A Phase 1/2, Multicenter, Dose-Escalating Study To Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy Of Quizartinib Administered in Combination with Re-Induction Chemotherapy, and as a Single-Agent Continuation Therapy, in Pediatric Relapsed/Refractory AML Subjects Aged 1 Month to <18 Years (and Young Adults Aged up to 21 Years) with FLT3-ITD mutations

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This study has been transitioned to CTIS with ID 2023-510009-16-00 check the CTIS register for the current data. Primary Objectives:• Phase 1 Only: To determine the recommended Phase 2 dose(RP2D) of quizartinib, in combination with chemotherapy,...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON52604

Source
ToetsingOnline

Brief title
AC220-A-U202

Condition

- Leukaemias

Synonym
cancer of the bone marrow, leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Daiichi Pharmaceutical
Source(s) of monetary or material Support: Daiichi Sankyo Inc.

Intervention

Keyword: NA

Outcome measures

Primary outcome

Primary Endpoints:

Safety:

* The safety profile of quizartinib administered in combination with reinduction

chemotherapy for up to 2 cycles, with optional consolidation

chemotherapy, and as a single-agent maintenance therapy over <=12 cycles.

* Phase 1 only: Number of DLTs in dose cohorts in Re-Induction Cycle 1.

Efficacy (i.e., the primary outcome measure):

* CRc rate after completion of up to 2 Re-Induction Cycles.

Pharmacokinetic:

* Estimates of AUC, apparent clearance (CL/F), and apparent volume of

distribution (Vd) for quizartinib and AC886 by the use of

PopPK modeling or other applicable methods.

Secondary outcome

Secondary Endpoints for Phases 1 and 2:

Efficacy (i.e., the secondary outcome measures):

* Duration of CR.

* Duration of CRc (i.e., from first documented CRc until documented

relapse).

* CR rate after completion of Re-Induction Cycle 1.

* CR rate after completion of up to 2 Re-Induction Cycles.

* CRc rate after completion of Re-Induction Cycle 1.

* Time to relapse, the rate of relapse after 1, 2 and 3 years, and the

cumulative incidence of relapse at the end of the study.

* OS, defined as the time from the start of Re-Induction

therapy until death from any cause.

* EFS defined as the time from the start of Re-Induction

therapy until the earliest date of the following:

* Refractory disease (or treatment failure) at the end of Re-Induction.

* Relapse after CR or CRi.

Death from any cause at any time during the study.

* Number of subjects proceeding to high-dose conditioning therapy/HSCT

(including transplant-related mortality).

Pharmacodynamic:

* Inhibition of FLT3-ITD and FLT3-wild-type autophosphorylation

activity in an ex-vivo PIA during Re-Induction, Maintenance, and at the

time of relapse.

* FLT3-ITD to FLT3-wild-type allelic ratio at Screening, during Re-Induction, and at the time of relapse.

* Mutations present in blasts (e.g., in the kinase and juxtamembrane domains of FLT3-ITD and other mutations known to be associated with AML) at Screening and at the time of refractory disease or relapse.

Biomarker:

* MRD for subjects who are in CR or CRi at Screening, end of Re-Induction Cycle 1, end of Re-Induction Cycle 2, and at the time of relapse by next generation sequencing.

Others:

* Acceptability including palatability of quizartinib formulations.

Exploratory Endpoints:

* The relationship between quizartinib and AC886 exposure and clinical response.

Study description

Background summary

The main purpose of this study is to gather information about an investigational drug, called quizartinib that may help to treat your disease. An investigational drug is a medication that is still being studied and has not yet been approved for use in your country (by the European Medicine Agency (EMA) in Europe) Quizartinib was designed to work against cancer cells that have FLT3-ITD. It is currently being tested in other studies to see if it works in adults with this type of AML.
This study has been granted approval by an Institutional Review Board/Ethics Committee, an independent group of experts who ensure your rights, safety and well-being are protected. Children and young adults from 1 month old up to 21

years old may be part of this study. We expect that about 52 patients with AML may take part in this research study, which is being conducted at approximately 35 study sites around the world (in the United States and Europe).
You may not participate in this study if:
• you are an employee of the study site;
• You are an immediate family member of an employee of the study staff. An immediate family member means a spouse, parent, child or sibling. Family members can be biological or legally adopted, or
• You are an employee of Daiichi Sankyo, Inc., the sponsor of this study.
There may be other reasons that you are not able to participate. The Study Doctor will discuss these reasons with you.
Throughout the rest of this consent form, Daiichi Sankyo, Inc. will be referred to as the *Sponsor*. Daiichi Sankyo, Inc. is a pharmaceutical (drug) company and is responsible for organizing and funding this study including paying your research team to perform the study.
Your study doctor and research team will ask you many questions about your current and past health. Please be honest in answering these questions (including past and present medications), or else it may not be safe for you to be in this study. If you agree to take part in this study, you must first read and sign this consent form. You will get a signed copy of this consent form for your records.

Study objective

This study has been transitioned to CTIS with ID 2023-510009-16-00 check the CTIS register for the current data.

Primary Objectives:
• Phase 1 Only: To determine the recommended Phase 2 dose (RP2D) of quizartinib, in combination with chemotherapy, for subjects in the older (>=1 year old to <=21 years old) and younger (>=1 month old to <12 months old) age groups.
• To determine the composite complete remission (CRc) rate (i.e., complete remission [CR] + CR with incomplete recovery [CRi]) after completion of up to 2 Re-Induction Cycles.
• To determine the safety and cumulative toxicity of quizartinib administered in combination with re-induction therapy for up to 2 cycles, with optional consolidation chemotherapy, and as a single-agent maintenance therapy over <=12 cycles.
• To determine estimates of individual PK parameters of quizartinib and AC886 (metabolite of quizartinib).
Secondary Objectives:
• To determine the CR rate after completion of up to 2 Re-Induction Cycles.
• To determine the durations of CRc and CR.
• To assess the time to relapse, the rate of relapse after 1, 2 and 3 years, and the cumulative incidence of relapse at the end of study (when the

last subject enrolled has had 3 years of follow-up from the date of enrollment).
• To determine the rates of CR and CRc after completion of Re-Induction Cycle 1.
• To assess overall survival (OS) and event-free survival (EFS) at 1, 2, and 3 years.
• To assess the number of subjects proceeding to high-dose conditioning therapy/ hematopoietic stem cell transplantation (HSCT).
• To assess the activity of quizartinib on FLT3-ITD and FLT3-wildtype autophosphorylation activity by an ex-vivo plasma inhibitory activity assay (PIA) during Re-Induction, Maintenance, and at the time of relapse.
• To assess the FLT3-ITD/FLT3-wild-type allelic ratio at Screening, during Re-Induction, and at the time of relapse.
• To evaluate somatic mutations present in blasts (e.g., in the kinase and juxtamembrane domains of FLT3-ITD and other mutations known to be associated with AML) at Screening and at the time of refractory disease or relapse.

• To assess rate of CRc (CR, CrRi) without minimal residual disease (MRD) using next generation sequencing
• To assess the acceptability including palatability of quizartinib formulations.
Exploratory Objectives:
• To explore the relationship between quizartinib (and AC886) exposure and clinical response

Study design

This is a global open-label, multi-center, single arm, Phase 1/2 study to evaluate the
safety, PK, PD, and efficacy of quizartinib administered in combination with fludarabine / cytarabine (FLA) + liposomal daunorubicin (DNX) (Re-Induction Cycle 1) and FLA (Re-Induction Cycle 2) chemotherapy for re-induction, with optional consolidation chemotherapy, and as a single agent maintenance therapy (after optional, but strongly encouraged, HSCT per standard of care), in pediatric subjects with R/R FLT3-ITD (+) AML aged >=1 month old to <18 years old (and young adults up to 21 years old) with FLT3-ITD mutations.
Dose-Escalation/De-escalation and Dose-Expansion:

Phase 1 (Dose Escalation/De-escalation):
In Phase 1, cohorts of up to 9 subjects per dose-level will be enrolled to determine the recommended Phase 2 dose (RP2D) of quizartinib in the older age group first. In Re-Induction Cycle 1, subjects will be administered the FLA + DNX regimen on Days 1 to 5, followed by quizartinib on Days 6 to 28. Dose-limiting toxicities (DLTs) will be assessed during Re-Induction Cycle 1.

In Re-Induction Cycle 2, subjects will be administered the FLA regimen on Days 1 to 5, followed by quizartinib on Days 6 to 28.
Following Re-Induction, subjects should be thoroughly evaluated for eligibility to undergo allogeneic HSCT according to standard of care. Subjects may receive optional consolidation therapy if an allogeneic HSCT is not available immediately. Subjects in remission after HSCT and subjects who do not undergo HSCT, but who achieve at least a partial remission (PR) or morphologie leukemia-free state (MLFS) after Re-
Induction, will be treated with up to 12 continuous 28-day cycles of quizartinib maintenance therapy.
The safety and PK data for the older age group will be used, along with population PK (PopPK) modeling (if available) to determine the RP2D for the older group and the starting dose of quizartinib for the younger age group.
Once the recommended Phase 1 starting dose for the younger age group has been determined from the data collected in the older age group, the younger age group will be enrolled using a Rolling 6 dose escalation/de-escalation design to determine the RP2D for younger subjects.
In the older age group, PK data is required from at least 9 subjects for a dose to
be considered as the RP2D. Additional PK data will be collected in Phase 2 to confirm the validity of the model established in Phase 1.
Older Age Group (>=1 Year Old to <=21 Years Old):
In the older age group, up to 9 subjects will be enrolled at Dose Level 1: 40 mg/m2 once daily for a BSA <1.5 m2 and a flat dose of 60 mg once daily for a BSA >=1.5 m2. Enrollment will be suspended once 9 subjects have been enrolled or >= 3 DLTs have been observed. Additional dose cohorts may be enrolled based on the observed DLTs and the PK data collected for the first cohort, as indicated in the dose escalation/de-escalation design. Following completion of enrollment for subjects at Dose Level 1, the doses of quizartinib to be used at other Dose Levels will be determined based upon a review of the available PK data. A PopPK model will also be used, if available. Once the RP2D has been determined for the older age group, enrollment in the Phase 2 dose-expansion portion of the study will be initiated for this age group. The Phase 2 expansion cohort can enroll the older age group before the Phase 1 dose escalation/de-escalation study has been completed in the younger age group.
Younger Age Group (>=1 Month Old to <12 Months Old):
Three subjects in the younger age group will be enrolled and treated at the quizartinib starting dose determined after the full data review has been completed for the older age group. Additional subjects and dose cohorts may be enrolled, as indicated in the Rolling 6 dose escalation/de-escalation design. Once the RP2D has been determined for the younger age group, enrollment in the Phase 2 dose-expansion portion of the study will be initiated for this age group. However, recognizing the difficulties in enrolling in this younger age group, the study may be closed by the sponsor prior to completing enrollment in this age group.
Phase 2 (Dose-Expansion):

Subjects enrolled in Phase 2 will receive the RP2D of quizartinib for their respective age group, administered in combination with FLA + DNX (ReInduction Cycle 1) and FLA (Re-Induction Cycle 2) chemotherapies for Re-Induction.
Following Re-Induction, subjects should be thoroughly evaluated for eligibility to undergo allogeneic HSCT. Subjects may receive optional consolidation therapy if an allogeneic HSCT is not available immediately. Subjects in remission after HSCT and subjects who are not eligible for HSCT, but who achieve at least (PR) or MLFS after Re-Induction will be treated with up to 12 continuous 28-day cycles of quizartinib maintenance therapy, given at the same dose as used during Re-Induction.
Study Treatment:
Re-Induction (2 Cycles):
Re-Induction Cycle 1 (FLA + DNX + Quizartinib)
Subjects will be administered the following medications during Re-Induction Cycle 1:
• Intrathecal (IT) triple chemotherapy prophylaxis may be given within 1 week prior to beginning Re-Induction Cycle 1. It is recommended that IT prophylaxis be administered at least 24 hours prior to the start of Re-Induction Cycle 1, Day 1 chemotherapy. Cycle 1, Day 1 is defined as the start date of the fludarabine, cytarabine, and daunorubicin chemotherapy (not IT chemotherapy).
Investigators will administer IT cytarabine, methotrexate, and either prednisolone or hydrocortisone. Doses will be based on the subject*s age and standard practice at each site.
Additional IT chemotherapy may be administered at the investigator*s discretion for subjects with central nervous system (CNS)2 disease during Re-Induction. For CNS3 disease, IT chemotherapy will be administered until the cerebrospinal fluid (CSF) is clear of blasts, then 1 additional dose of IT chemotherapy will be administered
• Fludarabine: 30 mg/m2/ day IV infusion given over 30 minutes on Days 1 through 5.
• Cytarabine: 2000 mg/m2/day IV infusion given over 3 hours on Days 1 through 5 (begin 4 hours after the start of fludarabine).
• Liposomal daunorubicin: 60 mg/m2/day IV infusion given over 120 minutes on Days 1, 3 and 5 (administer after fludarabine).
• Quizartinib: orally once daily starting on Day 6 and continuing through Day 28. If quizartinib is interrupted, missed doses will not be made up.
* Phase 1: dose will be assigned at study entry.
* Phase 2: subjects will be treated at the RP2D.
• IT triple chemotherapy prophylaxis will also be given after Re-Induction Cycle 1 Day 28, but before the start of Re-Induction Cycle 2.
Investigators will administer IT cytarabine, methotrexate, and either prednisolone or hydrocortisone. Doses will be based on the subject*s age and standard practice at each site.
Additional IT chemotherapy may be administered at the Investigator*s discretion for subjects with CNS2 disease during Re-Induction. For CNS3

disease, IT chemotherapy will be administered until the CSF is clear of blasts,then 1 additional dose of IT chemotherapy will be administered.
A bone marrow aspirate will be collected upon blood count recovery or on Day 29 (±1 Day), whichever occurs first. If the marrow is hypoplastic or if response cannot be determined, then collect weekly complete blood counts with differentials (CBC) until count recovery or Day 56, whichever occurs first. A repeat marrow aspirate should be obtained upon count recovery up to Day 56. If counts have not recovered by Day 56, perform the repeat marrow aspiration and collect a CBC on Day 56 (±3 Days).

Re-Induction Cycle 2 (FLA + Quizartinib):
At the Investigator*s discretion, to allow for blood counts to recover or other reasons, the second Re-Induction cycle may start up to 70 days after Day 1 of the first Re-Induction cycle. Subjects are eligible to receive Re-Induction Cycle

Intervention

NA

Study burden and risks

A: Medicine or other interactions
There are risks associated with taking part in any research study. One risk is that subject may get a drug or dose of a drug that does not help treat his disease, or that makes his condition worse. Another risk is that the drugs can cause side effects which may be mild and reversible but that can be very severe, long lasting and life threatening. Side effects can even cause death. Subject will be watched carefully for side effects. For investigational drugs, including quizartinib, there may be side effects that we do not know about at this time. During the study, subject will be told about newly discovered side effects or important findings which may affect his health or his willingness to stay on the study. Subject may be asked to read and sign a new Informed Consent Form that shows that Subject have been given new information relating to this study.
Since many drugs used to treat leukemia make fast-growing cancer cells slow down or die, they can also make fast-growing normal cells slow down or die. This includes the blood cells that help fight infection (white blood cells), the blood cells that help blood clot (platelets), and the blood cells that carry oxygen (red blood cells). While subject is taking part in this study, his blood cell counts will be checked closely, and subject may need blood and/or platelet transfusions if subject have anemia (not have enough red blood cells) or have a low platelet count or are bleeding.
Subject need to tell the study doctor or a study staff immediately if subject have any side effects. In particular, watch for any of the following:
• A fever of 38.1°C or above. This could be a sign of an infection. If subject

have a low white blood cell count, an infection with fever could be serious, life threatening or fatal. subject may have to take drugs to fight infections and/or go into the hospital.
• Any kind of infection.
• Tiredness or shortness of breath. This could be a sign of anemia. If anemia gets severe, subject may need a red blood cell transfusion.
• If subject bruise or bleed easily or do not stop bleeding when you get hurt. This could be a sign that his platelet count is low. A low platelet count could be serious or life threatening. subject may need a platelet transfusion.
• Any kind of irregular heartbeat, heart pounding, fainting or blackouts. This could be a sign that the study treatment, and/or other medications, could be interfering with the way your heart works.
• Any rashes or skin ulcers. These can have severe complications, so the doctor may need to treat these right away.
If subject have side effects, the doctor may also choose to stop the study treatments until he get better, lower the dose of quizartinib or permanently stop the study treatments.
B: Side effects of the study medicinal product
Find detailed information in Appendix D of the informed consent..
C: Contraception, pregnancy and breast-feeding
The drugs used in this study may affect an unborn baby or a breastfeeding infant. If subject are pregnant or become pregnant, the study medication may cause birth defects or death to the unborn baby. Breast-feeding could expose the baby to study medication. If you are a pregnant woman, nursing or intend to nurse the baby, subject cannot take part in this study.
Find detailed information in Appendix D of the informed consent.
D: Risks associated with the evaluation procedures specific to the study
Find detailed information in Appendix D of the informed consent..

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

1. Diagnosis of AML according to the World Health Organization (WHO) 2008 classification with >=5% blasts in bone marrow, with or without extramedullary disease.
2. Subjects must be in first relapse or refractory to first-line high-dose chemotherapy with no more than 1 attempt (1 to 2 cycles of induction chemotherapy) at remission induction. Prior HSCT is permitted.
3. Presence of the FLT3-ITD activating mutation in bone marrow or peripheral blood that is confirmed by central testing. The results of FLT3 ITD testing must be obtained prior to the first dose of quizartinib (Re-Induction Cycle 1, Day 6). Subjects may be enrolled and begin treatment with the systemic protocol therapy pending the result of the FLT3 ITD testing; however, subjects with a negative central and local FLT3 ITD test who are enrolled and have begun systemic protocol treatment will be discontinued from the study. Subjects may also be enrolled and begin treatment based upon the results of a local FLT3-ITD laboratory test (performed on or after the date of diagnosis of R/R disease); however, a sample must be sent to the central laboratory for confirmation. Subjects with a negative central FLT3-ITD test who are enrolled and have begun treatment based upon results of a FLT3-ITD test conducted at a local laboratory may continue on the study at the investigator*s discretion after discussion with the medical monitor.

4. Subjects must be between 1 month and <=21 years of age at the time the ICF is signed.
5. Karnofsky performance status score of >50% for subjects >16 years of age, and a Lansky performance status score of >50% for subjects <=16 years of age.

6. Subjects must have fully recovered from the acute clinically significant toxicity effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to Re-Induction Cycle 1, Day 1:
a. Myelosuppressive chemotherapy:
* For subjects who relapse while they are receiving cytotoxic therapy, at least 21 days must have elapsed since the completion of cytotoxic therapy.
* Cytoreduction with hydroxyurea can be initiated and continued for up to 1 day prior to the start of systemic protocol therapy. Subjects may also receive low dose cytarabine (100 mg/m2/dose once daily for up to 5 days) for cytoreduction and completed up to 1 day prior to the start of systemic protocol therapy.
* Subjects who have received other FLT3 inhibitors (eg, lestaurtinib, sorafenib), with the exception of quizartinib, are eligible for this study.
b. Hematopoietic growth factors: At least 3 days since the completion of therapy with a growth factor.
c. Biologic (anti-neoplastic agent): At least 7 days since the completion of therapy with a biologic agent. However, for agents that have known adverse events (AEs) occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs are known to occur. The duration of this interval must be discussed with the medical monitor.
d. >=14 days for local external radiation therapy (XRT) for CNS chloromas.
e. >=90 days must have elapsed if prior total body radiation (TBI) or craniospinal XRT occurred.
f. At least 90 days must have elapsed since HSCT. For subjects with a history of graft versus host disease (GVHD), immunosuppressive therapy must be stable for >=2 weeks in subjects with a history of <= Grade 2 GVHD and for >=4 weeks in subjects with a history of Grade 3/4 GVHD.
g. Investigational drug/device: at least 30 days or 5 half-lives since the completion of therapy, whichever is longer.
7. Adequate renal and hepatic functions as indicated by the following laboratory values:
a. Serum creatinine concentration <=1.5 × institutional upper limit of normal (ULN) based on the age and sex, or creatinine clearance (CrCl) >0.84 mL/s (as measured preferably by a nuclear glomerular filtration rate scan, timed urine collection for CrCl, or calculated by the Schwartz formula [for subjects <18 years] or Cockcroft-Gault [for subjects >=18 years] and normalized to a BSA of 1.73m2).
b. Total bilirubin <1.5 × ULN for age or normal conjugated bilirubin (<5 × ULN if related to leukemic involvement).
c. Alanine aminotransferase (ALT) <5 × ULN (<10 × ULN if related to

leukemic involvement).
8. Left Ventricular (LV) fractional shortening of >=29% by echocardiogram, OR a left ventricular ejection fraction (LVEF) of >=50% by echocardiogram or radionuclide angiogram.
9. Female subjects of childbearing potential must have a negative urine or serum pregnancy test confirmed within 2 weeks prior to enrollment. Female subjects of childbearing potential must be willing to use highly effective birth control upon enrollment, during the treatment period, and for 6 months following the last dose of quizartinib, etoposide, fludarabine, methotrexate or cytarabine, whichever is later. Female subjects are considered of childbearing potential following menarche, unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy). Female subjects must not donate or retrieve for their own use ova from the time of Screening and throughout the treatment period, and for at least 6 months following the last dose of quizartinib, etoposide, fludarabine, methotrexate, or cytarabine, whichever is later.

10. Female subjects with infants must agree not to breastfeed their infants while on this study.
11. Male subjects must be surgically sterile or willing to use highly effective birth control during the treatment period, and for 6 months following the last dose of quizartinib, etoposide, fludarabine, methotrexate, or cytarabine, whichever is later. Male subjects must not freeze or donate sperm starting at Screening and throughout the treatment period, and at least 6 months following the last dose of quizartinib, etoposide, fludarabine, methotrexate or cytarabine, whichever is later.
12. Subjects and/or their parents or legal guardians must be capable of understanding the investigational nature, potential risks, and benefits of the study. All subjects and/or their parents or legal guardians must sign a written ICF prior to the start of any study-specific qualification procedures. Age appropriate assent will be obtained per institutional guidelines.

Inclusion Criteria*Continuation:
Subjects must satisfy all of the following criteria to receive continuation therapy:
1. Must have achieved at least a PR in Re-Induction or continue to be in remission as defined by local practice standards after HSCT.
2. Subject's absolute neutrophil count (ANC) must be >=0.5 × 109/L and platelets (PLTs) must be >=50 × 109/L at the time of initiating continuation therapy.
3. All Grade 3 and 4 toxicities have resolved to Grade 2 or less.
4. Able to begin Continuation Phase within 70 days of the previous Re-Induction Cycle Day 1 (for those who do not undergo HSCT) or 30*180 days after allogeneic HSCT.
5. For subjects with a history of GVHD, immunosuppressive therapy must be stable for >=2 weeks in subjects with a history of <= Grade 2 GVHD and for >=4

weeks in subjects with a history of Grade 3/4 GVHD.

Exclusion criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:
1. Diagnosis of isolated CNS relapse (CNS2/3 disease is allowed if treated with additional IT chemotherapy).
2. Diagnosis of acute promyelocytic leukemia (APL), juvenile myelomonocytic leukemia (JMML), French-American-British (FAB) classification M3 or WHO classification of APL with translocation, t(15;17)(q22;q12), or myeloid proliferations related to Down syndrome.
3. Uncontrolled or significant cardiovascular disease, including:
a. Diagnosed or suspected congenital long QT syndrome.
b. History of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de Pointes [TdP]); any history of arrhythmia will be discussed with the medical monitor prior to subject*s entry into the study.
c. QT interval corrected >450 ms:
* QTc interval corrected with Bazett*s formula (QTcB) for subjects < 6 years of age at the time of enrollment.
* QTc interval corrected with Fridericia*s formula (QTcF) for subjects >= 6 years of age at the time of enrollment.
d. History of uncontrolled angina pectoris or myocardial infarction within 6 months.
e. History of second (Mobitz II) or third degree heart block (subjects with pacemakers are eligible if they have no history of fainting or clinically relevant arrhythmias while using the pacemaker).
f. Heart rate <50 beats/minute on screeening electrocardiogram (ECG).
g. Uncontrolled hypertension (i.e., systolic blood pressure and /or diastolic blood pressure that is, on repeated measurement, at or above the 95th percentile for sex, age, and height).
h. History of complete left bundle branch block.
i. History of New York Heart Association Class 3 or 4 heart failure.
4. Subjects will be excluded if they have a systemic fungal, bacterial, viral or other infection that is exhibiting ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment. The subject needs to be off vasopressors and have negative blood cultures for at least 48 hours prior to the start of systemic protocol therapy..
5. Known active clinically relevant liver disease (e.g., active hepatitis B or active hepatitis C).
6. Known history of human immunodeficiency virus (HIV).
7. History of hypersensitivity to any of the study medications or their

excipients.
8. Subject is receiving or is anticipated to receive concomitant chemotherapy, radiation, or immunotherapy other than as specified in the protocol.
9. Any significant concurrent disease, illness, psychiatric disorder or social issue that would compromise subject safety or compliance, interfere with consent/assent, study participation, follow up, or interpretation of study results.
10. Currently participating in other investigational interventional procedures (does not include observational procedures or long-term follow-up for previous interventional studies).
11. Otherwise considered inappropriate for the study by the Investigator

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-04-2020
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N-[(5-tert-butyl)isoxazol-3-yl]({4-[7-(2-morpholin-4-ylethoxy)(4-)
Generic name:	Quizartinib dihydrochloride

Ethics review

Approved WMO Date:	26-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-01-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	15-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-510009-16-00
EudraCT	EUCTR2016-002919-18-NL
CCMO	NL65309.078.18