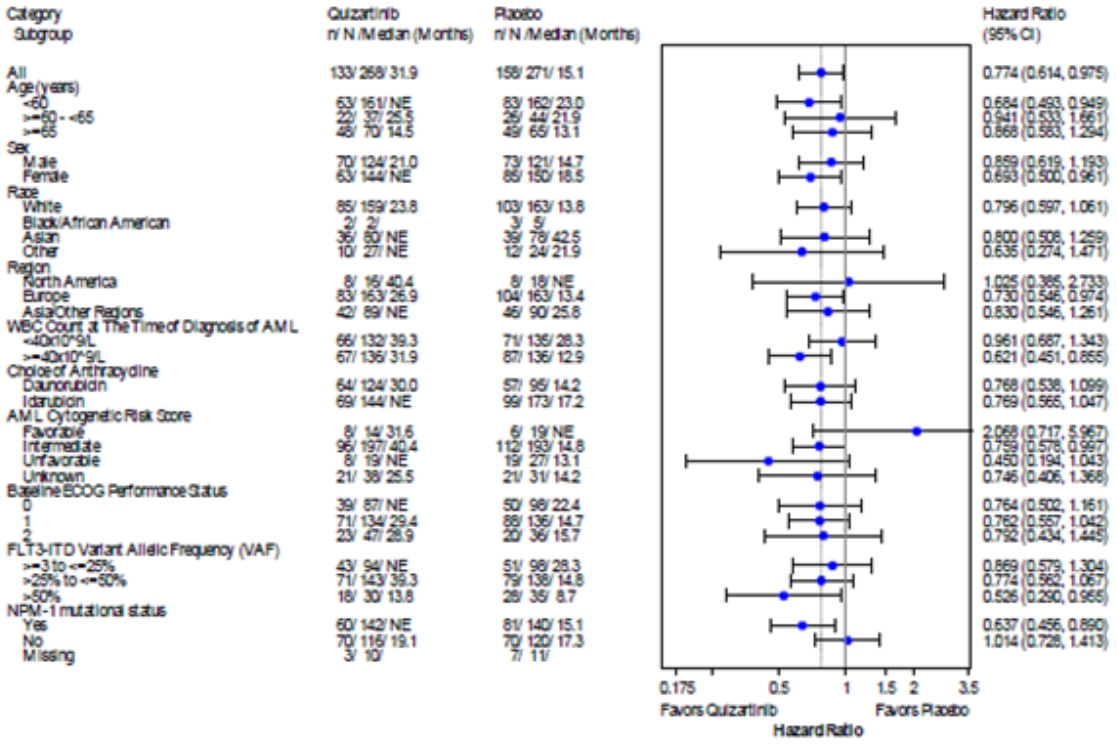
| | **Quizartinib (N = 268)** | **Placebo (N = 271)** | **Analysis (Quizartinib vs. Placebo)** |
|---|---|---|---|
| Alive at the time of data cutoff date | 120 (44.8) | 103 (38.0) | |
| Lost to Follow-up | 2 (0.7) | 1 (0.4) | |
| Withdrawal of Consent | 13 (4.9) | 9 (3.3) | |
| RMST Estimate (months) at 36 months cutoff | 23.2 | 20.4 | |
| p-value (2-sided)[a] | | | 0.0248 |
| Difference relative to placebo (95% CI) | | | 2.75 (0.35, 5.15) |
| RMST Estimate (months) at 42 months cutoff | 26.2 | 22.9 | |
| p-value (2-sided)[a] | | | 0.0262 |
| Difference relative to placebo (95% CI) | | | 3.26 (0.39, 6.13) |
| RMST Estimate (months) at 48 months cutoff | 29.1 | 25.2 | |
| p-value (2-sided)[a] | | | 0.0257 |
| Difference relative to placebo (95% CI) | | | 3.81 (0.46, 7.16) |

Landmark analysis for OS (95% CI) in the quizartinib group vs. the placebo group:

- 12 months, 67.4% (61.3, 72.7) vs. 57.7% (51.6, 63.4)
- 24 months, 54.7% (48.4, 60.5) vs. 44.7% (38.7, 50.6)
- 36 months, 49.9% (43.7, 55.9) vs. 41.1% (35.0, 47.0)
- 48 months, 48.4% (41.9, 54.5) vs. 37.0% (29.8, 44.2)

Predefined subgroup analyses for OS were performed based on demographics (age, sex, race, and geographical region) and baseline disease characteristics (baseline ECOG performance status, white blood cell (WBC) count at the time of diagnosis, choice of anthracycline used during the Induction Phase, AML cytogenetic risk score, *FLT3*-ITD VAF at Randomisation, and *NPM1* mutational status). (Figure 12)

**Figure 32. Forest plot of overall survival (ITT analysis set)**

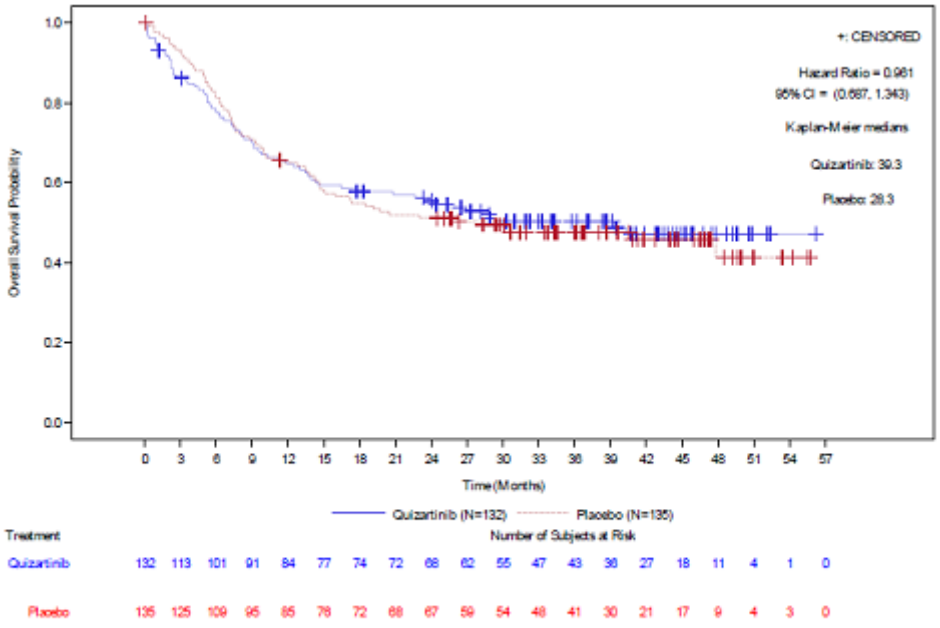



AML = acute myeloid leukemia; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; *FLT3*-ITD = FMS-like tyrosine kinase 3 internal tandem duplication; ITT = intent-to-treat; NE = not estimable; NPM1 = nucleophosmin 1; OS = overall survival; WBC = white blood cell
Notes: Hazard ratio was obtained from unstratified Cox proportional hazard model. The dotted line indicates the hazard ratio for the overall OS analysis. Median, median OS from Kaplan-Meier analysis.
Data cutoff date: 13 Aug 2021

In Study AC220-A-U302, WBC count at the time of diagnosis of AML was one of the stratification factors at randomisation, enabling similar distribution of subjects with low and high WBC counts in the overall population and between the quizartinib and placebo groups (ie, 50.5 vs. 49.5%, in the overall population, 50.4% vs. 49.6% in the quizartinib group, and 50.6% vs. 49.4% in the placebo group). For subjects with low WBC count, the HR was 0.961 (95% CI: 0.687, 1.343) with no clear separation of the curves (Figure 13).

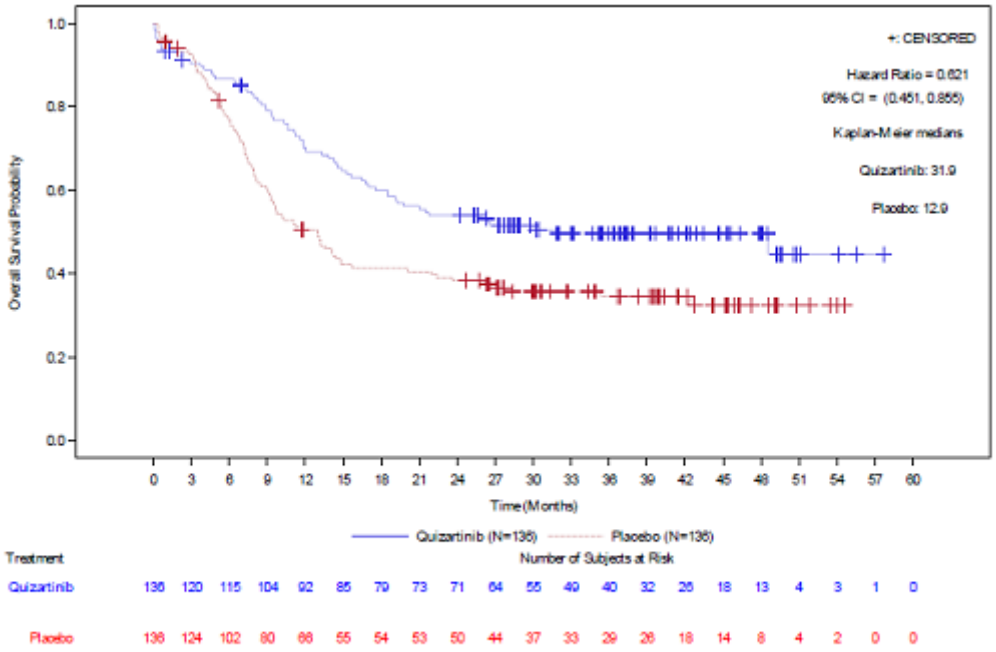
For subjects with high WBC count, the Kaplan-Meier curves (Figure 14) showed a clear separation between the 2 treatment groups in favour of quizartinib, with an HR of 0.621 (95% CI: 0.451, 0.855).

**Figure 43. Kaplan-Meier plot of overall survival in subjects with white blood cell count <40 × 109/L at diagnosis in study AC220-A-U302 (intent-to-treat analysis set)**




CI = confidence interval
Note: Statistical model for hazard ratio: unstratified Cox proportional hazard model.

**Figure 54. Kaplan-Meier plot of overall survival in subjects with white blood cell count ≥40 × 109/L at diagnosis in study AC220-A-U302 (intent-to-treat analysis set)**




CI = confidence interval
Note: Statistical model for hazard ratio: unstratified Cox proportional hazard model.

The demographics and baseline disease characteristics of subjects with low and high WBC count at AML diagnosis has been provided. No notable differences were observed for the subgroup of low WBC

between quizartinib and placebo-treated subjects in the low WBC count subgroup, except for antecedent haematological disorders, which was reported with higher incidence in the quizartinib group compared with the placebo group (15.9% vs. 9.6%), including myelodysplastic syndrome (12.1% vs. 6.7%). The proportion of subjects with NPM1 co-mutation was lower in the quizartinib group than in the placebo group (40.9% vs. 48.1%).

- **Secondary endpoints**

The primary analysis for EFS was based on a response of CR as assessed by the IRC (Table **1**12). For this analysis, induction treatment failure (ITF) was defined as not achieving CR within 42 days from the start of the last cycle of induction chemotherapy, per the FDA AML guidance (FDA, 2020). Based on this definition, there was no statistically significant difference between the quizartinib and placebo arms in EFS (HR [95% CI] = 0.916 [0.754, 1.114], p = 0.2371 by stratified log-rank test). The sensitivity and supplementary analyses ( Table 12 and 13) for EFS are based on CR or CRc evaluation in the Induction Phase (without the 42-day window but up to Day 56 from the start of the last cycle of induction chemotherapy, as per protocol).

**Table 12. Analysis of event-free survival – IRC assessment (ITT analysis set)**

| Statistics | Quizartinib (N = 268) | Placebo (N = 271) | Analysis (Quizartinib vs. Placebo) |
|---|---|---|---|
| **Subjects (%) with events** | 198 (73.9) | 213 (78.6) | — |
| Refractory disease | 136 (50.7) | 131 (48.3) | — |
| Relapse | 30 (11.2) | 53 (19.6) | — |
| Death | 32 (11.9) | 29 (10.7) | — |
| **Subjects (%) without events (censored)** | 70 (26.1) | 58 (21.4) | — |
| No postbaseline response assessment, no death date | 1 (0.4) | 1 (0.4) | — |
| Had CR, no relapse, no death date | 69 (25.7) | 57 (21.0) | — |
| **Stratified log-rank test[a]** | | | |
| p-value (2-sided) | — | — | 0.2371 |
| **Stratified Cox regression analysis[a]** | | | |
| Hazard ratio (relative to placebo) | — | — | 0.916 |
| 95% CI | — | — | (0.754, 1.114) |

| Statistics | Quizartinib (N = 268) | Placebo (N = 271) | Analysis (Quizartinib vs. Placebo) |
|---|---|---|---|
| **Median EFS (months)[b]** | 0.03 | 0.71 | — |
| 95% CI | (0.03, 0.95) | (0.03, 3.42) | — |
| **EFS rate (%) (95% CI)[c] at:** | | | |
| 2 months | 43.1 (37.1, 48.9) | 48.5 (42.4, 54.3) | — |
| 6 months | 40.0 (34.1, 45.8) | 35.5 (29.7, 41.2) | — |
| 12 months | 34.2 (28.5, 40.0) | 25.0 (19.9, 30.4) | — |
| 18 months | 30.5 (24.9, 36.1) | 22.9 (17.9, 28.2) | — |
| 24 months | 26.9 (21.6, 32.5) | 20.7 (15.9, 25.9) | — |
| 30 months | 25.4 (20.2, 31.0) | 20.2 (15.5, 25.4) | — |
| 36 months | 24.1 (18.8, 29.7) | 19.2 (14.5, 24.3) | — |

AML = acute myeloid leukemia; CI = confidence interval; CR = complete remission; EFS = event-free survival; IRC = Independent Review Committee; ITT = intent-to-treat; WBC = white blood cell

[a] Stratification factors include region (North America, Europe, Asia/other regions), age (<60, ≥60 years old), and WBC count at the time of diagnosis of AML (<40 × $10^9$/L, ≥40 × $10^9$/L).

[b] Median EFS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.

[c] Estimated using the Kaplan-Meier method.

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

EFS was defined as the time from the date of Randomization to the date of refractory disease, relapse, or death from any cause, whichever occurred first. The primary analysis for EFS was based on the response assessment by IRC with response of CR only, using a 42-day window from the start of the last cycle in induction for CR evaluation as defined in the AML guidance.[22]

Data cutoff date: 13 Aug 2021.

**Table 13. Event-free survival primary and sensitivity and supplementary analyses –IRC assessment (ITT analysis set)**

| Analysis | Median EFS (months)[b] (95% CI) | | Hazard Ratio[a] Relative to Placebo (95% CI) | 2-sided p-value (Stratified LR Test[a]) |
|---|---|---|---|---|
| | Quizartinib (N = 268) | Placebo (N = 271) | | |
| Primary analysis of EFS – ITF defined as not achieving CR by the end of the Induction Phase, using a 42-day window from the start of the last cycle in induction for CR evaluation | 0.03 (0.03, 0.95) | 0.71 (0.03, 3.42) | 0.916 (0.754, 1.114) | 0.2371 |
| ITF defined as not achieving CR by the end of induction (without a 42-day window) | 5.0 (1.8, 9.0) | 3.4 (1.7, 5.5) | 0.818 (0.669, 0.999) | 0.0323 |
| ITF defined as not achieving CRc by the end of induction (original protocol-defined primary endpoint without a 42-day window) | 11.9 (8.1, 16.5) | 5.7 (4.0, 6.9) | 0.729 (0.592, 0.897) | 0.0031 |

AML = acute myeloid leukemia; CI = confidence interval; CR = complete remission; CRc = composite complete remission; EFS = event-free survival; ITF = induction treatment failure; IRC = Independent Review Committee; ITT = intent-to-treat; LR = log-rank; WBC = white blood cell

[a] Stratification factors include region (North America, Europe, Asia/other regions), age (<60, ≥60 years old), and WBC count at the time of diagnosis of AML (<40 × $10^9$/L, ≥40 × $10^9$/L)

[b] Median EFS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.

Note: EFS was defined as the time from the date of Randomization to the date of refractory disease, relapse, or death from any cause, whichever occurred first.

Data cutoff date: 13 Aug 2021.

Because the analysis of EFS per FDA criteria was not statistically significant, formal hierarchical testing was not continued. Thus the results of the other secondary efficacy endpoints should only be considered descriptive. (Table 14) It is unclear whether patients with missing assessments may have had their EFS time overestimated given these patients were in follow up until date of death or censoring at last follow up for survival and any other EFS-related events were unknown.

Rates of CR, CR with FLT3-ITD MRD negativity, and CRc with FLT3-ITD MRD negativity at the end of induction were similar between treatment arms. A difference was observed for CRi (also reflected in the CRc rate) between the quizartinib and placebo arm (45 [16.8%] subjects vs. 26 [9.6%] subjects), however CRi is a less stringent definition of CR as incomplete hematologic recovery.

**Table 14. Analysis of other secondary endpoints – IRC assessment (ITT analysis set)**

| Statistics | Quizartinib (N = 268) | Placebo (N = 271) |
|---|---|---|
| **CR** | | |
| n (%) | 147 (54.9) | 150 (55.4) |
| 95% CI[a] | (48.7, 60.9) | (49.2, 61.4) |
| **CR with *FLT3*-ITD MRD negativity[b]** | | |
| n (%) | 54 (20.1) | 51 (18.8) |
| 95% CI[a] | (15.5, 25.5) | (14.3, 24.0) |
| **CRc (CR + CRi)** | | |
| n (%) | 192 (71.6) | 176 (64.9) |
| 95% CI[a] | (65.8, 77.0) | (58.9, 70.6) |
| **CRc with *FLT3*-ITD MRD negativity[b]** | | |
| n (%) | 66 (24.6) | 58 (21.4) |
| 95% CI[a] | (19.6, 30.2) | (16.7, 26.8) |
| **CRi[c]** | | |
| n (%) | 45 (16.8) | 26 (9.6) |
| 95% CI[a] | (12.5, 21.8) | (6.4, 13.7) |
| **CRi with *FLT3*-ITD MRD negativity[b, c]** | | |
| n (%) | 12 (4.5) | 7 (2.6) |
| 95% CI[a] | (2.3, 7.7) | (1.0, 5.2) |

AML = acute myeloid leukemia; CI = confidence interval; CR = complete remission; CRc = composite complete remission; CRi = complete remission with incomplete neutrophil or platelet recovery; CSR = clinical study report; *FLT3*-ITD = FMS-like tyrosine kinase 3-internal tandem duplication; IRC = Independent Review Committee;ITT = Intent-to-Treat; MRD = minimal or measurable residual disease; WBC = white blood cell

[a] Based on the Clopper-Pearson method.

[b] MRD negativity based on assessments by the end of induction on all clones and cutoff of 0.0001.

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

Notes: Denominator for percentages is the number of subjects in the ITT Analysis Set. Data cutoff date: 13 Aug 2021.

- **Exploratory endpoints**

The exploratory endpoints (relapse-free survival [RFS] and duration of complete remission [CR]) appear to show a difference between quizartinib and placebo in favour of quizartinib (Table 15).

An increased RFS and duration of CR was reported by the applicant with quizartinib (median RFS; 39.3 and 13.6 months, and median duration of CR of 38.6 months versus 12.4 months quizartinib vs placebo).

**Table 15. exploratory analyses of relapse-free survival and duration of complete remission – IRC assessment (ITT analysis set)**

| Parameter | Quizartinib (N = 268) | Placebo (N = 271) | Analysis (Quizartinib versus Placebo) |
|---|---|---|---|
| **RFS – subjects with CR in Induction, n[a]** | 147 | 150 | — |
| Subjects (%) with events | 65 (44.2) | 88 (58.7) | — |
| Median (months) (95% CI)[b] | 39.3 (22.6, NE) | 13.6 (9.7, 23.7) | — |
| **RFS rate (%)[C] (95% CI) at:** | | | |
| 6 months | 88.1 (81.6, 92.5) | 71.8 (63.8, 78.4) | — |
| 12 months | 73.4 (65.2, 80.0) | 52.4 (43.9, 60.2) | — |
| 18 months | 65.0 (56.4, 72.4) | 46.4 (37.9, 54.4) | — |
| 24 months | 57.8 (48.9, 65.7) | 40.9 (32.7, 49.0) | — |
| 30 months | 54.3 (45.3, 62.4) | 40.1 (31.8, 48.2) | — |
| 36 months | 51.7 (42.5, 60.1) | 38.2 (30.0, 46.4) | — |
| **RFS – subjects with CR in Induction who entered the Continuation Phase, n[a]** | 94 | 72 | — |
| Subjects (%) with events | 30 (31.9) | 29 (40.3) | — |
| Median (months) (95% CI)[b] | 48.6 (48.6, NE) | NE (30.1, NE) | — |
| **RFS – subjects with CRc (CR + CRi) in Induction, n[c]** | 192 | 176 | — |
| Subjects (%) with events | 95 (49.5) | 102 (58.0) | — |
| Median (months) (95% CI)[b] | 28.5 (18.5, NE) | 12.6 (9.7, 23.7) | — |
| **Duration of CR – subjects with CR, n[d]** | 147 | 150 | — |
| Median (months) (95% CI)[e] | 38.6 (21.9, NE) | 12.4 (8.8, 22.7) | — |

*CI = confidence interval; CR = complete remission; CRc = composite complete remission; CRi = complete remission with incomplete neutrophil or platelet recovery; CSR = clinical study report; IRC = Independent Review Committee; ITT = Intent-to-Treat; NE = not estimable; RFS = relapse-free survival. a Used as denominator for percentage calculation. Subjects without a documented response of CR are excluded from the analysis. b Median RFS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. c Used as denominator for percentage calculation. Subjects without a documented response of CRc are excluded from the analysis. d Subjects without a documented response of CR are excluded from the analysis.*

Subjects were permitted to undergo allo-HSCT after CR or CRi was achieved per protocol. Allogeneic HSCT was to be performed after the Induction Phase, anytime during the Consolidation Phase or, if certain criteria were met, within 3 months of the Continuation Phase. The number of subjects receiving allo-HSCT was numerically slightly higher in subjects in the quizartinib arm (38.1%) versus 33.6% subjects in the placebo. Any HSCTs after treatment discontinuation were specified as non-protocol HSCTs. A total of 83 subjects underwent non-protocol-specified HSCT (44 and 39 subjects in the

quizartinib and placebo groups, respectively). Overall, no major differences were observed between the quizartinib and placebo groups. Most subjects had non-protocol-specified HSCT after the Induction Phase (N = 48, including 24 subjects in each group) or the Consolidation Phase (N = 20, including 9 and 11 subjects in the quizartinib and placebo groups, respectively). A total of 14 subjects had non-protocol specified allo-HSCT during the Continuation Phase (ie, 10 subjects in the quizartinib group and 4 subjects in the placebo group). The non-protocol HSCTs are reported based on data recorded in the CSR, these data are likely to be incomplete as not all patients had data available on subsequent therapies after discontinuing treatment.

The impact of NPM1 mutation status on the secondary endpoints of EFS and CR/CRc is summarised in table 16 and table 17. Consistent with the well-established role of NPM1wt as an adverse prognostic factor, better outcomes were observed in NPM1mut subjects compared to NPM1wt subjects, including the longer median EFS based on the primary and 2 sensitivity EFS analyses, as well as the higher rates of CR and CRc in NPM1mut subjects versus NPM1wt subjects.

**Table 16. Analysis of event-free survival based on NPM1 mutation status in study AC220-A-U302-IRC assessment (ITT analysis set)**

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

CI = confidence interval; CR = complete remission; CSR = clinical study report; EFS = event-free survival; HR = hazard ratio; IRC = Independent Review Committee; ITF = induction treatment failure; ITT = intent-to-treat; NE = not estimable; *NPM1* = nucleophosmin 1; PH = proportional hazards.

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

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

n* includes subjects with an EFS event and n represents the number of subjects in each *NPM1* mutation status subgroup.

Note: EFS is defined as the time from the date of randomisation to the date of refractory disease, relapse, or death from any cause, whichever occurred first.

**Table 17. Analysis of response rate based on NMP1 mutation status in study AC220-A-U302-IRC assessment (ITT analysis set)**

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

CI = confidence interval; CR = complete response; CRc = composite complete remission; CSR = clinical study report; IRC = Independent Review Committee; ITT = intent-to-treat; *NPM1* = nucleophosmin 1.

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

- **Ancillary analyses**

N/A

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table18. Summary of efficacy for trial AC220-A-U302**

| **Title:** A Phase 3, Double-blind, Placebo-controlled Study of Quizartinib Administered in Combination with Induction and Consolidation Chemotherapy, and Administered as Continuation Therapy in Subjects 18 to 75 Years Old with Newly Diagnosed FLT3-ITD (+) Acute Myeloid Leukaemia (QuANTUM-First) | | | |
|---|---|---|---|
| Study identifier | AC220-A-U302 | | |
| Design | Placebo controlled. Double blind, randomised multicentre study. | | |
| | Duration of main phase:<br><br>Duration of Run-in phase:<br>Duration of Extension phase: | | First subject first visit date: 18 Aug 2016; Data cutoff (DCO) date: 13 Aug 2021<br>not applicable<br>not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | Quizartinib (quiz) | | Quizartinib + anthracycline (daunorubicin or idarubicin) + cytarabine. N = 268 |
| | Placebo (placebo) | | Placebo + anthracycline (daunorubicin or idarubicin) + cytarabine n=271 |
| Endpoints and definitions | Primary endpoint | Overall survival (OS) | defined as the time from Randomisation until death from any cause. Subjects alive or lost to follow-up at the time of analysis were to be censored at the date when they were last known to be alive. |
| | Secondary endpoint | EFS per FDA recommendation | defined as the time from Randomisation to failure to achieve CR within 42 days of the start of the last cycle of induction chemotherapy |

| | | | |
|---|---|---|---|
| **Title:** A Phase 3, Double-blind, Placebo-controlled Study of Quizartinib Administered in Combination with Induction and Consolidation Chemotherapy, and Administered as Continuation Therapy in Subjects 18 to 75 Years Old with Newly Diagnosed FLT3-ITD (+) Acute Myeloid Leukaemia (QuANTUM-First) | | | |
| Study identifier | AC220-A-U302 | | |
| | Secondary endpoint | EFS | defined as the time from Randomisation to failure to achieve a CR (based on IRC assessment) or relapse or death of any cause, whichever occurred first |
| Database lock | Data Cutoff (DCO) for This Report: 13 Aug 2021 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Intent to treat<br>DCO: 13 Aug 2021 | | |
| Descriptive statistics and estimate variability | Treatment group | QUIZ | placebo |
| | Number of subject | 268 | 271 |
| | Median OS (Months) | 31.9 | 15.1 |
| | 95% CI<br>P value | 21.0, NE | 13.2, 26.2 |
| | Median EFS (ITF defined as not achieving CR by the end of the Induction Phase, using a 42-day window from the start of the last cycle of induction for CR evaluation) (months) | 0.03 | 0.71 |
| | (95% CI) | (0.03, 0.95) | (0.03, 3.42) |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint | Comparison groups | Quizartinib vs placebo |
| | | Hazard Ratio | 0.776 |
| | | 95% CI | 0.615, 0.979 |
| | | P-value | 0.0324 |
| | Secondary: EFS | Comparison groups | Quizartinib vs placebo |
| | | Hazard Ratio | 0.916 |
| | | 95% CI | 0.754, 1.114 |
| | | P-value | 0.2371 |
| | | | |

#### *2.6.5.3. Clinical studies in special populations*

No dedicated study was performed in special populations.

| | Age 65 to 74 years[a]<br><br>n (%) | Age 75 to 84 years[a]<br><br>n (%) | Age 85+ years[a]<br><br>n (%) |
|---|---|---|---|
| Controlled studies | 120 (11.1) | 13 (1.2) | 0 |
| Noncontrolled studies | 184 (17.0) | 43 (4.0) | 4 (0.4) |
| Total | 304 (28.1) | 56 (5.2) | 4 (0.4) |

#### *2.6.5.4. In vitro biomarker test for patient selection for efficacy*

Detection of FLT3-ITD-Activating Mutation in AML Studies is discussed in the PD section of the overview**.**

## 2.6.6. Discussion on clinical efficacy

***Design and conduct of clinical studies***

The application presents one pivotal trial Quantum-First (study AC2200-A-U302), a randomised, double-blind, parallel-group, and placebo-controlled study. The add-on study design with standard induction and consolidation treatment as background therapy was intended to establish efficacy over an active comparator in the first part of the study (induction + consolidation). The target patient population (patients with ≥3% FLT3-mutated alleles), the comparator (standard induction and consolidation chemotherapy plus placebo), was accepted and considered standard of care in current treatment guidelines (NCCN and ELN guideline) for the treatment of newly diagnosed AML FLT3-ITD+ patients. An issue raised during SA (EMEA/CHMP/SAWP/209069/2007) was the fact that induction/consolidation and maintenance/continuation were tested together without the possibility to conclude on the contribution of each component, this uncertainty remains and implies a B/R assessment of the complete quizartinib treatment strategy as studied.

The proposed dosing strategy during the induction and consolidation phase of the pivotal trial was standard cytarabine and anthracycline with quizartinib 40 mg or matching placebo (QD for 14 days). This dose of 40 mg/day for induction and consolidation seems reasonable as a safe and effective recommended dose. During the Continuation Phase of Study AC220-A-U302, subjects received quizartinib at a starting dose of 30 mg QD increasing to 60 mg QD for subjects if QTcF was ≤450 ms for which the applicant concludes that this is a safe and effective dose, this is accepted although long-term data is limited.

The patient inclusion and exclusion criteria were considered adequate and the enrolled patient population was considered to be a representative of a relatively healthy adult population with FLT3-ITD positive newly–diagnosed AML with adequate performance status, and organ function to be eligible for the induction and consolidation therapy. A positive FLT3-ITD result is defined as an allelic ratio of FLT3-ITD to total FLT3 ≥ 3% in bone marrow or peripheral blood. Given the risk of QTc prolongation, patients with uncontrolled or significant cardiovascular disease were excluded. Also, adequate renal

and hepatic function is needed for inclusion. The indication wording is according to the proposed inclusion criteria of the pivotal trial.

The chosen primary endpoint, OS is considered adequate to demonstrate clinical benefit in the context of first-line treatment of AML. The secondary endpoints, EFS, CRc , CR, CR with FLT3-ITD MRD negativity are considered adequate endpoints and relevant in the context of the studied population. Several changes occurred during the trial with respect to the endpoint selection. Initially the primary endpoint was EFS. However, in Protocol Amendment 5 the primary endpoint was changed from EFS to dual primary endpoints of EFS and OS. Subsequently, based on FDA feedback EFS was then changed to a secondary endpoint in Protocol Amendment 6, and the definition of EFS was changed in Protocol Amendment 7. Under the final protocol amendment with OS as the sole primary endpoint, the study met its primary objective.

***Efficacy data and additional analyses***

A relatively high number of major protocol violations occurred in the pivotal study. The nature of the protocol deviations and the distribution across treatment arms did not appear to impact the conclusions regarding efficacy and safety drawn from the submitted data to a relevant extent. The main amendment pertained to the definition of the secondary endpoint EFS (per FDA criteria, including a 42 day time window).

Demographic and baseline characteristics for subjects in the ITT Analysis Set were generally well balanced between the two arms. Approximately 25% of patients was older than 65 years. Subjects were evenly distributed among treatment arms by age, sex, race. Patients could be considered as relatively fit with ECOG 0-2 (only 15% had ECOG: 2). Baseline AML characteristics were generally comparable between the 2 treatment arms, the median time from initial diagnosis to randomisation was short, 1.86 (0.9, 5.3) weeks in the quizartinib arm and 1.71 (1.0, 9.1) weeks in the placebo arm, this small delay between diagnosis and randomisation was due to the time needed for FLT3-ITD analysis confirming FLT3-ITD positivity. The majority of subjects in both the quizartinib and placebo arms had an intermediate or unfavourable cytogenetic risk (80.6% vs 81.2%). NPM1 mutations were reported in 282 (52.3%) subjects with a similar distribution in the quizartinib and placebo arms.

Around a third of patients in both arms discontinued study treatment by the end of the induction phase. Even though the number of discontinuations during the induction phase was very similar between the study arms, there was an imbalance between in reason for discontinuation of treatment with more patients in the quizartinib arm discontinuing due to an AE, or following a decision by the subject or investigator.

The study met its primary endpoint of OS with a HR of 0.776 (0.615- 0.979) and a 2-sided p value: 0.03. Comparison of the median OS values (quiz;31.9, placebo: 15.1 months) is not informative since the Kaplan-Meier curves plateau around the median and estimates of the median do not describe the true treatment effect. The median follow-up time was 39.2 months (95% CI of 37.2 to 41.5 months) in the quizartinib arm. The quizartinib arm had a higher plateau, with 49.9% (95%CI: 43.7-55.9) of the patients surviving at the 3-year time point, versus 41.1% (95%CI: 35.0-47.0) of the patients in the placebo arm. There is a suggestion of early OS detriment (up to approximately 5 months), more early deaths (i.e., deaths within 30/60 days of initiation of study drug) occurred with quizartinib compared to placebo, this will be further discussed in conjunction with safety (B/R section).

The early OS detriment with crossing of the survival curves after ~5 months and the survival curves reaching a plateau means that the proportional hazards assumption is not fulfilled. The log-rank test remains a valid test of the null hypothesis of equal survival when hazards are non-proportional (i.e. type 1 error is not inflated), although the power is optimal under proportional hazards. However, non-proportional hazards imply that the HR may not be an ideal summary measure of the treatment effect.

Therefore, the treatment effect should be supported by additional effect measures. One possibility is the difference in survival probability at milestones. Another effect measure is the restricted mean survival time (RMST) difference, which provides the difference in life expectancy until a given time point τ. The applicant provided an exploratory analysis of RMST (difference) using cutoff time points of 36, 42, and 48 months. RMST (95% CI) survival time for subjects who received quizartinib was prolonged by 2.75 months (0.35, 5.15) at 36 months, 3.26 months (0.39, 6.13) at 42 months, 3.81 months (0.46, 7.16) at 48 months, and 4.53 months (0.55, 8.51) at 55.8 months. The observed differences between the quizartinib and placebo groups were in line with the primary OS analysis results.

The study design did not disentangle the contribution of different stages of quizartinib treatment on the overall survival and the potential influence of subsequent therapies and treatment decisions, but it is agreed that the OS analysis is compliant with the usual regulatory standard for OS analysis, i.e. the estimand is targeted where all intercurrent events are accounted for by the treatment policy strategy (patients are followed for survival irrespective of the occurrence of intercurrent events such as treatment discontinuations). During follow up for OS, in addition to receiving already approved AML therapies and HSCT as subsequent treatment options, patients in the study also moved over to a new clinical trial for another investigational drug or received treatments that may not be available to all patients in Europe.

Subjects were permitted to undergo allo-HSCT after CR or CRi was achieved per protocol. Allogeneic HSCT was to be performed after the Induction Phase, anytime during the Consolidation Phase or, if certain criteria were met, within 3 months of the Continuation Phase. A slightly higher number of subjects in the quizartinib than in the placebo arms underwent protocol-specified allo-HSCT after Induction Phase (102 [38.1%] subjects in the quizartinib arm and 91 [33.6%] in the placebo arm). With respect to non-protocol HSCTs, the applicant has clarified that any HSCTs after treatment discontinuation were non-protocol-specified. Most subjects had non-protocol-specified HSCT after the Induction Phase or the Consolidation Phase and no relevant difference between arms was observed (44 quiz and 39 placebo subjects). Data with regard to non-protocol AML and non-protocol HSCT are considered unreliable as there is an indication that not all subsequent (non-protocol) therapies were recorded for all patients. Given there is information missing on subsequent therapies for some patients who discontinued treatment, it is likely that more patients received non-protocol-specified HSCTs.

The subgroup analysis for OS for sex, race, ECOG status, choice of anthracycline show consistent results, although older patients (age>=60 years) appear to show less benefit of quizartinib treatment compared to placebo. It is acknowledged that this subgroup analysis was not powered to determine the B/R in elderly and age alone does not determine eligibility for intensive therapy, but this should be assessed in conjunction with the observed toxicity in this population (discussed further in B/R section). NPM1 mutation alone is indicative for favourable prognosis, however the superior prognosis is limited to those with NPM1 mutation who do not have a FLT3-ITD mutation and a normal karyotype. In this study quizartinib treatment indicated a lower HR for the patients with a NPM1 mutation than for patients without a NPM1 mutation. Additional subgroup analysis for FLT3-ITD %VAF subgroups plus NPM1-status to confirm that there is a benefit and no clinically relevant negative (detrimental) effect on the primary endpoint OS in all subgroups and especially those such as FLT3-ITD low plus NPM1wt will be presented in a separate biomarker report expected Q1/2024. The HR for the subgroup for low white blood cell counts at diagnosis (WBC <40x10^9/L) was higher than for the subgroup with WBC ≥40x10^9/L (i.e. HR 0.961 compared to HR 0.621, respectively). There were no continuous WBC data available at initial diagnosis to investigate clinical outcomes by several WBC cut-off points, hampering determination of a WBC level at which treatment is less effective. Moreover, lower efficacy is likely not dependent on low WBC alone but influenced by multiple factors. As such, no restriction of the indication is proposed. In order to exclude confounding factors for the observed difference in OS, the

applicant has presented the baseline demographics of both subgroups in which several imbalances were observed possibly impacting prognosis (genetic abnormalities, e.g. mutated NPM1, ECOG 2 score, race, and % of subjects ≥65 years). In order to understand the potential influence of these factors, adjusted Kaplan-Meier curves and adjusted estimates of the treatment effects for the factors expected to impact prognosis have been presented during assessment, supporting the primary OS results.

The key secondary endpoint of EFS was based on a response of CR as assessed by the IRC. For this analysis, ITF was defined as not achieving CR within 42 days from the start of the last cycle of induction chemotherapy, per the FDA AML guidance (FDA, 2020). Based on this definition, there was no statistically significant difference between the quizartinib and placebo arm. This is likely due to the low median EFS values (0.03 months quizartinib arm versus 0.71 months in the placebo arm, this is in part caused by the stringent definition of induction treatment failure ITF (i.e. a large number of subjects with refractory disease were considered to have EFS events on Day 1 due to the 42-day window requirement). Additionally, the applicant has defined EFS in 2 different ways (the initial protocol definition and FDA's definition without considering the 42 days timepoint. These did show a numerical difference between the 2 treatment arms, in favour of quizartinib and in support of the primary endpoint, e.g. FDA's definition without the 42 day restriction (median EFS 5.0 vs 3.4 months, HR: 0.828, 95%CI 0.669-0.999), per protocol definition (median EFS 11.9 months vs 5.7 months, HR: 0.729, 95%CI 0.592-0.897). However, since the analysis of EFS was not statistically significant, formal hierarchical testing was not continued for the secondary endpoints.

Numerically there was no difference in rates of CR, CR with FLT3-ITD MRD negativity, and CRc with FLT3-ITD MRD negativity at the end of induction were similar between treatment arms. Higher rates of CRi in the quizartinib arm (45 [16.8%] subjects) compared with the placebo arm (26 [9.6%] subjects) were observed, however CRi is a less stringent definition of CR as hematologic recovery is incomplete. The clinical relevance of this finding is uncertain because of non-relapse mortality due to infections. An increased RFS and duration of CR was observed with quizartinib (median RFS;39.3 and 13.6 months, and median duration of CR of 38.6 months versus 12.4 months quizartinib vs placebo). The study was not designed to detect a difference for these parameters, therefore these results provide limited support in terms of the durability of effect of quizartinib. With respect to the duration of response, although the percentage of patients with CR is similar between the arms, the DOR is not based on a randomised comparison because it only includes patients based on a post treatment event, ie: those who had complete remission. It is reassuring that the demographic/baseline characteristics of the patients who achieved CR indicated no relevant differences between the two treatment groups, in particular with regard to cytogenetic risk groups, FLT3-ITD VAF subgroups and NPM1 mutations status. Several sensitivity analyses have been presented during the assessment and the results from these are consistent with the original DOR results.

While the single pivotal trial is positive on its primary endpoint, the measured effect on OS is not supported by a convincing impact on relevant pharmacodynamic endpoints, such a CR or MRD. This is of particular concern considering the limited statistical strength of the evidence for efficacy (p=0.03). Based on these concerns, the SAG-O was consulted. Following the rationale of the SAG-O, the OS benefit is considered to be established with reasonable certainty since other exploratory data support this effect. Lack of an effect on FLT3-ITD MRD negativity is not considered to weaken the conclusions as the surrogacy of MRD in this population is far from being established and the FLT3-ITD assay may not detect all mutations. Furthermore, although EFS rate based on failure to achieve CR at 42 days after last chemotherapy did not show convincing activity for quizartinib, the more relevant timepoint would be 56 days, which showed a more consistent effect in exploratory analyses. Furthermore, a longer duration of response was observed for quizartinib v. placebo in exploratory analyses, indicating higher activity in the experimental arm. Overall, the effect on OS is considered convincing and sufficiently supported by exploratory data.

***Additional expert consultation***

***Scientific advice group (SAG)***

The opinion of a SAG-O on the clinical relevance of the treatment effect was requested. The following question was addressed during the meeting;

*While the single pivotal trial of this study is positive on its primary endpoint, the measured effect on OS is not supported by a convincing impact on pharmacodynamic endpoints, such a CR or MRD, that would isolate the activity of quizartinib. This is of particular concern considering the limited statistical strength of the evidence for efficacy (p=0.03). Given these concerns, the SAG was asked whether it considered that the efficacy of quizartinib has been established with reasonable certainty.*

The SAG agreed that study AC220-A-U302 met its primary endpoint (overall survival; OS).

The majority of SAG considered this study to be sufficiently convincing due to the statistically and clinically significant effects observed in terms of the relevant primary endpoint OS, although the statistical evidence was considered low (P=0.03) and prespecified secondary endpoints (CR-rate at day 42 after last chemotherapy, MRD negativity and event-free-survival; EFS) failed to demonstrate a statistical significance in support of OS for the experimental arm.

Nevertheless, the OS benefit was considered to be established with reasonable certainty since other exploratory data support this effect.

Lack of an effect on FLT3-ITD MRD negativity was not considered to weaken the conclusions as the surrogacy of MRD in this population is far from being established and the FLT3-ITD assay may not detect all mutations.

Furthermore, although EFS rate based on failure to achieve CR at 42 days after last chemotherapy did not show convincing activity for quizartinib, it was considered that the more relevant timepoint would be 56 days, which showed a more consistent effect in exploratory analyses. Furthermore, a longer duration of response was observed for quizartinib v. placebo in exploratory analyses, indicating higher activity in the experimental arm.

Overall, the majority of the SAG concluded that the effect on OS was convincing and sufficiently supported by exploratory data.

A small minority disagreed, considering that the statistical significance was not compelling if seen in the context of a single pivotal study with failed planned secondary endpoints in multiplicity-adjusted analyses, variable endpoint definitions and adjudication for event-free survival, lack of an effect on MRD negativity, the considerable additional toxicity, early higher death rate, imbalances in induction regimens, and protocol amendments.

## 2.6.7. Conclusions on the clinical efficacy

The single pivotal trial in a newly diagnosed AML add-on treatment setting met its primary endpoint demonstrating an OS difference of quizartinib add-on compared to placebo. The single pivotal trial showed an approximate 10% difference in potential cure rate, as evidenced by the plateaus of the KM-curves, but this is not supported by clinically relevant differences in secondary endpoints. The OS benefit is considered to be established with reasonable certainty since other exploratory data (EFS following 56 day definition, and DOR) support this effect. While exploratory, reliability of these endpoints was supported by several additional sensitivity analyses presented during assessment. Altogether, efficacy of quizartinib in the applied indication is considered to be sufficiently established.

## 2.6.8. Clinical safety

The safety profile of quizartinib has been characterised based on safety data from pivotal clinical Phase 3 Study AC220-A-U302 (QuANTUM-First).

Main additional support is provided by a pooled analysis of safety data from pivotal Study AC220-A-U302 and 9 completed clinical studies in AML (n=1081): 2 studies in newly diagnosed *FLT3*-ITD (+) AML and 7 studies in relapsed/refractory (R/R) *FLT3*-ITD (+) AML.

### *2.6.8.1. Patient exposure*

*Study AC220-A-U302*

The median overall treatment duration was 75.0 days for quizartinib and 66.5 days for placebo. Approximately 44% of subjects received quizartinib as monotherapy in the Continuation Phase with a median treatment duration of 67 weeks, and approximately 30% of patients (n=79) in the quizartinib arm were treated for >365 days (*Table* 19).

The median average daily dose was the same in both treatment groups (40 mg); the median cumulative dose was higher in the quizartinib arm than in the placebo arm (1640.0 mg vs 1140.0 mg, respectively). The median relative dose intensity (RDI =dose intensity/planned dose intensity x 100) was 100% for both treatment arms (range: 20.97% to 207.14% with quizartinib and 40.46% to 200.00% with placebo).

In the Continuation Phase, patients in the quizartinib group were treated for a median (min, max) of 16.0 (1, 36) cycles. The median dose intensity was 37.00 mg/day. A total of 28.4% of subjects received ≥12 to <24 cycles, 36.2% received ≥24 to ≤36 cycles, and 15.5% received 36 cycles. The median RDI for the overall study period was 85%, The majority of the patients in the quizartinib arm had a quizartinib dose escalation to 60 mg in the Continuation Phase. A total of 43 out of the 116 subjects in the quizartinib group who entered the Continuation Phase had no dose escalation, mostly due to use of concomitant strong CYP3A4 inhibitors or TEAEs.

*All AML Pool*

Median overall treatment duration was 84 days in the 30 to 60 mg group of the All AML Pool, the median average daily dose was 40 mg, with a median cumulative dose of 2880 mg. In the >60 mg group of the All AML Pool, the median cumulative dose was 7605.0 mg.

**Table 19. Summary of study drug exposure (safety analysis set)**

| | Study AC220-A-U302 | | All AML Pool | | | |
|---|---|---|---|---|---|---|
| | Quizartinib N = 265 | Placebo N = 268 | Quizartinib <30 mg N = 30 | Quizartinib 30 to 60 mg N = 669 | Quizartinib >60 mg N = 382 | Total Quizartinib N = 1081 |
| **Treatment duration[a] (days)** | | | | | | |
| Mean (SD) | 286.9 (367.90) | 237.7 (343.94) | 81.6 (119.89) | 209.7 (308.43) | 104.0 (118.15) | 168.8 (258.62) |
| Median | 75.0 | 66.5 | 53.5 | 84.0 | 69.0 | 74.0 |
| Min, max | 1, 1289 | 3, 1273 | 7, 645 | 1, 1689 | 2, 1126 | 1, 1689 |
| **Total subject-years of exposure** | 208.2 | 174.4 | 6.7 | 384.1 | 108.7 | 499.5 |
| **Treatment duration group (days), n (%)** | | | | | | |
| 0 – 30 | 82 (30.9) | 95 (35.4) | 9 (30.0) | 127 (19.0) | 72 (18.8) | 208 (19.2) |
| 31 – 90 | 60 (22.6) | 65 (24.3) | 13 (43.3) | 229 (34.2) | 165 (43.2) | 407 (37.7) |
| 91 – 180 | 22 (8.3) | 25 (9.3) | 6 (20.0) | 140 (20.9) | 93 (24.3) | 239 (22.1) |
| 181 – 365 | 22 (8.3) | 24 (9.0) | 1 (3.3) | 58 (8.7) | 35 (9.2) | 94 (8.7) |
| 366 – 730 | 31 (11.7) | 23 (8.6) | 1 (3.3) | 54 (8.1) | 15 (3.9) | 70 (6.5) |
| ≥731 | 48 (18.1) | 36 (13.4) | 0 | 61 (9.1) | 2 (0.5) | 63 (5.8) |

AML = acute myeloid leukemia; max = maximum; min = minimum; N = total number of subjects; n = number of subjects in the category; SD = standard deviation

[a] Treatment duration (days) = date of last dose - date of first dose + 1.

### *2.6.8.2. Adverse events*

An overview of TEAEs is shown in Table 20.

**Table 60. Overview of TEAEs (safety analysis set)**

| Category | Study AC220-A-U302 | | All AML Pool | | | |
|---|---|---|---|---|---|---|
| | Quizartinib N = 265 n (%) | Placebo N = 268 n (%) | Quizartinib <30 mg N = 30 n (%) | Quizartinib 30 to 60 mg N = 669 n (%) | Quizartinib >60 mg N = 382 n (%) | Total Quizartinib N = 1081 n (%) |
| Any TEAE | 264 (99.6) | 265 (98.9) | 29 (96.7) | 664 (99.3) | 380 (99.5) | 1073 (99.3) |
| Grade ≥3 (including Grade 5) | 244 (92.1) | 240 (89.6) | 22 (73.3) | 598 (89.4) | 345 (90.3) | 965 (89.3) |
| Associated with death as outcome | 30 (11.3) | 26 (9.7) | 5 (16.7) | 104 (15.5) | 148 (38.7) | 257 (23.8) |
| Associated with study drug discontinuation | 54 (20.4) | 23 (8.6) | 3 (10.0) | 135 (20.2) | 119 (31.2) | 257 (23.8) |
| Associated with study drug interruption | 90 (34.0) | 54 (20.1) | 2 (6.7) | 213 (31.8) | 111 (29.1) | 326 (30.2) |
| Study drug-related TEAEs[a] | 160 (60.4) | 97 (36.2) | 19 (63.3) | 501 (74.9) | 332 (86.9) | 852 (78.8) |
| TESAEs | 143 (54.0) | 123 (45.9) | 9 (30.0) | 412 (61.6) | 304 (79.6) | 725 (67.1) |
| Study drug-related TESAE[a] | 41 (15.5) | 29 (10.8) | 2 (6.7) | 150 (22.4) | 183 (47.9) | 335 (31.0) |

AE = adverse event; AML = acute myeloid leukemia; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects in the category; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

[a] Causality assessments were based on investigator-reported causality.

Notes: Percentage is calculated using number of subjects in the column heading as denominator.

AEs were coded using MedDRA Version 24.0.

**Common TEAEs**

*Study AC220-A-U302*

The most frequently reported types of TEAEs by system organ class (SOC) in the pivotal study were gastrointestinal disorders, infections, general disorders, and blood disorders in both treatment arms (Table 21). Infections, blood disorders, metabolism disorders, and investigations occurred more frequently (higher incidence of ≥5 pp) with quizartinib than with placebo.

The most frequently reported preferred terms (PTs; >30% of subjects) in the quizartinib arm were febrile neutropenia, pyrexia, diarrhoea, hypokalaemia, and nausea, all of which occurred at similar frequencies to the placebo arm. Among the TEAEs reported in >10% of subjects, the events of neutropenia, ALT increased, ECG QT prolonged, neutrophil count decreased, and headache occurred more frequently (≥5 pp higher incidence) in the quizartinib arm than in the placebo.

*All AML Pool*

Generally, the pattern and incidence of TEAEs in the 30 to 60 mg group of the All AML Pool were consistent with those in the quizartinib arm of Study AC220-A-U302.

**Table 21. Most frequent (≥10% in the quizartinib arm of study AC220-A-U302 or in the all AML pool) all-grade TEAEs by SOC and PT (safety analysis set)**

| SOC<br>PT | Study AC220-A-U302 | | All AML Pool | | | |
|---|---|---|---|---|---|---|
| | Quizartinib<br>N = 265<br>n (%) | Placebo<br>N = 268<br>n (%) | Quizartinib<br><30 mg<br>N = 30<br>n (%) | Quizartinib<br>30 to 60 mg<br>N = 669<br>n (%) | Quizartinib<br>>60 mg<br>N = 382<br>n (%) | Total Quizartinib<br>N = 1081<br>n (%) |
| **Subjects with any TEAEs** | **264 (99.6)** | **265 (98.9)** | **29 (96.7)** | **664 (99.3)** | **380 (99.5)** | **1073 (99.3)** |
| **Gastrointestinal disorders** | **215 (81.1)** | **209 (78.0)** | **24 (80.0)** | **530 (79.2)** | **331 (86.6)** | **885 (81.9)** |
| Nausea | 90 (34.0) | 84 (31.3) | 13 (43.3) | 272 (40.7) | 199 (52.1) | 484 (44.8) |
| Diarrhoea | 98 (37.0) | 94 (35.1) | 11 (36.7) | 220 (32.9) | 152 (39.8) | 383 (35.4) |
| Vomiting | 65 (24.5) | 53 (19.8) | 8 (26.7) | 195 (29.1) | 148 (38.7) | 351 (32.5) |
| Constipation | 56 (21.1) | 69 (25.7) | 4 (13.3) | 131 (19.6) | 74 (19.4) | 209 (19.3) |
| Abdominal pain | 46 (17.4) | 38 (14.2) | 2 (6.7) | 104 (15.5) | 54 (14.1) | 160 (14.8) |
| Stomatitis | 57 (21.5) | 56 (20.9) | 7 (23.3) | 111 (16.6) | 23 (6.0) | 141 (13.0) |
| Dyspepsia | 30 (11.3) | 23 (8.6) | 1 (3.3) | 65 (9.7) | 62 (16.2) | 128 (11.8) |
| Abdominal pain upper | 29 (10.9) | 25 (9.3) | 3 (10.0) | 57 (8.5) | 35 (9.2) | 95 (8.8) |
| **General disorders and administration site conditions** | **177 (66.8)** | **173 (64.6)** | **19 (63.3)** | **473 (70.7)** | **303 (79.3)** | **795 (73.5)** |
| Pyrexia | 112 (42.3) | 109 (40.7) | 8 (26.7) | 258 (38.6) | 120 (31.4) | 386 (35.7) |
| Fatigue | 29 (10.9) | 23 (8.6) | 2 (6.7) | 136 (20.3) | 133 (34.8) | 271 (25.1) |
| Oedema peripheral | 30 (11.3) | 37 (13.8) | 6 (20.0) | 105 (15.7) | 104 (27.2) | 215 (19.9) |
| Asthenia | 16 (6.0) | 21 (7.8) | 2 (6.7) | 60 (9.0) | 71 (18.6) | 133 (12.3) |
| **Infections and infestations** | **204 (77.0)** | **188 (70.1)** | **15 (50.0)** | **473 (70.7)** | **271 (70.9)** | **759 (70.2)** |
| Pneumonia | 39 (14.7) | 41 (15.3) | 4 (13.3) | 101 (15.1) | 78 (20.4) | 183 (16.9) |
| **Blood and lymphatic system disorders** | **168 (63.4)** | **143 (53.4)** | **17 (56.7)** | **461 (68.9)** | **257 (67.3)** | **735 (68.0)** |
| Febrile neutropenia | 117 (44.2) | 113 (42.2) | 7 (23.3) | 260 (38.9) | 151 (39.5) | 418 (38.7) |

| SOC<br>PT | Study AC220-A-U302 | | All AML Pool | | | |
|---|---|---|---|---|---|---|
| | Quizartinib<br>N = 265<br>n (%) | Placebo<br>N = 268<br>n (%) | Quizartinib<br><30 mg<br>N = 30<br>n (%) | Quizartinib<br>30 to 60 mg<br>N = 669<br>n (%) | Quizartinib<br>>60 mg<br>N = 382<br>n (%) | Total Quizartinib<br>N = 1081<br>n (%) |
| Anaemia | 29 (10.9) | 19 (7.1) | 6 (20.0) | 165 (24.7) | 113 (29.6) | 284 (26.3) |
| Thrombocytopenia | 30 (11.3) | 30 (11.2) | 3 (10.0) | 125 (18.7) | 58 (15.2) | 186 (17.2) |
| Neutropenia | 54 (20.4) | 27 (10.1) | 2 (6.7) | 128 (19.1) | 43 (11.3) | 173 (16.0) |
| **Metabolism and nutrition disorders** | **165 (62.3)** | **153 (57.1)** | **17 (56.7)** | **401 (59.9)** | **206 (53.9)** | **624 (57.7)** |
| Hypokalaemia | 93 (35.1) | 96 (35.8) | 8 (26.7) | 205 (30.6) | 71 (18.6) | 284 (26.3) |
| Decreased appetite | 46 (17.4) | 36 (13.4) | 7 (23.3) | 122 (18.2) | 98 (25.7) | 227 (21.0) |
| Hypomagnesaemia | 30 (11.3) | 30 (11.2) | 1 (3.3) | 86 (12.9) | 40 (10.5) | 127 (11.7) |
| Hypocalcaemia | 26 (9.8) | 29 (10.8) | 1 (3.3) | 67 (10.0) | 41 (10.7) | 109 (10.1) |
| Hypophosphataemia | 27 (10.2) | 24 (9.0) | 4 (13.3) | 66 (9.9) | 12 (3.1) | 82 (7.6) |
| **Investigations** | **140 (52.8)** | **105 (39.2)** | **13 (43.3)** | **394 (58.9)** | **197 (51.6)** | **604 (55.9)** |
| ECG QT prolonged | 36 (13.6) | 11 (4.1) | 3 (10.0) | 133 (19.9) | 106 (27.7) | 242 (22.4) |
| ALT increased | 42 (15.8) | 27 (10.1) | 3 (10.0) | 92 (13.8) | 26 (6.8) | 121 (11.2) |
| AST increased | 28 (10.6) | 19 (7.1) | 1 (3.3) | 67 (10.0) | 19 (5.0) | 87 (8.0) |
| Neutrophil count decreased | 27 (10.2) | 12 (4.5) | 1 (3.3) | 70 (10.5) | 14 (3.7) | 85 (7.9) |
| **Skin and subcutaneous tissue disorders** | **152 (57.4)** | **158 (59.0)** | **16 (53.3)** | **366 (54.7)** | **205 (53.7)** | **587 (54.3)** |
| Rash | 69 (26.0) | 66 (24.6) | 4 (13.3) | 129 (19.3) | 51 (13.4) | 184 (17.0) |
| Petechiae | 9 (3.4) | 12 (4.5) | 4 (13.3) | 42 (6.3) | 73 (19.1) | 119 (11.0) |
| Pruritus | 35 (13.2) | 40 (14.9) | 1 (3.3) | 65 (9.7) | 19 (5.0) | 85 (7.9) |
| **Respiratory, thoracic and mediastinal disorders** | **123 (46.4)** | **115 (42.9)** | **14 (46.7)** | **347 (51.9)** | **214 (56.0)** | **575 (53.2)** |
| Cough | 50 (18.9) | 44 (16.4) | 5 (16.7) | 132 (19.7) | 70 (18.3) | 207 (19.1) |
| Epistaxis | 40 (15.1) | 29 (10.8) | 3 (10.0) | 86 (12.9) | 69 (18.1) | 158 (14.6) |
| Dyspnoea | 14 (5.3) | 21 (7.8) | 3 (10.0) | 92 (13.8) | 62 (16.2) | 157 (14.5) |
| Oropharyngeal pain | 27 (10.2) | 18 (6.7) | 3 (10.0) | 71 (10.6) | 20 (5.2) | 94 (8.7) |
| **Nervous system disorders** | **103 (38.9)** | **97 (36.2)** | **15 (50.0)** | **287 (42.9)** | **203 (53.1)** | **505 (46.7)** |
| Headache | 73 (27.5) | 53 (19.8) | 5 (16.7) | 157 (23.5) | 56 (14.7) | 218 (20.2) |
| Dysgeusia | 9 (3.4) | 5 (1.9) | 4 (13.3) | 40 (6.0) | 81 (21.2) | 125 (11.6) |
| Dizziness | 16 (6.0) | 19 (7.1) | 4 (13.3) | 66 (9.9) | 50 (13.1) | 120 (11.1) |
| **Musculoskeletal and connective tissue disorders** | **91 (34.3)** | **108 (40.3)** | **10 (33.3)** | **277 (41.4)** | **168 (44.0)** | **455 (42.1)** |
| Arthralgia | 29 (10.9) | 35 (13.1) | 5 (16.7) | 88 (13.2) | 28 (7.3) | 121 (11.2) |
| **Vascular disorders** | **71 (26.8)** | **70 (26.1)** | **7 (23.3)** | **188 (28.1)** | **112 (29.3)** | **307 (28.4)** |
| Hypotension | 23 (8.7) | 17 (6.3) | 4 (13.3) | 78 (11.7) | 41 (10.7) | 123 (11.4) |
| Hypertension | 29 (10.9) | 33 (12.3) | 1 (3.3) | 48 (7.2) | 13 (3.4) | 62 (5.7) |

| SOC PT | Study AC220-A-U302 | | All AML Pool | | | |
|---|---|---|---|---|---|---|
| | Quizartinib N = 265 n (%) | Placebo N = 268 n (%) | Quizartinib <30 mg N = 30 n (%) | Quizartinib 30 to 60 mg N = 669 n (%) | Quizartinib >60 mg N = 382 n (%) | Total Quizartinib N = 1081 n (%) |
| **Psychiatric disorders** | **57 (21.5)** | **50 (18.7)** | **7 (23.3)** | **145 (21.7)** | **91 (23.8)** | **243 (22.5)** |
| Insomnia | 37 (14.0) | 30 (11.2) | 1 (3.3) | 72 (10.8) | 31 (8.1) | 104 (9.6) |

AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; ECG = electrocardiogram; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects in the category; QT = interval between the start of the Q wave and the end of the T wave; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event
Notes: Percentage is calculated using number of subjects in the column heading as denominator.
PTs are presented in descending order of incidence by SOC and PT in the total quizartinib column.
AEs were coded using MedDRA Version 24.0.

**TEAE with toxicity Grade 3 or 4**

*Study AC220-A-U302*

In the pivotal trial, the proportions of subjects with Grade 3/4 events were similar between the treatment arms (~80%; Table 22). The most frequently reported Grade 3/4 TEAEs (≥10% incidence) in the quizartinib arm included cytopenias (febrile neutropenia and neutropenia), hypokalaemia, and infections (pneumoniae), of which the event of neutropenia occurred at a ≥5 pp higher incidence in the quizartinib arm than in the placebo arm (18.1% vs. 8.6%). Among less frequently reported Grade 3/4 TEAEs, neutrophil count decreased also occurred at a ≥5 pp higher incidence in the quizartinib arm than in the placebo arm (8.7% vs. 3.4%).

*All AML Pool*

Generally, the pattern and incidence of Grade 3/4 TEAEs in the 30 to 60 mg group of the All AML Pool were consistent with those in the quizartinib arm of Study AC220-A-U302. Blood cytopenias were the most frequently reported Grade 3/4 events in the All AML Pool with no consistent trend according to dose. Infections (pneumoniae and sepsis) were the second most frequently reported types of severe TEAE; no dose-dependent trend was noted for these TEAEs.

The incidence of Grade 3/4 TEAEs of ECG QT prolonged was highest in the >60 mg group of the All AML Pool.

**Table 22. Most frequent (≥3% in the quizartinib arm of study AC220-A-U302 or the all AML pool) grade 3/4 TEAEs by PT (safety analysis set)**

| 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 Grade 3/4 TEAEs** | **214 (80.8)** | **214 (79.9)** | **17 (56.7)** | **495 (74.0)** | **198 (51.8)** | **710 (65.7)** |
| Febrile neutropenia | 115 (43.4) | 110 (41.0) | 6 (20.0) | 249 (37.2) | 148 (38.7) | 403 (37.3) |
| Anaemia | 15 (5.7) | 14 (5.2) | 5 (16.7) | 128 (19.1) | 101 (26.4) | 234 (21.6) |
| Thrombocytopenia | 21 (7.9) | 26 (9.7) | 3 (10.0) | 108 (16.1) | 55 (14.4) | 166 (15.4) |
| Neutropenia | 48 (18.1) | 23 (8.6) | 2 (6.7) | 118 (17.6) | 40 (10.5) | 160 (14.8) |
| Pneumonia | 30 (11.3) | 30 (11.2) | 2 (6.7) | 65 (9.7) | 56 (14.7) | 123 (11.4) |
| Hypokalaemia | 50 (18.9) | 44 (16.4) | 4 (13.3) | 84 (12.6) | 23 (6.0) | 111 (10.3) |
| Platelet count decreased | 14 (5.3) | 7 (2.6) | 2 (6.7) | 61 (9.1) | 27 (7.1) | 90 (8.3) |
| Neutrophil count decreased | 23 (8.7) | 9 (3.4) | 1 (3.3) | 63 (9.4) | 14 (3.7) | 78 (7.2) |
| ECG QT prolonged | 8 (3.0) | 3 (1.1) | 0 | 21 (3.1) | 40 (10.5) | 61 (5.6) |
| Leukopenia | 6 (2.3) | 4 (1.5) | 1 (3.3) | 29 (4.3) | 30 (7.9) | 60 (5.6) |
| WBC count decreased | 5 (1.9) | 7 (2.6) | 3 (10.0) | 46 (6.9) | 11 (2.9) | 60 (5.6) |
| Sepsis | 11 (4.2) | 24 (9.0) | 0 | 34 (5.1) | 18 (4.7) | 52 (4.8) |
| Hypophosphataemia | 18 (6.8) | 16 (6.0) | 3 (10.0) | 34 (5.1) | 7 (1.8) | 44 (4.1) |
| Fatigue | 1 (0.4) | 0 | 1 (3.3) | 18 (2.7) | 24 (6.3) | 43 (4.0) |
| ALT increased | 12 (4.5) | 13 (4.9) | 1 (3.3) | 28 (4.2) | 12 (3.1) | 41 (3.8) |
| Pyrexia | 12 (4.5) | 13 (4.9) | 0 | 26 (3.9) | 14 (3.7) | 40 (3.7) |
| Decreased appetite | 13 (4.9) | 5 (1.9) | 2 (6.7) | 25 (3.7) | 11 (2.9) | 38 (3.5) |
| Asthenia | 2 (0.8) | 2 (0.7) | 1 (3.3) | 11 (1.6) | 24 (6.3) | 36 (3.3) |
| Hypotension | 8 (3.0) | 5 (1.9) | 2 (6.7) | 22 (3.3) | 12 (3.1) | 36 (3.3) |
| Diarrhoea | 10 (3.8) | 10 (3.7) | 1 (3.3) | 19 (2.8) | 14 (3.7) | 34 (3.1) |
| Bacteraemia | 10 (3.8) | 6 (2.2) | 0 | 21 (3.1) | 10 (2.6) | 31 (2.9) |
| Blood bilirubin increased | 10 (3.8) | 6 (2.2) | 0 | 20 (3.0) | 7 (1.8) | 27 (2.5) |
| Hypertension | 13 (4.9) | 18 (6.7) | 1 (3.3) | 17 (2.5) | 5 (1.3) | 23 (2.1) |
| Stomatitis | 12 (4.5) | 8 (3.0) | 0 | 17 (2.5) | 5 (1.3) | 22 (2.0) |
| GGT increased | 14 (5.3) | 13 (4.9) | 2 (6.7) | 19 (2.8) | 0 | 21 (1.9) |
| Rash | 8 (3.0) | 3 (1.1) | 0 | 11 (1.6) | 1 (0.3) | 12 (1.1) |

AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; ECG = electrocardiogram; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects in the category; PT = preferred term; QT = interval between the start of the Q wave and the end of the T wave; TEAE = treatment-emergent adverse event; WBC = white blood cell
Notes: percentage is calculated using number of subjects in the column heading as denominator.
PTs are presented in descending order of incidence in the total quizartinib column.
AEs were coded using MedDRA Version 24.0.

**Treatment-related TEAEs**

*Study AC220-A-U302*

A higher proportion of patients in the quizartinib arm experienced TEAEs that were assessed as related to study drug by the investigator compared with the placebo arm (60.4% vs. 36.2%; Table **23**23). The most frequent (≥5%) reported related TEAEs in the quizartinib arm included cytopenias (neutropenia, thrombocytopenia, neutrophil count decreased, febrile neutropenia, and anaemia), ECG QT prolonged, gastrointestinal disorders (nausea and diarrhea), ALT increased, and pyrexia. Neutropenia, neutrophil count decreased, and ECG QT prolonged occurred at a frequency ≥5 pp higher with quizartinib than with placebo.

Related Grade 3/4 TEAEs were reported in 43% vs. 22.8%, of which cytopenias were most frequently reported and neutropenia the only event with a frequency ≥5 pp higher with quizartinib than with placebo (15.5% vs. 3.7%).

*All AML Pool*

The proportion of patients with related TEAEs increased with higher dose levels (63.3% at <30 mg to 86.9% with >60 mg dose). The types of study drug-related TEAEs reported in the 30 to 60 mg group of the All AML Pool were consistent with the quizartinib arm of Study AC220-A-U302. PTs showing highest increases (>10%) with dose were ECG QT prolonged, anaemia, vomiting, febrile neutropenia, diarrhoea, fatigue and decreased appetite.

**Table 23. most frequent (≥5% in the quizartinib arm of study AC220-A-U302 or in the all AML pool) all-grade study drug-related TEAES by PT (safety analysis set).**

| 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 study drug-related TEAE** | **160 (60.4)** | **97 (36.2)** | **19 (63.3)** | **501 (74.9)** | **332 (86.9)** | **852 (78.8)** |
| Nausea | 24 (9.1) | 12 (4.5) | 7 (23.3) | 141 (21.1) | 136 (35.6) | 284 (26.3) |
| ECG QT prolonged | 31 (11.7) | 8 (3.0) | 3 (10.0) | 122 (18.2) | 104 (27.2) | 229 (21.2) |
| Anaemia | 15 (5.7) | 9 (3.4) | 1 (3.3) | 106 (15.8) | 85 (22.3) | 192 (17.8) |
| Vomiting | 7 (2.6) | 6 (2.2) | 2 (6.7) | 70 (10.5) | 93 (24.3) | 165 (15.3) |
| Febrile neutropenia | 23 (8.7) | 20 (7.5) | 3 (10.0) | 84 (12.6) | 77 (20.2) | 164 (15.2) |
| Diarrhoea | 18 (6.8) | 19 (7.1) | 3 (10.0) | 70 (10.5) | 81 (21.2) | 154 (14.2) |
| Fatigue | 4 (1.5) | 5 (1.9) | 0 | 59 (8.8) | 91 (23.8) | 150 (13.9) |
| Neutropenia | 46 (17.4) | 10 (3.7) | 1 (3.3) | 96 (14.3) | 32 (8.4) | 129 (11.9) |
| Thrombocytopenia | 18 (6.8) | 13 (4.9) | 1 (3.3) | 86 (12.9) | 42 (11.0) | 129 (11.9) |
| Decreased appetite | 5 (1.9) | 9 (3.4) | 1 (3.3) | 42 (6.3) | 66 (17.3) | 109 (10.1) |
| Dysgeusia | 3 (1.1) | 2 (0.7) | 3 (10.0) | 23 (3.4) | 71 (18.6) | 97 (9.0) |
| Pyrexia | 14 (5.3) | 10 (3.7) | 0 | 45 (6.7) | 40 (10.5) | 85 (7.9) |
| Platelet count decreased | 10 (3.8) | 6 (2.2) | 1 (3.3) | 58 (8.7) | 23 (6.0) | 82 (7.6) |
| Hypokalaemia | 10 (3.8) | 8 (3.0) | 2 (6.7) | 38 (5.7) | 34 (8.9) | 74 (6.8) |
| ALT increased | 15 (5.7) | 7 (2.6) | 2 (6.7) | 51 (7.6) | 19 (5.0) | 72 (6.7) |
| Neutrophil count decreased | 21 (7.9) | 5 (1.9) | 0 | 59 (8.8) | 9 (2.4) | 68 (6.3) |
| Oedema peripheral | 2 (0.8) | 3 (1.1) | 3 (10.0) | 20 (3.0) | 45 (11.8) | 68 (6.3) |
| Dyspepsia | 6 (2.3) | 3 (1.1) | 0 | 21 (3.1) | 43 (11.3) | 64 (5.9) |
| WBC count decreased | 6 (2.3) | 5 (1.9) | 3 (10.0) | 48 (7.2) | 10 (2.6) | 61 (5.6) |
| Headache | 3 (1.1) | 3 (1.1) | 2 (6.7) | 33 (4.9) | 21 (5.5) | 56 (5.2) |
| Abdominal pain | 6 (2.3) | 6 (2.2) | 0 | 28 (4.2) | 26 (6.8) | 54 (5.0) |
| Constipation | 5 (1.9) | 3 (1.1) | 1 (3.3) | 22 (3.3) | 31 (8.1) | 54 (5.0) |

AE = adverse event; ALT = alanine aminotransferase AML = acute myeloid leukemia; ECG = electrocardiogram; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects in the category; QT = interval between the start of the Q wave and the end of the T wave; PT = preferred term; TEAE = treatment-emergent- adverse event; WBC = white blood cell
Notes: Percentage is calculated using number of subjects in the column heading as denominator.
PTs are presented in descending order of incidence in the total quizartinib column.
AEs were coded using MedDRA Version 24.0.

### *2.6.8.3. Serious adverse event, deaths and other significant events*

**SAEs**

An overview of TESAEs is shown in Table 24.

*Study AC220-A-U302*

Overall, 54.0% of patients in the quizartinib arm and 45.9% of patients in the placebo arm had at least 1 TESAE. In both treatment arms, the most frequently reported types of TESAEs were infections (pneumoniae, septic shock and sepsis) and blood disorders (febrile neutropenia).

Related SAEs were reported for 15.5% of patients in the quizartinib arm and 10.8% in the placebo arm. The most frequently reported (≥1% incidence) study drug-related TESAEs in the quizartinib arm were febrile neutropenia (2.6% with quizartinib vs. 1.5% with placebo), pneumoniae (1.5% vs. 0.7%), neutropenia (1.1% vs. 0%), and myelosuppression (1.1% vs. 0%).

*All AML Pool*

The proportion of patients who experienced a SAE increased with increasing dose levels (30% at <30 mg dose to 79.6% with >60 mg dose). Largest increases (>10%) were observed for febrile neutropenia and AML/disease progression.

In the 30 to 60 mg group of the All AML Pool, 61.6% of patients had at least 1 TESAE. Generally, the types of TESAEs reported in the 30 to 60 mg group of the All AML Pool were consistent with those reported in Study AC220-A-U302.

Related SAEs were reported for 22.4% of patients in the 30-60 mg group. As with the overall TESAEs, the incidence of study drug-related TESAEs was highest in the >60 mg group of the All AML Pool (47.9%), which was primarily driven by higher rates of febrile neutropenia, pneumonia, and ECG QT prolonged.

**Table 24. Summary of Treatment-emergent SAEs (≥1% of subjects in the quizartinib arm of study AC220-A-U302 or in the all AML pool) by PT (safety analysis set)**

| 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 TESAE** | **143 (54.0)** | **123 (45.9)** | **9 (30.0)** | **412 (61.6)** | **304 (79.6)** | **725 (67.1)** |
| Febrile neutropenia | 29 (10.9) | 22 (8.2) | 0 | 106 (15.8) | 131 (34.3) | 237 (21.9) |
| Pneumonia | 17 (6.4) | 15 (5.6) | 2 (6.7) | 62 (9.3) | 52 (13.6) | 116 (10.7) |
| Acute myeloid leukaemia[a] | 0 | 0 | 0 | 11 (1.6) | 72 (18.8) | 83 (7.7) |
| Sepsis | 10 (3.8) | 14 (5.2) | 0 | 32 (4.8) | 26 (6.8) | 58 (5.4) |
| Pyrexia | 8 (3.0) | 5 (1.9) | 0 | 26 (3.9) | 20 (5.2) | 46 (4.3) |
| ECG QT prolonged | 1 (0.4) | 1 (0.4) | 0 | 8 (1.2) | 36 (9.4) | 44 (4.1) |
| Disease progression[a] | 0 | 0 | 3 (10.0) | 11 (1.6) | 17 (4.5) | 31 (2.9) |
| Anaemia | 2 (0.8) | 2 (0.7) | 0 | 11 (1.6) | 14 (3.7) | 25 (2.3) |
| Septic shock | 11 (4.2) | 8 (3.0) | 0 | 19 (2.8) | 6 (1.6) | 25 (2.3) |
| Urinary tract infection | 3 (1.1) | 2 (0.7) | 0 | 11 (1.6) | 12 (3.1) | 23 (2.1) |
| Bacteraemia | 2 (0.8) | 1 (0.4) | 0 | 10 (1.5) | 10 (2.6) | 20 (1.9) |
| Cellulitis | 2 (0.8) | 0 | 0 | 12 (1.8) | 8 (2.1) | 20 (1.9) |
| Vomiting | 2 (0.8) | 2 (0.7) | 1 (3.3) | 12 (1.8) | 7 (1.8) | 20 (1.9) |
| Thrombocytopenia | 2 (0.8) | 8 (3.0) | 0 | 7 (1.0) | 12 (3.1) | 19 (1.8) |
| Acute kidney injury | 4 (1.5) | 2 (0.7) | 1 (3.3) | 13 (1.9) | 4 (1.0) | 18 (1.7) |
| Atrial fibrillation | 1 (0.4) | 3 (1.1) | 1 (3.3) | 5 (0.7) | 11 (2.9) | 17 (1.6) |
| Nausea | 0 | 0 | 1 (3.3) | 10 (1.5) | 6 (1.6) | 17 (1.6) |
| Pneumonia fungal | 4 (1.5) | 1 (0.4) | 0 | 9 (1.3) | 8 (2.1) | 17 (1.6) |
| Gastrointestinal haemorrhage | 1 (0.4) | 0 | 0 | 4 (0.6) | 12 (3.1) | 16 (1.5) |
| Neutropenia | 4 (1.5) | 5 (1.9) | 0 | 10 (1.5) | 4 (1.0) | 14 (1.3) |
| Haemorrhage intracranial | 0 | 2 (0.7) | 0 | 7 (1.0) | 5 (1.3) | 12 (1.1) |
| Diarrhoea | 1 (0.4) | 0 | 0 | 5 (0.7) | 6 (1.6) | 11 (1.0) |
| Neutropenic sepsis | 0 | 0 | 0 | 8 (1.2) | 3 (0.8) | 11 (1.0) |
| Respiratory failure | 3 (1.1) | 3 (1.1) | 1 (3.3) | 6 (0.9) | 4 (1.0) | 11 (1.0) |
| Klebsiella sepsis | 7 (2.6) | 1 (0.4) | 0 | 9 (1.3) | 0 | 9 (0.8) |
| Graft-versus-host disease in gastrointestinal tract | 4 (1.5) | 0 | 0 | 8 (1.2) | 0 | 8 (0.7) |
| Colitis | 3 (1.1) | 3 (1.1) | 0 | 6 (0.9) | 1 (0.3) | 7 (0.6) |
| Herpes zoster | 5 (1.9) | 1 (0.4) | 0 | 6 (0.9) | 1 (0.3) | 7 (0.6) |
| Neutrophil count decreased | 4 (1.5) | 0 | 0 | 6 (0.9) | 0 | 6 (0.6) |
| Anal fistula | 4 (1.5) | 0 | 0 | 4 (0.6) | 0 | 4 (0.4) |
| COVID-19 | 3 (1.1) | 0 | 0 | 3 (0.4) | 0 | 3 (0.3) |
| Myelosuppression | 3 (1.1) | 0 | 0 | 3 (0.4) | 0 | 3 (0.3) |

AE = adverse event; AML = acute myeloid leukemia; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects in the category; NA = not applicable; QT = interval between the start of the Q wave and the end of the T wave; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

[a] In Study 2689-CL-2004 and AC220-002, death due to disease progression or worsening of AML was recorded as a TEAE.

Notes: Percentage is calculated using number of subjects in the column heading as denominator.

AEs were coded using MedDRA Version 24.0.

## Deaths

On-treatment deaths were defined as death that occurred between the first dose date and ≤30 days after the last dose of study drug. In Study AC220-A-U302, all on-treatment deaths were required to be reported as AEs on the death form of the electronic case report form. However, in Studies AC220-002 and 2689-CL-2004 included in the all AML pool, AML progression could have been selected as the cause of death for on-treatment deaths. An overview of on-treatment death and Treatment-emergent Adverse Events Associated with Death are shown in Table 25 and table 26 respectively.

*Study AC220-A-U302*

For most patients, the primary cause of death was an AE, the majority of which were not considered related to study drug by the investigator. In both treatment arms, the most frequently reported types of TEAEs with an outcome of death were infections (septic shock and sepsis). These events were more common in the quizartinib arm than the placebo arm.

**Table 25. Summary of on-treatment deaths by primary causes of death (safety analysis set)**

| Primary Cause of Death | 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 = 582 n (%) | Quizartinib >60 mg N = 382 n (%) | Total Quizartinib N = 994 n (%) |
| **All on-treatment deaths** | 32 (12.1) | 25 (9.3) | 6 (20.0) | 136 (23.4) | 148 (38.7) | 290 (29.2) |
| AML disease progression | 0 | 2 (0.7) | 4 (13.3) | 67 (11.5) | 89 (23.3) | 160 (16.1) |
| Adverse event | 30 (11.3) | 23 (8.6) | 2 (6.7) | 65 (11.2) | 57 (14.9) | 124 (12.5) |
| Other/unknown[a] | 2 (0.8) | 0 | 0 | 4 (0.7) | 2 (0.5) | 6 (0.6) |

AML = acute myeloid leukemia; N = total number of subjects; n = number of subjects in the category
[a]The primary cause of death in Studies 2689-CL-0011 and 2689-CL-2004 was not collected; all deaths for these studies are summarized in the other/unknown category.
Note: On-treatment death is defined as death that occurred between the first dose date and ≤30 days after the last dose of study drug.

**Table 26. Treatment-emergent adverse events associated with death as an outcome in ≥3 subjects in the quizartinib arm of study AC220-A-U302 or in the all AML pool (safety analysis set)**

| SOC<br>PT | Study AC220-A-U302 | | All AML Pool | | | |
|---|---|---|---|---|---|---|
| | Quizartinib<br>N = 265<br>n (%) | Placebo<br>N = 268<br>n (%) | Quizartinib<br><30 mg<br>N = 30<br>n (%) | Quizartinib<br>30 to 60 mg<br>N = 669<br>n (%) | Quizartinib<br>>60 mg<br>N = 382<br>n (%) | Total Quizartinib<br>N = 1081<br>n (%) |
| **Subjects with any TEAEs associated with death as an outcome** | **30 (11.3)** | **26 (9.7)** | **5 (16.7)** | **104 (15.5)** | **148 (38.7)** | **257 (23.8)** |
| **Infections and infestations** | **20 (7.5)** | **12 (4.5)** | **1 (3.3)** | **44 (6.6)** | **34 (8.9)** | **79 (7.3)** |
| Pneumonia | 1 (0.4) | 4 (1.5) | 0 | 13 (1.9) | 9 (2.4) | 22 (2.0) |
| Sepsis | 4 (1.5) | 2 (0.7) | 0 | 7 (1.0) | 9 (2.4) | 16 (1.5) |
| Septic shock | 8 (3.0) | 3 (1.1) | 0 | 11 (1.6) | 3 (0.8) | 14 (1.3) |
| Klebsiella sepsis | 3 (1.1) | 0 | 0 | 3 (0.4) | 0 | 3 (0.3) |
| Pneumonia fungal | 0 | 0 | 0 | 0 | 3 (0.8) | 3 (0.3) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **0** | **0** | **0** | **12 (1.8)** | **67 (17.5)** | **79 (7.3)** |
| Acute myeloid leukaemia[a] | 0 | 0 | 0 | 10 (1.5) | 67 (17.5) | 77 (7.1) |
| **General disorders and administration site conditions** | **1 (0.4)** | **5 (1.9)** | **3 (10.0)** | **14 (2.1)** | **23 (6.0)** | **40 (3.7)** |
| Disease progression[a] | 0 | 0 | 3 (10.0) | 10 (1.5) | 16 (4.2) | 29 (2.7) |
| Multiple organ dysfunction syndrome | 0 | 1 (0.4) | 0 | 2 (0.3) | 2 (0.5) | 4 (0.4) |
| **Nervous system disorders** | **3 (1.1)** | **4 (1.5)** | **0** | **10 (1.5)** | **11 (2.9)** | **21 (1.9)** |
| Haemorrhage intracranial | 0 | 1 (0.4) | 0 | 5 (0.7) | 4 (1.0) | 9 (0.8) |
| Cerebral haemorrhage | 0 | 0 | 0 | 2 (0.3) | 2 (0.5) | 4 (0.4) |
| **Cardiac disorders** | **2 (0.8)** | **0** | **1 (3.3)** | **6 (0.9)** | **5 (1.3)** | **12 (1.1)** |
| Cardiac arrest | 1 (0.4) | 0 | 0 | 2 (0.3) | 2 (0.5) | 4 (0.4) |
| Cardiac failure | 0 | 0 | 0 | 1 (0.1) | 2 (0.5) | 3 (0.3) |
| **Respiratory, thoracic and mediastinal disorders** | **2 (0.8)** | **4 (1.5)** | **0** | **9 (1.3)** | **4 (1.0)** | **13 (1.2)** |
| Respiratory failure | 0 | 2 (0.7) | 0 | 2 (0.3) | 2 (0.5) | 4 (0.4) |
| **Blood and lymphatic system disorders** | **1 (0.4)** | **0** | **0** | **7 (1.0)** | **4 (1.0)** | **11 (1.0)** |
| Disseminated intravascular coagulation | 0 | 0 | 0 | 2 (0.3) | 1 (0.3) | 3 (0.3) |
| **Renal and urinary disorders** | **0** | **0** | **0** | **2 (0.3)** | **1 (0.3)** | **3 (0.3)** |
| Acute kidney injury | 0 | 0 | 0 | 2 (0.3) | 1 (0.3) | 3 (0.3) |
| **Immune system disorders** | **1 (0.4)** | **0** | **0** | **3 (0.4)** | **0** | **3 (0.3)** |
| GVHD in gastrointestinal tract | 1 (0.4) | 0 | 0 | 3 (0.4) | 0 | 3 (0.3) |

AE = adverse event; AML = acute myeloid leukemia; GVHD = graft-versus-host disease; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects in the category; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event

[a] In Studies 2689-CL-2004 and AC220-002, death due to disease progression or worsening of AML was recorded as a TEAE.

Notes: Percentage is calculated using number of subjects in the column heading as denominator.

AEs are presented in descending order of incidence by SOC and PT in the total quizartinib column.

AEs were coded using MedDRA Version 24.0.

More early deaths (ie, deaths within 60 days of initiation of study drug) occurred with quizartinib compared with placebo. In total, 17 (6.4%) vs. 11 (4.1%) patients, respectively died due to an TEAE within 60 days of study drug initiation, of which 14 (5.3%) vs. 8 (3.0%) patients, respectively, died within 30 days of study drug initiation (Table 27). Two additional patients in the quizartinib arm died after Randomisation but before receiving study drug. Infections (i.e. sepsis or septic shock) were the most common cause of early death in both treatment groups. Patients in the quizartinib group who died within 60 days of the first dose of study drug were older than those who did not (ie, 55.0% vs. 23.7% of subjects were ≥65 years old). In addition, patients who died early in the quizartinib group had worse ECOG PS than those who did not (ie, 35.0% vs. 15.5% of subjects had ECOG PS of 2). Similar trends for older age and worse ECOG PS were observed for patients who died early vs. those who did not in the placebo group.

**Table 27. Summary of early deaths (safety analysis set, study AC220-A-U302)**

| Deaths | Quizartinib (N = 265) n (%) | Placebo (N = 268) n (%) |
|---|---|---|
| **Deaths within 30 days of study drug initiation** | **15 (5.7)** | **9 (3.4)** |
| **Primary reason of death within 30 days of study drug initiation** | | |
| AML disease progression | 0 | 1 (0.4) |
| Adverse event | 14 (5.3) | 8 (3.0) |
| Other | 1 (0.4) | 0 |
| **Deaths within 60 days of study drug initiation** | **20 (7.5)** | **13 (4.9)** |
| **Primary reason of death within 60 days of study drug initiation** | | |
| AML disease progression | 2 (0.8) | 2 (0.7) |
| Adverse event | 17 (6.4) | 11 (4.1) |
| Other | 1 (0.4) | 0 |

AML = acute myeloid leukemia
Data cutoff date: 13 Aug 2021.

*All AML Pool*

In the 30-60 mg group, 23.4% of patients died while on treatment and TEAEs associated with death occurred in 11.2% of patients. The incidence of on-treatment death was highest in the >60 mg group of the All AML Pool, predominantly due to a higher proportion of AML disease progression (due to differences in reporting between the early studies and Study AC220-A-U302).

**TEAEs by treatment duration**

*Study AC220-A-U302*

The incidences of study drug-related TEAEs, Grade 3/4 TEAEs, TESAEs, and TEAEs associated with study drug interruption increased with longer treatment durations.

The incidences of TEAEs associated with study drug discontinuation and death as outcome decreased with longer treatment duration.

Of the TEAEs reported in ≥20% of subjects in the quizartinib arm, febrile neutropenia, neutropenia, neutrophil count decreased, insomnia, oedema peripheral, thrombocytopenia, fatigue, upper respiratory tract infection, muscle spasms, cough, and rash occurred more frequently with longer treatment duration. Similar results were observed in the placebo arm. Apart from blood cytopenias, the rest of the events were generally acute, intermittent events.

**TEAEs by phase (induction, consolidation, continuation)**

Induction and Consolidation Phase

During the Induction and Consolidation Phases, frequencies of (related) grade ≥3 TEAEs and (related) SAEs and (related) TEAEs associated with study drug discontinuation were in general lower compared to the overall study period and the continuation phase in the quizartinib and placebo arm (Table 28). For most categories, differences between quizartinib and placebo treatment arms became smaller than those of the overall study period. The type of the most frequently reported TEAEs in both treatment arms were similar to the overall study period.

However, the proportion of patients with a TEAEs associated with death were numerically higher in the quizartinib arm than in the placebo arm during the Induction and Consolidation Phases (19 [7.2%] subjects versus 13 [4.9%] and 8 [4.6%] subjects versus 5 [2.9%], respectively), whereas the opposite was observed for the continuation phase (2.6% vs. 7.6% in the quizartinib and placebo arms). During both the induction and consolidation phases, similar to the overall study period, infections were the most frequent TEAEs associated with death as outcome.

**Table 28. Overview of All TEAEs, Overall Study Period and by Phase (Safety Analysis Set)**

| | Overall | | Induction Phase | | Consolidation Phase | | Continuation Phase | |
|---|---|---|---|---|---|---|---|---|
| Category | Quizartinib (N = 265) n (%) | Placebo (N = 268) n (%) | Quizartinib (N = 265) n (%) | Placebo (N = 268) n (%) | Quizartinib (N = 173) n (%) | Placebo (N = 175) n (%) | Quizartinib (N = 116) n (%) | Placebo (N = 92) n (%) |
| Any TEAE | 264 (99.6) | 265 (98.9) | 260 (98.1) | 261 (97.4) | 160 (92.5) | 160 (91.4) | 109 (94.0) | 84 (91.3) |
| Grade ≥3 (including Grade 5) | 244 (92.1) | 240 (89.6) | 187 (70.6) | 200 (74.6) | 120 (69.4) | 121 (69.1) | 91 (78.4) | 53 (57.6) |
| Associated with death as outcome | 30 (11.3) | 26 (9.7) | 19 (7.2) | 13 (4.9) | 8 (4.6) | 5 (2.9) | 3 (2.6) | 7 (7.6) |
| Associated with study drug discontinuation | 54 (20.4) | 23 (8.6) | 26 (9.8) | 11 (4.1) | 10 (5.8) | 5 (2.9) | 18 (15.5) | 7 (7.6) |
| Associated with study drug dose interruption | 90 (34.0) | 54 (20.1) | 24 (9.1) | 30 (11.2) | 14 (8.1) | 13 (7.4) | 65 (56.0) | 22 (23.9) |
| Associated with study drug dose reduction | 50 (18.9) | 17 (6.3) | 7 (2.6) | 3 (1.1) | 4 (2.3) | 0 | 42 (36.2) | 14 (15.2) |
| TESAEs | 143 (54.0) | 123 (45.9) | 75 (28.3) | 66 (24.6) | 59 (34.1) | 54 (30.9) | 39 (33.6) | 34 (37.0) |
| Any study drug-related TEAE[a] | 160 (60.4) | 97 (36.2) | 102 (38.5) | 77 (28.7) | 50 (28.9) | 48 (27.4) | 85 (73.3) | 34 (37.0) |
| Grade ≥3 (including Grade 5)[a] | 118 (44.5) | 65 (24.3) | 56 (21.1) | 43 (16.0) | 34 (19.7) | 26 (14.9) | 62 (53.4) | 16 (17.4) |
| Associated with death as outcome[a] | 4 (1.5) | 4 (1.5) | 2 (0.8) | 1 (0.4) | 2 (1.2) | 2 (1.1) | 0 | 0 |
| Associated with study drug discontinuation[a] | 23 (8.7) | 7 (2.6) | 7 (2.6) | 2 (0.7) | 4 (2.3) | 2 (1.1) | 12 (10.3) | 3 (3.3) |
| Associated with study drug dose interruption[a] | 57 (21.5) | 25 (9.3) | 8 (3.0) | 14 (5.2) | 6 (3.5) | 5 (2.9) | 46 (39.7) | 11 (12.0) |
| Associated with study drug dose reduction[a] | 35 (13.2) | 9 (3.4) | 3 (1.1) | 1 (0.4) | 2 (1.2) | 0 | 32 (27.6) | 8 (8.7) |
| TESAEs[a] | 41 (15.5) | 29 (10.8) | 21 (7.9) | 14 (5.2) | 16 (9.2) | 11 (6.3) | 8 (6.9) | 5 (5.4) |

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

[a] Causality assessments were based on investigator-reported causality.

Note: If a subject had reported one or more AEs, the subject was counted only once per subject level.

AEs were coded using the MedDRA Version 24.0.

Data cutoff date: 13 Aug 2021.

Continuation Phase

In total, 116 (43.8%) subjects in the quizartinib arm and 92 (34.3%) subjects in the placebo arm entered the Continuation Phase. Frequencies of almost all TEAE categories increased compared to the

induction and consolidation phase. Highest increases were observed for drug-related TEAE and (related) TEAEs associated with study drug interruption or reduction:

- Related Grade ≥3 TEAEs were reported more frequently in the continuation phase (53.4% in continuation phase vs. 21.1% and 19.7%, in respectively induction and consolidation phase). This substantial increase was not observed in the placebo arm. Among the most commonly reported study drug-related TEAEs during the Continuation Phase, the events of neutropenia, thrombocytopenia, ECG QT prolonged, neutrophil count decreased, anemia, nausea, and leukopenia occurred more frequently (≥5 pp higher incidence) in the quizartinib arm than in the placebo arm. The most commonly reported study drug-related Grade 3/4 TEAEs during the Continuation Phase (≥3% of subjects in either arm) were cytopenias which occurred at a higher incidence in the quizartinib arm than in the placebo arm (neutropenia [28.4% vs. 3% with placebo], neutrophil count decreased [8.6% vs. 0%], and thrombocytopenia [6.9% vs. 2.2%]).
- TEAEs and related TEAEs associated with study drug dose discontinuation, and in particular interruption and reduction were more frequently reported in the continuation phase compared to the induction and consolidation phase. Cytopenias (thrombocytopenia, neutropenia, anemia, and cytopenia) and gastrointestinal disorders (nausea, diarrhea, and vomiting) were the most frequent events associated with study drug discontinuation during this phase and were reported by subjects only in the quizartinib arm. Cytopenias (neutropenia, neutrophil count decreased, thrombocytopenia, and platelet count decreased), infections (COVID-19 and pneumonia), and ECG QT prolonged were the most frequent events associated with study drug interruption during this phase and were primarily reported in subjects in the quizartinib arm. Dose reductions were most frequently associated with cytopenias and ECG QT prolonged.

Contrary to the induction and consolidation phase, the proportion of patients with TEAEs with death as outcome were lower in the quizartinib arm than in the placebo arm during the Continuation Phase (2.6% with quizartinib vs. 7.6% with placebo).

There did not appear to be any evidence of increasing toxicity with long-term treatment with quizartinib for up to 36 cycles in the Continuation Phase. For certain events, the incidence appeared higher (≥5 pp higher incidence) in the quizartinib arm with continued treatment (neutropenia and diarrhoea), although due to the low number of subjects with treatment for >12 cycles and the fact this category includes all cycles from Cycles 12 to 36, no consistent trend could be identified.

AlloSCT

During the study, a total of 102 (38.1%) patients in the quizartinib arm and 91 (33.6%) patients in the placebo arm underwent protocol-specified allo-HSCT, mostly during the consolidation phase. Of these, 57 (55.9%) and 41 (45.1%) subjects, respectively, had posttransplant-related complications, with a higher proportion of acute and chronic GvHD reported for quizartinib-treated patients.

**AEs of Special Interest**

QT prolongation

Quizartinib prolongs QT interval on ECG in a dose-dependent and exposure-dependent manner. This was observed in Phase 1-2 studies, including the higher incidence of QTcF prolongation in females compared with males. Therefore, risk minimisation measures for the monitoring and management of subjects with QTcF prolongation were incorporated into the subsequent study protocols, including Phase 3 Study AC220-A-U302.

*Study AC220-A-U302*

In total, 49 (18.5%) subjects in the quizartinib arm and 30 (11.2%) subjects in the placebo arm experienced events in the TdP/QT Prolongation SMQ. The majority of these events were nonserious and mild or moderate in severity, resolved without any action taken with study drug, or were managed by study drug interruption or dose reduction.

In both treatment arms, ECG QT prolonged was the most common event, reported in a higher percentage of subjects in the quizartinib arm than in the placebo arm (13.6% vs. 4.1%). The other most common TEAEs included syncope, fall, and presyncope, all of which were nonserious, and none of which was associated with any evidence of ventricular arrhythmia as a cause of the event.

Two subjects in the quizartinib arm (no subject on placebo) experienced TESAEs of cardiac arrest that were associated with recorded ventricular fibrillation on ECG, which both occurred in the context of Grade 3 or 4 hypokalaemia. An additional subject in the quizartinib arm died after the last dose of quizartinib (TESAE of death) which was associated to altered maximum average QTcF. The exact cause of death was unknown.

*ECG* - The incidence of Grade 3 QTcF prolongation (QTcF of >500 ms) based on central ECG reading was 2.3% with quizartinib vs. 0.7%s in the placebo arm. Higher percentages of subjects in the quizartinib arm had increases in QTcF of >30 ms or >60 ms from Baseline compared with the placebo arm. The median time (range) to Grade 2 QTcF prolongation was 64.0 (4 to755) days in the quizartinib arm, and to Grade 3 QTcF prolongation 82 days (1 to 130).

*All AML pool*

In the 30 to 60 mg group of the All AML Pool, 173 (25.9%) subjects experienced events in the TdP/QT Prolongation SMQ. The types of events in the 30 to 60 mg group of the All AML Pool were similar to those in Study AC220-A-U302, with most TEAEs being 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.

There was a single case of TdP in the All AML Pool (>60 mg group [quizartinib 90 mg]), which resolved spontaneously after study drug discontinuation.

TESAEs of 'death' occurred in 2 patients in the All AML Pool and 6 (0.6%) patients experienced cardiac arrest. Five (0.5%) subjects experienced events of ventricular tachycardia, of which 3 had nonserious events with no action taken with quizartinib and 2 had serious events.

In the >60 mg group of the All AML Pool, 2 patients experienced events of arrhythmia (type not specified), both of which were nonserious with no action taken with quizartinib.

*ECG* - In line with the pivotal trial, 2.5% of patients in the 30-60 mg group of the All AML Pool had a QTcF of >500 ms. In general, there was a dose-response between quizartinib dose and QTcF prolongation in the All AML Pool.

**Table 29. TEAEs identified by the TdP/QT prolongation SMQ search (safety analysis set)**

| 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 |

AE = adverse event; AML = acute myeloid leukemia; ECG = electrocardiogram; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects in the category; QT = interval between the start of the Q wave and the end of the T wave; PT = preferred term; SAP = Statistical Analysis Plan; SMQ = standardized MedDRA query
Note: Percentage is calculated using number of subjects in the column heading as denominator.
PTs are presented in descending order of incidence in the total quizartinib column.
AEs were coded using MedDRA Version 24.0.

Other cardiac TEAEs

*Cardiac failure*

In the pivotal trial, 2.6% of patients in the quizartinib arm and 2.2% of patients in the placebo arm had a TEAE related to cardiac failure. Grade ≥3 events were reported by 5 (1.9%) and 2 (0.7%) patients in the quizartinib and placebo arms, respectively; none resulted in a fatal outcome. One patient (quizartinib arm) discontinued the study drug due to the event and there were 3 patients (1 quizartinib; 2 placebo) for whom the dose was interrupted.

Results in the 30 to 60 mg group of the All AML Pool were similar to those in the pivotal trial.

*Ischaemic heart disease*

In total, 1 (0.4%) and 6 (2.2%) subjects in the quizartinib and placebo arms, respectively, experienced TEAEs related to ischemic heart disease. Grade 3/4 events were reported by 1 (0.4%) and 4 (1.5%) patients, respectively, and 0 and 3 (1.1%) patients had TESAEs. No event resulted in a fatal outcome. One patient (placebo arm) discontinued study drug due to the event and there were 2 patients (both placebo) for whom the dose was interrupted. Results in the 30 to 60 mg group of the All AML Pool were similar to the pivotal trial.

Hepatic function abnormalities

In total, 34.3% and 27.2% of patients in the quizartinib and placebo arms, respectively, experienced hepatic TEAEs in Study AC220-A-U302 (Table 30). Medical review of the cases with combined elevations in aminotransferases and total bilirubin (TBL) in the quizartinib arm did not reveal any cases meeting Hy's Law criteria or serious events of drug-induced liver injury. Most of the events identified by the MedDRA search were non-serious and none resulted in a fatal outcome. In both treatment arms, the most common TEAEs (≥5%) included ALT increased, AST increased, gamma-glutamyltransferase (GGT) increased, and blood bilirubin increased.

**Table 70. Hepatic TEAEs (≥2% of subjects in the quizartinib arm of study AC220-A-U302 or in the all AML pool) - MedDRA search (safety analysis set)**

| PT | Study AC220-A-U302 | | All AML Pool | | | |
|---|---|---|---|---|---|---|
| | Quizartinib N = 265 n (%) | Placebo N = 268 n (%) | Quizartinib <30 mg N = 30 n (%) | Quizartinib 30 to 60 mg N = 669 n (%) | Quizartinib >60 mg N = 382 n (%) | Total Quizartinib N = 1081 n (%) |
| **Subjects with any identified events** | **91 (34.3)** | **73 (27.2)** | **10 (33.3)** | **208 (31.1)** | **73 (19.1)** | **291 (26.9)** |
| ALT increased | 42 (15.8) | 27 (10.1) | 3 (10.0) | 92 (13.8) | 26 (6.8) | 121 (11.2) |
| AST increased | 28 (10.6) | 19 (7.1) | 1 (3.3) | 67 (10.0) | 19 (5.0) | 87 (8.0) |
| Blood bilirubin increased | 16 (6.0) | 14 (5.2) | 0 | 47 (7.0) | 13 (3.4) | 60 (5.6) |
| GGT increased | 24 (9.1) | 25 (9.3) | 4 (13.3) | 36 (5.4) | 1 (0.3) | 41 (3.8) |
| Hyperbilirubinaemia | 8 (3.0) | 8 (3.0) | 0 | 12 (1.8) | 12 (3.1) | 24 (2.2) |
| Hepatic function abnormal | 7 (2.6) | 4 (1.5) | 1 (3.3) | 10 (1.5) | 0 | 11 (1.0) |

AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects in the category; PT = preferred term; SAP = Statistical Analysis Plan; SMQ = Standardized MedDRA Queries
Percentage is calculated using number of subjects in the column heading as denominator.
AEs were coded using MedDRA Version 24.0.

Infections

During the overall study period, the proportions of patients experiencing TEAEs, Grade 3/4 TEAEs, and TESAEs of infection were similar in the quizartinib group (77.0%, 45.3%, and 28.7%, respectively) and placebo group (70.1%, 45.9%, and 26.5%, respectively). Infections TEAEs associated with study drug discontinuation and TEAEs associated with death were reported in a slightly higher proportion of subjects in the quizartinib group than in the placebo group (7.2% vs. 4.1% and 7.5% vs. 4.5%, respectively).

The most commonly reported infections events in the study overall (ie, in >10% of subjects in either treatment group) were pneumonia (14.7% vs. 15.3%) and sepsis (5.7% vs. 10.4%). Septic shock, which was reported with a similar frequency in the quizartinib and placebo groups (in 12 [4.5%] and 8

[3.0%] patients, respectively), was the only event that led to death in >2% of patients (ie, 8 [3.0%] and 3 [1.1%] subjects, respectively).

During the Continuation Phase, TEAEs, Grade 3/4 TEAEs, and TESAEs of infection were reported with higher frequency in the quizartinib group than in the placebo group (61.2% vs. 46.7%, 19.8% vs. 15.2%, and 19.0% vs. 16.3%). TEAEs associated with study drug discontinuation and TEAEs associated with death were reported in ≤1.7% of patients in both treatment groups. The most common event was upper respiratory tract infection (17.2% vs. 9.8%).

The majority of the infectious events, including the serious and fatal infections, occurred in patients presenting with Grade 3 or 4 neutropenia and/or lymphopenia at the time of the event.

Haemorrhage

During the overall study period, the proportions of patients experiencing TEAEs and TESAEs of haemorrhage were similar in the quizartinib group (36.6% and 3.0%, respectively) and placebo group (40.3% and 3.4%, respectively), while TEAEs of Grade 3/4 were reported slightly more frequently in the quizartinib group than in the placebo group (7.2% vs. 4.5%). Haemorrhage TEAEs associated with study drug discontinuation and TEAEs associated with death were reported with very low frequencies (≤1.5%) in both treatment groups.

The most frequently reported events (ie, in >5% of patients in either treatment group) were epistaxis (15.1% vs. 10.8%, mostly mild/moderate in severity) and gingival bleeding (5.3% vs. 4.9%).

Similar to what was observed for the overall study period, TEAEs of haemorrhage during the Continuation Phase were reported with comparable frequency in the quizartinib group (12.9%) and placebo group (10.9%).

The majority of the bleeding events, including the serious and fatal infections, occurred in subjects presenting with Grade 3 or 4 thrombocytopenia at the time of the event.

Differentiation syndrome

No events of differentiation syndrome were reported in subjects with newly diagnosed AML from Study AC220-A-U302. Of the 1081 subjects treated with quizartinib in the All AML Pool, 2 (0.2%) subjects (both in the >60 mg group) had investigator-reported TEAEs of differentiation syndrome in the setting of R/R AML.

Tumour lysis syndrome

No events of TLS were reported in the quizartinib arm of Study AC220-A-U302 (1 event was reported in the placebo arm). In total, 7 (0.6%) patients in the All AML Pool were reported to have TLS, 4 (0.6%) in the 30 to 60 mg group and 3 (0.8%) in the >60 mg group. None of the cases of TLS were associated with death as outcome. No conclusive evidence of causal association between quizartinib and TLS was identified.

### *2.6.8.4. Laboratory findings*

No additional safety signals have been detected based on laboratory findings, vital signs or ECG measurement, except for myelosuppression related AEs, hepatic function abnormalities and QT prolongation that were discussed in the respective safety sections above.

### *2.6.8.5. In vitro biomarker test for patient selection for safety*

N/A

### *2.6.8.6. Safety in special populations*

Age

Higher incidences of TESAEs, TEAEs associated with death as outcome, and TEAEs associated with study drug discontinuation were observed in older subjects (≥65 years) compared with younger subjects (<60 and 60 to <65 years) in both treatment arms.

While the type and incidence of TEAEs were generally similar across age subgroups, gastrointestinal disorders (diarrhoea, nausea, stomatitis, abdominal pain, and decreased appetite), and pruritus occurred more frequently in older subjects in the quizartinib arm, this pattern was not observed in the placebo arm. Fatal infections have occurred more frequently with quizartinib in elderly patients (i.e., older than 65 years), compared to younger patients (13% vs. 5.7%), especially in the early treatment period.

Gender

In the pivotal trial, Grade 4 TEAEs and TESAEs were reported more frequently in females compared to males. The difference in Grade 4 TEAEs was mainly driven by a higher incidence of infections and cytopenic events in female subjects. In the quizartinib group, the PTs reported with higher frequency (ie, >2 pp) in females than males were: neutropenia, (9.2% in females vs. 6.5% in males), febrile neutropenia (6.4% vs. 3.2%) and septic shock (2.8% vs. 0%). The difference in TESAEs was mainly driven by the higher incidence of infections in female patients. In the quizartinib arm, differences >2pp were reported for the PTs of colitis and urinary tract infection (both 2.1% of females vs. 0% of males).

Race/Geographic region

TEAEs associated with death as an outcome were reported more frequently in White subjects compared to Asian subjects or subjects of other races and in the North American and European subgroups than in the Asian subgroup of the 30-60 All AML pool.

Concomitant use of strong CYP3A inhibitors

In Study AC220-A-U302, 166 (62.6%) and 162 (60.4%) subjects in the quizartinib and placebo arms, respectively, used at least one concomitant strong CYP3A inhibitor during the study.

Grade ≥3 TEAEs, TESAEs, 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, whereas the opposite was true for TEAEs associated with death as an outcome and TEAEs associated with study drug discontinuation.

Hepatic/renal impairment

Based on the PK in patients with mild and moderate hepatic or renal impairment, no dose adjustment is required for these patients (please refer to PK section of this report). Safety in patients with severe hepatic or renal impairment is unknown. This is reflected in SmPC section 4.2.

### *2.6.8.7. Immunological events*

none

### *2.6.8.8. Safety related to drug-drug interactions and other interactions*

Several drug-drug-interaction studies have been performed of which results are presented in the PK section of this report.

No clinical studies have been conducted that assess the use of quizartinib during pregnancy or breastfeeding. No pregnancies have been reported in quizartinib-treated subjects in the clinical development programme.

Given the target patient population and nature of quizartinib, withdrawal, rebound effects or drug abuse were not anticipated, and consequently no studies were conducted to assess these effects.

Available safety data do not indicate any issues related to the effects on the ability to drive or operate machinery or the impairment of mental ability.

### *2.6.8.9. Discontinuation due to adverse events*

Overall, the percentage of patients with TEAEs associated with study drug discontinuation was higher with quizartinib than with placebo (20.4% vs. 8.6%). This difference was observed in all treatment phases with the highest incidence in the Continuation Phase (15.5% vs. 7.6%). The most common TEAEs associated with study drug discontinuation were infections (7.2% vs. 4.1%) and cytopenias (3.0% vs. 0). ECG QT prolonged associated with study drug discontinuation was reported by 0.8% vs. 0 patients in the placebo arms.

The number of patients who discontinued quizartinib due to TEAEs in the 3 treatment phases were 26/265 (9.8%), 10/173 (5.8%), and 18/116 (15.5%) in the Induction, Consolidation, and Continuation Phases, respectively.

In the Continuation Phase, cytopenias (thrombocytopenia, neutropenia, and anaemia) and gastrointestinal disorders (nausea, diarrhoea, and vomiting) were the most frequent events associated with study drug discontinuation and were reported by patients only in the quizartinib arm.

Generally, the incidence and types of TEAEs associated with discontinuation in the 30 to 60 mg group were consistent with those reported in the pivotal trial.

**TEAEs leading to dose reduction**

The percentage of patients with TEAEs associated with study drug dose reduction was higher with quizartinib than with placebo (18.9% vs. 6.3%). This difference was primarily observed during the Continuation Phase. The most frequently reported TEAEs associated with study drug dose reduction in the quizartinib arm were cytopenias (neutropenia [6% vs. 1.1%], neutrophil count decreased [3.4% vs. 0%], thrombocytopenia [3% vs. 0.7%] and platelet count decreased [1.5% vs. 0%]) and ECG QT prolonged (3.8% vs. 0.4%). Apart from neutropenia, no events occurred at a >5 pp higher incidence in the quizartinib arm compared with the placebo arm.

Integration of data for the All AML Pool was not performed, as data on dose reductions due to a TEAE were not captured across all clinical studies included in the All AML Pool in a manner consistent enough to allow for pooled analysis.

**TEAEs leading to dose interruption**

During the overall study period, the percentage of subjects with TEAEs associated with study drug interruption was higher with quizartinib than with placebo (34.0% vs. 20.1%), this difference was primarily observed during the Continuation Phase. The most frequently reported TEAEs associated with study drug interruption in the quizartinib arm were cytopenias (neutropenia, neutrophil count decreased, thrombocytopenia, platelet count decreased, myelosuppression, and febrile neutropenia), ECG QT prolonged, pneumonia, AST increased, diarrhoea, and stomatitis. Apart from neutropenia (7.2% vs. 0.7%), no other events occurred at a >5 pp higher incidence in the quizartinib arm compared with the placebo arm.

In the 30 to 60 mg group, 31.8% of patients had TEAEs associated with study drug interruption. Generally, the incidence and types of TEAEs associated with study drug interruption were consistent with those reported in the pivotal trial.

### *2.6.8.10. Post marketing experience*

Cumulatively, from 18 Jun 2019 to 28 Oct 2021, 228 patients are estimated to have received quizartinib in the post-marketing setting, all of whom were in Japan. During this period, AEs were reported in 134 cases with 269 events in the post-marketing setting. Out of the 134 cases, SAEs were reported in 66 cases with 96 events, and common SAEs (more than 5 events) were disease progression (14 events), neutrophil count decreased (8 events), and febrile neutropenia (5 events). AEs leading to fatal outcome were reported in 34 cases, and common AEs leading to fatal outcome were disease progression (14 events), death (4 events; also mostly due to AML progression), AML (2 events), and sepsis (2 events). There were no cardiac events with fatal outcome. In total, 29 AEs of ECG QT prolonged were reported (25 nonserious and 4 SAEs).

### *2.6.8.11. Summary of Adverse Drug Reaction*

The most common adverse reactions were increased alanine aminotransferase (58.9%), decreased platelet count (40.0%), decreased haemoglobin (37.4%), diarrhoea (37.0%), nausea (34.0%), abdominal pain (29.4%), headache (27.5%), vomiting (24.5%) and decreased neutrophil count (21.9%).

The most common Grade 3 or 4 adverse reactions were decreased platelet count (40%), decreased haemoglobin (35.5%), decreased neutrophil count (21.5%), increased alanine aminotransferase (12.1%), bacteraemia (7.2%) and fungal infections (5.7%). The most common serious adverse reactions in the Vanflyta arm were neutropenia (3.0%), fungal infections (2.3%) and herpes infections (2.3%). Adverse reactions with fatal outcome were fungal infections (0.8%) and cardiac arrest (0.4%).

The most common adverse reactions associated with dose interruption of quizartinib were neutropenia (10.6%), thrombocytopenia (4.5%) and prolonged electrocardiogram QT interval (2.6%). The most common adverse reactions associated with dose reduction were neutropenia (9.1%), thrombocytopenia (4.5%) and prolonged electrocardiogram QT interval (3.8%).

The most common adverse reaction associated with permanent discontinuation of quizartinib was thrombocytopenia (1.1%).

Adverse reactions are listed in table 38 below according to MedDRA System Organ Class (SOC). Within each SOC, the adverse reactions are ranked by frequency with the most frequent reactions first, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

**Table 31: Adverse reactions**

| Adverse reaction | All grades % | Grade 3 or 4 % | Frequency category (All grades) |
|---|---|---|---|
| **Infections and infestations** | | | |
| Upper respiratory tract infections[a] | 18.1 | 1.9 | Very common |

| | | | |
|---|---|---|---|
| Fungal infections[b] | 15.1 | 5.7 | Very common |
| Herpes infections[c] | 14.0 | 3.0 | Very common |
| Bacteraemia[d] | 11.3 | 7.2 | Very common |
| **Blood and lymphatic system disorders** | | | |
| Thrombocytopenia[e] | 40.0 | 40.0 | Very common |
| Anaemia[e] | 37.4 | 35.5 | Very common |
| Neutropenia[e] | 21.9 | 21.5 | Very common |
| Pancytopenia | 2.6 | 2.3 | Common |
| **Metabolism and nutrition disorders** | | | |
| Decreased appetite | 17.4 | 4.9 | Very common |
| **Nervous system disorders** | | | |
| Headache[f] | 27.5 | 0 | Very common |
| **Cardiac disorders** | | | |
| Cardiac arrest[g] | 0.8 | 0.4 | Uncommon |
| Ventricular fibrillation[g] | 0.4 | 0.4 | Uncommon |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Epistaxis | 15.1 | 1.1 | Very common |
| **Gastrointestinal disorders** | | | |
| Diarrhoea[h] | 37.0 | 3.8 | Very common |
| Nausea | 34.0 | 1.5 | Very common |
| Abdominal pain[i] | 29.4 | 2.3 | Very common |
| Vomiting | 24.5 | 0 | Very common |
| Dyspepsia | 11.3 | 0.4 | Very common |
| **Hepatobiliary disorders** | | | |
| ALT increased[e] | 58.9 | 12.1 | Very common |
| **General disorders and administration site conditions** | | | |
| Oedema[j] | 18.9 | 0.4 | Very common |
| **Investigations** | | | |
| Prolonged electrocardiogram QT[k] | 14.0 | 3.0 | Very common |

Standard chemotherapy = cytarabine (cytosine arabinoside) and anthracycline (daunorubicin or idarubicin).

[a] Upper respiratory tract infections include upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, tonsillitis, laryngopharyngitis, pharyngitis bacterial, pharyngotonsillitis, viral pharyngitis and acute sinusitis.

[b] Fungal infections include oral candidiasis, bronchopulmonary aspergillosis, fungal infection, vulvovaginal candidiasis, aspergillus infection, lower respiratory tract infection fungal, oral fungal infection, candida infection, fungal skin infection, mucormycosis, oropharyngeal candidiasis, aspergillosis oral, hepatic infection fungal, hepatosplenic candidiasis, onychomycosis, fungemia, systemic candida and systemic mycosis.

[c] Herpes infections include oral herpes, herpes zoster, herpes virus infections, herpes simplex, human herpesvirus 6 infection, genital herpes and herpes dermatitis.

[d] Bacteraemia includes bacteraemia, Klebsiella bacteraemia, Staphylococcal bacteraemia, Enterococcal bacteraemia, Streptococcal bacteraemia, device-related bacteraemia, Escherichia bacteraemia, Corynebacterium bacteraemia and Pseudomonal bacteraemia.

[e] Terms based on laboratory data.

[f] Headache includes headache, tension headache and migraine.

[g] One subject experienced two events (ventricular fibrillation and cardiac arrest).

[h] Diarrhoea includes diarrhoea and diarrhoea haemorrhagic.

[i] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower and gastrointestinal pain.

[j] Oedema includes oedema peripheral, face oedema, oedema, fluid overload, generalised oedema, peripheral swelling, localised oedema and face swelling.

[k] Electrocardiogram QT prolonged includes electrocardiogram QT prolonged and electrocardiogram QT interval abnormal.

## 2.6.9. Discussion on clinical safety

The total pooled safety database for quizartinib consists of 1081 patients, of whom 669 were treated at the targeted dose range of 30 to 60 mg. In total 115 patients (of whom 79 were included in the pivotal trial) received quizartinib 30-60 mg for 1 year or longer. The safety database is considered acceptable to establish the safety profile in newly diagnosed AML patients, although the possibility to identify rare adverse events is still limited. Long-term safety will continue to be monitored as part of the routine pharmacovigilance activities.

Almost all patients in Study AC220-A-U302 experienced one AE of any grade and approximately 92% of patients experienced at least one Grade 3 or higher AE with quizartinib treatment. This is also observed in the placebo arm and expected considering the intensive chemotherapy backbone therapy. Most other TEAE categories were reported with at least a numerical higher frequency in the quizartinib arm compared to the placebo arm, in particular TEAEs associated with discontinuation/interruption and treatment related TEAEs.

AEs were most frequently reported across the SOCs of gastrointestinal disorders, infections, general disorders, and blood disorders. The most frequently reported TEAEs in the quizartinib arm were febrile neutropenia, pyrexia, diarrhoea, hypokalaemia and nausea, all of which occurred at similar frequencies in both treatment arms. Largest differences compared to placebo were observed for the TEAEs of neutropenia (20.4% in quizartinib arm vs. 10.1% in placebo arm), ECG QT prolonged (13.6% vs. 4.1%), headache (27.5% vs. 19.8%), neutrophil count decreased (10.2% vs. 4.5%) and ALT increased (15.8% vs. 10.1%).

Most of these toxicities were also observed preclinically. The bone marrow and lymphoid organs were the principal target tissues affected. The cardiac effect on QT prolongation mainly via blockade of IKs current and hepatic enzyme abnormalities (as discussed below) were noted preclinically as well.

The most frequently reported Grade 3/4 TEAEs (≥10% incidence) in the quizartinib arm included cytopenias and infections, of which only neutropenia occurred with >5% higher incidence compared to the placebo arm (18.1% vs. 8.6%).

Treatment related TEAEs were reported more frequently in the quizartinib arm compared to the placebo arm: 60.4% vs. 36.2%. The most common related TEAEs reported with >5% difference compared to the placebo arm were: neutropenia (17.4% vs. 3.7%), ECG QT prolongation (11.7% vs. 3%) and neutrophil count decreased (7.9% vs. 1.9). Related Grade 3/4 TEAEs were reported in 43% vs. 22.8%, of which cytopenias were most frequently reported and again neutropenia the only event with a frequency ≥5 pp higher with quizartinib than with placebo (15.5% vs. 3.7%).

TESAEs were reported in 54% of quizartinib treated patients vs. 45.9% in the placebo group. In both treatment arms, the most frequently reported types were infections (pneumonia [6.4% vs. 5.6%], septic shock [4.2% vs. 3%] and sepsis [3.8% vs. 5.2%]) and blood disorders (febrile neutropenia [10.9% vs. 8.2%]). Related TESAEs were reported in 15.5% vs. 10.8%. The most frequently reported (≥1% incidence) related TESAEs were febrile neutropenia (2.6% with quizartinib vs. 1.5% with placebo), pneumonia (1.5% vs. 0.7%), neutropenia (1.1% vs. 0%), and myelosuppression (1.1% vs. 0%).

A higher incidence of TEAEs associated with death within 30 days after last dose of study drug was reported in the quizartinib arm (n=30, 11.3%) compared to the placebo arm (n=23, 8.6%). In particular, more early deaths (i.e., deaths within 60 days of initiation of study drug) occurred with quizartinib compared with placebo (7.5% vs. 4.9%). In the continuation phase, the proportion of deaths was lower compared to the early treatment phases, and also lower compared to the placebo arm.

Main causes of death in the early induction and consolidation treatment phases were infections (mostly sepsis/septic shock). Older age and worse ECOG PS were the only factors identified as potentially associated with the observed early deaths in Study AC220-A-U302. A similar trend for older age and worse ECOG PS was observed for patients who died early vs. those who did not in the placebo group and these factors are routinely considered when selecting patients for intensive chemotherapy. Although only 3 deaths were considered related to quizartinib treatment by the investigator, for most patients AEs of (febrile) neutropenia and infection were reported. Neutropenia and infection might indeed be secondary to AML or the intensive chemotherapy backbone, but it cannot be completely

ruled out that the myelosuppressive effect of quizartinib itself has contributed as well. The proposed risk minimazations in the SmPC are considered appropriate.

When analysing AEs by treatment phase, frequencies of almost all TEAE categories increased in the continuation phase compared to the earlier treatment phases, except for TEAEs with death as outcome. Most pronounced increases with quizartinib were observed for related TEAEs and (related) TEAEs associated with treatment interruption or reduction, mainly caused by cytopenias and ECG QT prolonged. This is reflected in the fact that only a small proportion of patients (7.9%) was able to fully complete the continuation phase up to 36 cycles. The optimal continuation duration (beyond 12 months) remains uncertain, as no further studies are planned to investigate this.

TEAEs associated with study drug discontinuation were more frequently reported for quizartinib (20.4% vs. 8.6%). The most common TEAEs resulting in discontinuation were infections/septic shock (7.2% vs. 4.1%) and cytopenias (3.0% vs. 0). The largest differences with placebo were observed in the continuation phase, mainly due to gastro-intestinal disorders and cytopenias. Dose reductions were reported in 18.9% vs. 6.3% of patients, mainly due to cytopenias and ECG QT prolonged. Apart from neutropenia (6% vs. 1.1%), no events occurred at a >5 pp higher incidence in the quizartinib arm compared with the placebo arm.

The safety profile of quizartinib in the 30-60 mg All AML Pool was generally comparable to the quizartinib arm of the pivotal trial.

For a total of 102 patients who underwent **HSCT**, the incidence of acute and chronic GvHD was higher in the quizartinib arm than for placebo (45.1% vs. 38.5% and 29.4% vs. 19.8%, respectively) and the grading of acute GvHD seemed slightly worse. Frequencies of the most common AEs seem to increase with restart of quizartinib after HSCT, but these adverse reactions are already included in the SmPC section 4.8 with frequency 'very common'. There are 3 patients in the 30-60 mg All AML Pool (of whom 1 was included in the pivotal trial vs. 0 in the placebo arm) who died due to GvHD. A higher proportion of patients with successful engraftment in the quizartinib group (83.3% vs. 78% in the placebo group) might partially explain some of the observed differences between the two treatment groups. Although contribution of quizartinib to GvHD cannot be fully ruled out, it is noted that the incidence of GvHD with quizartinib is consistent when indirectly compared with reported rates of GvHD after alloSCT for haematological malignancies in literature. As such, no further risk minimisation is warranted.

The quizartinib safety profile was worse in elderly. A similar pattern was observed in the placebo group, except for the increased risk for early non-relapse mortality. Moreover, the proportion of patients aged 65 or older that discontinued treatment due to TEAEs is almost a third (29% vs. 12% with placebo). As discussed above, a warning regarding fatal infections in elderly is included in SmPC section 4.4.

The safety profile seems slightly worse in females compared to males. Grade 4 TEAEs (mainly driven by infections and cytopenic evens) and TESAEs (mainly driven by infections), and QT prolongation were more frequently reported in females. The differences in PTs between males and females were small and infection and myelosuppression are known safety concerns for patients receiving intensive chemotherapy-based regimens. No additional risk minimisation is considered warranted.

In the 30 to 60 mg group of the All AML Pool, TEAEs associated with death as an outcome were reported more frequently in White patients (18.3%) compared to Asian subjects (7.1%). Similar findings were observed according to region, with 17.5% of the North American and 17.9% of patients in the European subgroups vs. 8.3% of patients in the Asian/Other subgroup experiencing TEAEs associated with death as outcome. Further data provided during the assessment clarified that there was no trend in patient risk factors across the races/regions that could explain the difference in frequency of fatal TEAEs.

Grade ≥3 TEAEs, TESAEs, 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. Clarifications have been provided indicating that this may be explained by the clinical need for those patients to receive azole antifungals for the treatment of an active infection. Overall, it is agreed that there is no consistent trend in the incidence of the different categories of TEAEs when comparing patients who concomitantly used a strong CYP3A inhibitor with those who did not. Relevant risk minimisation measure are though described in the SmPC in section 4.2 (dose adjustment) and section 4.5 (description of drug-drug interaction).

Toxicology studies revealed that quizartinib has a significant intrinsic haematotoxicity in terms of neutropenia and lymphocytopenia, hepato- and renal toxicity. Due to the overlap of disease symptoms and safety risks from concomitant therapies, identification of these toxicity in the human target population remained difficult.

**Main AEs of special interest**

*QT prolongation*
Quizartinib prolongs QT interval on ECG in a dose-dependent and exposure-dependent manner. Although most observed cases of QT prolongation were non-serious and resolved without any action taken with study drug, cardiac deaths were observed for which a causal relation with quizartinib treatment could not be completely ruled out. In order to identify patients at risk for developing significant sequelae early and manage them properly, measures regarding ECG monitoring and management of QT prolongation have been proposed with dose adjustments, comedication, treatment of electrolyte abnormalities, a contraindication for patients with congenital QT prolongation and a recommendation not to start treatment with a QTcF interval >450 ms. The apparent increase in incidence of QTcF prolongation with longer treatment duration might be due to accrual of events and lower absolute number of patients with longer follow-up as well. This is also supported by the analysis of time to onset of QTcF prolongation, as events tended to occur early. The QT prolongations observed with quizartinib were mostly asymptomatic ECG findings, with low incidence of ventricular arrythmia events. There were no Grade 3 or higher TEAEs of ECG QT prolonged the Continuation Phase and no patients discontinued quizartinib due to TEAEs of ECG QT prolonged. A weekly ECG is recommended in the SmPC for the period of dose initiation/escalation. This safety aspects are also part of the additional risk minimisation measure in the form of Physician educational material and Patient card with the aim to reinforce the prescriber's and patient/caregiver's awareness about the risk of serious ADRs related to QTc interval prolongation

*Other cardiac TEAEs*
Similar proportions of patients in the quizartinib and placebo arm had TEAEs related to cardiac failure and ischaemic heart disease.

*Hepatic function abnormalities*
A higher proportion of quizartinib treated patients compared to placebo-treated patients experienced hepatic TEAEs in the pivotal trial (34.3% vs. 27.2%), mostly being elevated aminotransferases. This is adequately reflected in the SmPC. No serious cases of hepatic failure or toxic hepatitis considered related to study drug were reported for the pivotal trial.

*Infections*
Infections TEAEs associated with study drug discontinuation and TEAEs associated with death were generally reported in a slightly higher proportion of subjects in the quizartinib group than in the placebo group (7.2% vs. 4.1% and 7.5% vs. 4.5%, respectively). The majority of the infectious events, including the serious and fatal infections, occurred in subjects presenting with Grade 3 or 4

neutropenia and/or lymphopenia at the time of the event. Myelosuppression and infections are appropriately described in the SmPC and RMP.

*Haemorrhages*, including serious intracranial/cerebral haemorrhages have been reported in patients treated with quizartinib. Epistaxis and thrombocytopenia have been included as adverse drug reactions.

There is no indication for other risks or new safety concerns based on the presented **post-marketing data** from approximately 228 patients treated with quizartinib in Japan.

*Differentiation syndrome*
Differentiation syndrome was not observed in the pivotal trial and with very low frequency in the all AML pool.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

## 2.6.10. Conclusions on the clinical safety

The safety profile of quizartinib is not negligible. Treatment with quizartinib leads to higher incidences of treatment-related AEs, SAEs and discontinuations/dose adjustments of study drug due to AEs compared to placebo, in the complex treatment schedule as studied, i.e. consisting of an induction, consolidation and maintenance phase. Almost all patients treated with quizartinib experienced at least one Grade ≥3 TEAE. In particular neutropenia, and QT prolongation were reported as related events occurring more frequently with quizartinib. However, most TEAEs were manageable by dose adjustment or standard supportive therapies. Still, there is an observed imbalance in fatal TEAEs (primarily infections), in early treatment phases. Older age and worse ECOG PS were identified as factors potentially associated with the observed early deaths. The proposed risk minimisations in SmPC sections 4.4 and 4.8 regarding fatal infections in elderly are acceptable. All in all considering the risk minimisations put in place and manageability of most of the TEAEs, the safety profile of quizartinib, even though not negligible, can be considered acceptable in the clinical setting specified in the indication.

# *2.7. Risk Management Plan*

## 2.7.1. Safety concerns

**Table 32. Summary of safety concerns**

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

The summary of safety concerns is acceptable.

## 2.7.2. Pharmacovigilance plan

In the current RMP [v0.4], the applicant proposes in their Pharmacovigilance plan only routine pharmacovigilance activities and no additional pharmacovigilance activities:

**Table 33. On-going 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* | | | | |

The PRAC, having considered the data submitted, is of the opinion that the proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

## 2.7.3. Risk minimisation measures

**Table 34. Risk minimisation measures**

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

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

### 2.7.4. Conclusion

The CHMP and the PRAC consider that the risk management plan version 1.0 dated 08 September 2023 is acceptable.

## *2.8. Pharmacovigilance*

### 2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### 2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 18 June 2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

## *2.9. Product information*

### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vanflyta (quizartinib) is included in the

additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Vanflyta (quizartinib) is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by Vanflyta (quizartinib) single-agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive.

### 3.1.2. Available therapies and unmet medical need

Based on eligibility criteria and patient preference, newly diagnosed AML patients receive either standard induction and consolidation chemotherapy or non-intensive treatment. However, patients with FLT3-ITD (+) AML have a higher risk of relapse compared with patients without FLT3-ITD mutations (Ciolli, 2004; Fröhling, 2002; Kottaridis, 2001). Current guidelines recommend molecular testing for FLT3 mutations at diagnosis and, when applicable, early incorporation of FLT3 inhibitors into the therapeutic regimen. The current approach is to combine them with standard chemotherapy in an attempt to increase the cytotoxic effect against leukaemia cells and reverse the poor prognosis for these patients. To date, only midostaurin, a multikinase inhibitor, has received approval for the treatment of FLT3 mutant newly diagnosed AML in combination with standard chemotherapy based on data from the RATIFY study, which included only subjects younger than 60 years of age with newly diagnosed FLT3-mutation positive AML with either ITD or TKD mutations. However, given the poor prognosis of patients with FLT3-ITD (+) AML, the higher risk of relapse, and the unmet medical need, new treatment options are needed.

### 3.1.3. Main clinical studies

The main clinical evidence is derived from the pivotal Phase 3 study, AC220-A-U302, which was conducted in the target population of subjects with newly diagnosed FLT3-ITD (+) AML. No other study contributed to the efficacy data in the proposed indication.

Patients were randomised (1:1) to receive quizartinib 40 mg or matching placebo (QD for 14 days) in each cycle in combination with standard chemotherapy (induction followed by consolidation for responding patients). During the Continuation Phase subjects received quizartinib/placebo at a starting dose of 30 mg QD increasing to 60 mg QD for subjects if QTcF was ≤450 ms for up to 36 cycles (28 days/cycle). Patients who proceeded to HSCT stopped receiving study treatment 7 days before the start of a conditioning regimen.

## *3.2. Favourable effects*

The pivotal study AC220-A-U302 met its primary endpoint of OS with a HR of 0.776 (95% CI: 0.615-0.979) and a 2-sided p value: 0.03. The median OS values (quizartinib 31.9 months and placebo 15.1 months) show a plateau around the median. The 3-year landmark analysis shows 49.9% (95%CI: 43.7-55.9) of the patients in the quizartinib arm versus 41.1% (95%CI: 35.0-47.0) of the patients in the placebo arm.

The RMST survival cut-off time to address the plateau phase in the OS curve using cutoff time points of 36, 42, and 48 months showed a difference between the quizartinib and placebo groups in line with the primary OS analysis results. RMST (95% CI) survival time for subjects who received quizartinib was prolonged by 2.75 months (0.35, 5.15) at 36 months, 3.26 months (0.39, 6.13) at 42 months, 3.81 months (0.46, 7.16) at 48 months, and 4.53 months (0.55, 8.51) at 55.8 months.

For the secondary endpoints, the applicant has defined EFS in 3 different ways, i.e. according to FDA' definition (induction treatment failure (ITF) defined as not achieving CR by the end of induction using a 42 day window), FDA's definition without the 42 day restriction and the initial protocol definition (ITF defined as not achieving CRc by end of induction). The key secondary endpoint (per FDA definition within 42 days) was not statistically significant (preventing statistical analysis for the other secondary endpoints), the other definitions of EFS did show a numerical difference between the 2 treatment arms, in favour of quizartinib, i.e. FDA's definition without the 42 day restriction (median EFS 5.0 vs 3.4 months, HR: 0.828, 95%CI 0.669-0.999) and EFS per protocol definition which is consistent with the recommendations from current AML guidelines (Cheson, 2003; Heuser, 2020) (median EFS 11.9 months vs 5.7 months, HR: 0.729, 95%CI 0.592-0.897).

Even though it was specified as an exploratory objective a difference in duration of response was observed between quizartinib and placebo treated patients.

## *3.3. Uncertainties and limitations about favourable effects*

- The application concerns a single pivotal trial with no additional support from exploratory studies.

- The key secondary endpoint EFS per FDA definition was not statistically significant different between the quizartinib and placebo arms (HR [95% CI] = 0.916 [0.754, 1.114], p = 0.2371 by stratified log-rank test). Interpretation is hampered by low median EFS values.

- The difference in overall survival of quizartinib compared to placebo is not supported by other secondary endpoints; rates of CR, CR with FLT3-ITD MRD negativity, and CRc with FLT3-ITD MRD negativity were similar between treatment arms.

- The HR for the subgroup for low white blood cell counts at diagnosis (WBC <40x10^9/L) was higher than for the subgroup with WBC ≥40x10^9/L (i.e. HR 0.961 compared to HR 0.621, respectively). There were no continuous WBC data available at initial diagnosis to investigate clinical outcomes by several WBC cut-off points, hampering determination of a WBC level at which treatment is less effective. Moreover, lower efficacy is likely not dependent on low WBC alone but influenced by multiple factors. As such, no restriction of the indication is proposed.

- OS efficacy results in subgroups of VAF demonstrated an obvious difference in the Hazard Ratios which is lower the higher the FLT3-ITD %VAF is and the results for both the lower VAF groups are not significant. The HR for NPM1-wt is above 1 for Overall Survival. Also the newly submitted analysis for response rates and EFS demonstrate a relation to NPM1wt/mut status, while not significant, differ for quizartinib treatment or placebo. Further subgroup analysis for FLT3-ITD %VAF subgroups plus NPM1-status need to confirm the benefit for all subgroups. These analyses will be submitted in a biomarker report, in the post-authorisation phase.

## 3.4. Unfavourable effects

Almost all patients in Study AC220-A-U302 in both treatment groups experienced a *TEAE* ( about 99%) or *Grade ≥3 TEAE* (>89%). Most TEAE categories were reported with at least a numerical higher frequency in the quizartinib arm compared to the placebo arm.

The most frequently (>30%) reported *TEAEs* in the quizartinib arm were febrile neutropenia (44.2%), pyrexia (42.3%), diarrhoea (37%), hypokalaemia (35.1%), and nausea (34%), all of which occurred at similar frequencies to the placebo arm. Largest differences with quizartinib treatment compared to placebo were observed for the TEAEs of neutropenia (20.4% vs. 10.1%), ECG QT prolonged (13.6% vs. 4.1%), headache (27.5% vs. 19.8%), neutrophil count decreased (10.2% vs. 4.5%) and ALT increased (15.8% vs. 10.1%).

*Grade 3/4 TEAEs* were reported in ~80% in both treatment arms. The most frequently reported Grade 3/4 TEAEs (≥10% incidence) in the quizartinib arm included cytopenias (febrile neutropenia [43.4% vs. 41%] and neutropenia [18.1% vs. 8.6%]), hypokalaemia [18.4% vs. 16.4%], and infections (pneumoniae [11.3% vs. 11.2%]), of which the event of neutropenia occurred at a ≥5 pp higher incidence in the quizartinib arm than in the placebo arm.

*Treatment related TEAEs* were reported in 60.4% vs. 36.2%. The most common related TEAEs reported with >5% difference compared to the placebo arm were: neutropenia (17.4% vs. 3.7%), ECG QT prolongation (11.7% vs. 3%) and neutrophil count decreased (7.9% vs. 1.9%). *Related Grade 3/4 TEAEs* were reported in 43% vs. 22.8%, of which cytopenias were most frequently reported and neutropenia the only event with a frequency ≥5 pp higher with quizartinib than with placebo (15.5% vs. 3.7%).

*TESAEs* were reported in 54% of quizartinib treated patients vs. 45.9% in the placebo group. In both treatment arms, the most frequently reported types were infections (pneumoniae [6.4% vs. 5.6%], septic shock [4.2% vs. 3%] and sepsis [3.8% vs. 5.2%]) and blood disorders (febrile neutropenia [10.9% vs. 8.2%]).

*Related TESAEs* were reported in 15.5% vs. 10.8%. The most frequently reported (≥1% incidence) related TESAEs were febrile neutropenia (2.6% with quizartinib vs. 1.5% with placebo), pneumoniae (1.5% vs. 0.7%), neutropenia (1.1% vs. 0%), and myelosuppression (1.1% vs. 0%).

TEAEs associated with *death* within 30 days after last dose of study drug were reported with larger incidence in the quizartinib arm (n=30, 11.3%) compared to the placebo arm (n=23, 8.6%). In particular, more *early deaths* (ie, deaths within 60 days of initiation of study drug) occurred with quizartinib compared with placebo (7.5% vs. 4.9%). Main causes of death were infections (mostly sepsis/septic shock) in the early induction and consolidation treatment phases.

When analysing AEs by *treatment phase*, frequencies of almost all TEAE categories increased in the continuation phase compared to the earlier treatment phases, except for TEAEs with death as outcome. Most pronounced increases with quizartinib were observed for related TEAEs and (related) TEAEs associated with treatment interruption or reduction (mainly caused by cytopenias and ECG QT prolonged).

TEAEs associated with *study drug discontinuation* were more frequently reported for quizartinib (20.4% vs. 8.6%). The most common TEAEs resulting in discontinuation were infections (7.2% vs. 4.1%) and cytopenias (3.0% vs. 0). Dose reductions were reported in 18.9% vs. 6.3% of patients, mainly due to cytopenias and ECG QT prolonged. Apart from neutropenia (6% vs. 1.1%), no events occurred at a >5 pp higher incidence in the quizartinib arm compared with the placebo arm.

For a total of 102 patients who underwent *HSCT*, the percentage of patients with acute and chronic GvHD appeared higher in the quizartinib arm than in the placebo arm (45.1% vs. 38.5% and 29.4% vs. 19.8%, respectively). The quizartinib safety profile was worse in *elderly*. This was also observed in the placebo arm, except for the increase in early non-relapse mortality. The proportion of patients aged 65 or older that discontinued treatment due to TEAEs is almost a third and higher than with placebo (29% vs. 12%). The safety profile seems slightly worse in *females* compared to males, as Grade 4 TEAEs and TESAEs, and QT prolongation were more frequently reported. TEAEs associated with death as an outcome were reported more frequently in *White* subjects compared to Asian subjects or subjects of other races, and in the *North American and European* subgroups than in the Asian subgroup.

*Main AEs of special interest*

*QT prolongation*- 18.5% of patients in the quizartinib arm and 11.2% in the placebo arm experienced Torsade de points (TdP)/ECG QT Prolongation related events. The incidence increased dose dependent in the All AML pool. Two (0.8%) patients treated with quizartinib experienced cardiac arrest with recorded ventricular fibrillation, one with a fatal outcome, both in the Induction phase in the setting of severe hypokalaemia.

*Hepatic function abnormalities*- A higher proportion of quizartinib treated patients compared to placebo treated patients experienced hepatic TEAEs in the pivotal trial (34.3% vs. 27.2%), mostly being elevated aminotransferases.

## *3.5. Uncertainties and limitations about unfavourable effects*

- A higher incidence of TEAEs associated with death was reported with quizartinib compared to placebo (n=30 [11.3%] vs. n=23 [8.6%]), mainly caused by infections (mostly sepsis/septic shock). Most deaths occurred in the early induction and consolidation treatment phases (7.5% vs. 4.9% with placebo within first 60 days of initiation of study drug). Older age and worse ECOG PS were identified as factors potentially associated with the observed early deaths in both the quizartinib and placebo arm. The proposed risk minimisations against fatal infections in elderly included in SmPC section 4.4 with additional clarification in SmPC section 4.8 are acceptable.
- It is uncertain whether the reported safety profile from the clinical development can be extrapolated to clinical practice. The study population was relatively healthy with a median age of 56.0 years, mostly ECOG PS=0 or 1 (>80%), adequate renal and hepatic function and lack of significant comorbidities like uncontrolled or significant cardiovascular disease.

## 3.6. Effects Table

**Table 358. Effects Table for quizartinib in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) positive (see section 5.1). Data cut-off: 13 Aug 2021.**

| Effect | Short Description | Unit | Quizartinib | Placebo | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| ***OS*** (95%CI) | Overall survival (median) | months | 31.9 (21.0, NE) | 15.1 (13.2, 26.2) | Comparison of the median OS values is not informative since the Kaplan-Meier curves plateau around the median. The median and estimates of the median do not describe the true treatment effect. | 1 |
| | KM estimate OS | HR (95%CI) | 0.776 (0.615-0.979) | P value: 0.0324 | - In the beginning of the OS curve (up to approx. 5 months) there is a crossing of the curves in favour of placebo treatment with more early deaths (i.e., deaths within 30 days of initiation of study drug) occurring with quizartinib compared to placebo.<br>- The shape of the OS-curves that are crossing and reach a plateau imply that the proportional hazard assumption is not fulfilled. | 1 |
| | Landmark OS @ 36 mo | | 49.9% (95%CI: 43.7-55.9) | 41.1% (95%CI: 35.0-47.0) | | |
| ***EFS*** (95 % CI) | Median EFS (ITF defined as not achieving CR by the end of the Induction Phase, using a 42-day window from the start of the last cycle of induction for CR evaluation) | months | 0.03 (0.03, 0.95) | 0.71 (0.03, 3.42) | Key secondary endpoint not statistically significant.<br><br>Interpretation hampered by low event number (due to stringent definition of ITF). | 1 |
| | KM estimate EFS | HR (95%CI) | 0.916 (0.754, 1.114) | p-value: 0.2371 | There was a lack of support for other secondary endpoints; rates of CR, CR with FLT3-ITD MRD negativity, and CRc with *FLT3*-ITD MRD negativity were similar between treatment arms. | 1 |
| **Unfavourable Effects** | | | | | | |

| Effect | Short Description | Unit | Quizartinib | Placebo | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Related TEAEs** | <br><br><br><br>Neutropenia<br>QT prolongation<br>Neutrophil count decreased | % | 60.4%<br><br><br><br>17.4%<br>11.7%<br>7.9% | 36.2%<br><br><br><br>3.7%<br>3%<br>1.9% | Relatively young and fit study population.<br><br>Largest differences vs. placebo were reported for these related TEAEs. | 1 |
| **Related Grade 3/4 AEs** | Overall<br><br>Neutropenia | % | 43%<br><br>15.5% | 22.8%<br><br>3.7% | <br><br>AE ≥5 pp higher with quizartinib than placebo | 1 |
| **SAEs** | Overall (treatment-related) | % | 54% (15.5%) | 45.9% (10.8%) | Mostly infections and cytopenias. | 1 |
| **AEs associated with death** | Overall | % | 11.3% | 8.6% | Largest difference with placebo in early treatment phases.<br>Main causes of death in the early induction and consolidation treatment phases were infections. | 1 |
| **AEs leading to discontinuation** | Overall | % | 20.4% | 8.6% | Most common: infections (7.2% vs. 4.1%) and cytopenias (3.0% vs. 0). | 1 |
| **AESI-TdP/QT prolongation** | Overall | % | 18.5% | 11.2% | Mostly mild. New QTcF > 500 ms reported in 2.3% vs. 0.7%.<br>2 cardiac arrests, 1 with fatal outcome in context of severe hypokalaemia. | 1 |

*Abbreviations: ITF= induction treatment failure*
*Notes: Reference 1 = pivotal trial AC220-A-U302*

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The pivotal study in newly diagnosed *FLT3-ITD* positive AML patients met its primary endpoint. The addition of quizartinib to standard of care induction, consolidation chemotherapy followed by a continuation phase resulted in a statistically significant difference for median OS between quizartinib and placebo. Comparison of the median OS values is not informative since the Kaplan-Meier curves plateau around the median and estimates of the median do not describe the true treatment effect. The quizartinib arm had a higher plateau, with 49.9% (95%CI: 43.7-55.9) of the patients surviving at the 3-year time point, versus 41.1% (95%CI: 35.0-47.0) of the patients in the placebo arm.

The secondary endpoint (EFS per the FDA AML guidance) did not demonstrate a statistically significant difference between the quizartinib and placebo arm thus formal hierarchical testing was not continued for the secondary endpoints.

Numerically there was no difference in rates of CR, CR with FLT3-ITD MRD negativity, and CRc with FLT3-ITD MRD negativity at the end of induction were similar between treatment arms. Higher rates of CRi in the quizartinib arm compared with the placebo arm were observed, however CRi is a less stringent definition of CR as incomplete hematologic recovery is not achieved, thus the clinical

relevance of this finding is uncertain because of non-relapse mortality due to infections. An increased RFS and duration of CR (exploratory endpoints) was observed with quizartinib.

While the single pivotal trial of this study was positive based on its primary endpoint, the statistical strength of evidence was initially considered weak (p = 0.03) and not supported by a convincing impact pharmacodynamic endpoints such as CR or MRD that would demonstrate the antitumoral activity of quizartinib. Based on these concerns, the SAG-O was consulted. Following the rationale of the SAG-O, the OS benefit is considered to be established with reasonable certainty since other exploratory data support the OS effect. Lack of an effect on FLT3-ITD MRD negativity is not considered to weaken the conclusions as the surrogacy of MRD in this population is far from being established and the FLT3-ITD assay may not detect all mutations. Furthermore, although EFS rate based on failure to achieve CR at 42 days after last chemotherapy did not show convincing activity for quizartinib, the more relevant timepoint would be 56 days, which showed a more consistent effect in exploratory analyses. Furthermore, a longer duration of response was observed for quizartinib vs. placebo in exploratory analyses, indicating higher activity in the experimental arm. Overall, the effect on OS is therefore considered convincing and sufficiently supported by exploratory data.

There is a suggestion of early OS detriment, as more early deaths (i.e, deaths within 30-60 days of initiation of study drug) occurred with quizartinib compared to placebo. Main causes of death in the early induction and consolidation treatment phases were infections (mostly sepsis/septic shock). Older age and worse ECOG PS were identified as factors potentially associated with the observed early deaths. The OS subgroup analysis for age also suggests a lower benefit of quizartinib treatment in patient older than 60. It is acknowledged that this subgroup analysis was not powered to determine the B/R in elderly and age alone does not determine eligibility for intensive therapy. Nevertheless, the proposed risk minimisation measures regarding fatal infections in elderly in SmPC section 4.4 with additional clarification in SmPC section 4.8 are acceptable, also in light of the relatively young and fit studied population lacking significant comorbidities.

The safety profile of quizartinib is not negligible. Treatment with quizartinib in combination with standard induction and consolidation chemotherapy and then continued as monotherapy for up to 36 cycles leads to higher incidences of treatment-related AEs, SAEs and discontinuations/dose adjustments of study drug due to AEs compared to placebo. In particular neutropenia, and QT prolongation were reported as related events occurring more frequently with quizartinib. Dose-dependent QTc interval prolongation has been observed with quizartinib. Although most observed cases of QT prolongation were non-serious and resolved without any action taken with study drug, cardiac deaths were observed for which a causal relation with quizartinib treatment could not be completely ruled out. It seems not excluded that the impact of cardiac risks may be underestimated from the currently available trial data. Nevertheless, it is agreed that the risk is appropriately communicated in SmPC 4.4 and 4.5. Most TEAEs were manageable by monitoring, study drug interruption or dose reduction, and/or standard supportive therapies.

In the continuation phase, almost all TEAE categories increased compared to the earlier treatment phases and only few patients were able to complete the 36 cycle continuation phase. In the continuation phase no increased risk for death due to AEs has been observed, and patients seem to be able to discontinue treatment when needed.

Toxicology studies revealed that quizartinib has a significant intrinsic haematotoxicity in terms of neutropenia and lymphocytopenia, hepato- and renal toxicity. Due to the similar nature of disease symptoms and safety risks from concomitant therapies, characterisation of the safety profile in the human target population remains difficult. Current proposed risk minimisations and information in the SmPC are considered adequate.

### 3.7.2. Balance of benefits and risks

In the newly diagnosed AML add-on treatment setting, reliable and robust results are needed in order to demonstrate a clinically relevant contribution of quizartinib on top of an active backbone. The difference in primary endpoint OS between the quizartinib arm and control arm of the pivotal trial is statistically significant in favour of quizartinib. While not supported by pharmacodynamic endpoints such as CR or MRD, the effect on OS is considered to be established with reasonable certainty based on exploratory data (i.e. DOR and and EFS using the 56 -day definition).

Although treatment with quizartinib is associated with substantial toxicity, the overall benefit /risk balance of quizartinib is considered positive.

### 3.7.3. Additional considerations on the benefit-risk balance

***Scientific advice group (SAG) outcome summary***

Overall, the majority of the SAG concluded that the effect on OS was convincing and sufficiently supported by exploratory data.

Lack of an effect on FLT3-ITD MRD negativity was not considered to weaken the conclusions of study AC220-A-U302 as the surrogacy of MRD in this population is far from being established and the FLT3-ITD assay may not detect all mutations.

Furthermore, EFS rate based on failure to achieve CR at 56 days after last chemotherapy showed a more consistent effect in exploratory analyses. Furthermore, a longer duration of response was observed for quizartinib v. placebo in exploratory analyses, indicating higher activity in the experimental arm.

## *3.8. Conclusions*

The overall benefit /risk balance of Vanflyta (quizartinib) is considered to be positive.

# 4. Recommendations

***Similarity with authorised orphan medicinal products***

The CHMP by Consensus is of the opinion that Vanflyta (quizartinib) is not similar to Dacogen, Rydapt, Mylotarg, Vyxeos Liposomal, Xospata, Daurismo, and Tibsovo within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vanflyta is favourable in the following indication(s):

*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 acute myeloid leukaemia (AML) that is FLT3-ITD positive*.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

***Other conditions and requirements of the marketing authorisation***

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **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 healthcare professionals 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 Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals 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 co-medications that are known to cause QT prolongation
- Frequency of ECG monitoring
- Serum electrolyte monitoring and management

**The patient information pack:**

- Package leaflet
- Patient card

The Patient card will contain the following key elements:

- A warning message for healthcare professionals that Vanflyta treatment may increase the risk of serious ADRs related to QTc interval prolongation
- Important information for healthcare professionals 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 a healthcare professional
- Contact details of the Vanflyta prescriber

These conditions fully reflect the advice received from the PRAC.

***New Active Substance Status***

Based on the CHMP review of the available data, the CHMP considers that quizartinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.