CHIP-AML22/Quizartinib: A phase II, single arm, open label, study on the safety, efficacy, pharmacokinetics and pharmacodynamics of quizartinib in combination with chemotherapy and as single-agent after high dose therapy in newly diagnosed pediatric FLT3-ITD positive and NPM1 wild type AML patients.
(A linked-trial of the CHIP-AML22/Master protocol by the NOPHO-DB-SHIP consortium)

Published: 16-01-2023
Last updated: 08-02-2025

This study has been transitioned to CTIS with ID 2023-505000-27-01 check the CTIS register for the current data. To investigate the safety and efficacy of quizartinib in children and adolescents with newly diagnosed FLT3-ITD positive AML with normal...

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

Summary

ID

NL-OMON53485

Source
ToetsingOnline

Brief title
CHIP-AML22/Quizartinib

Condition

- Leukaemias

Synonym
Acute Myeloid Leukemia (AML), blood cancer

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor Kinderoncologie
Source(s) of monetary or material Support: Daiichi Pharmaceutical,Daiichi Sankyo;Inc

Intervention

Keyword: Acute Myeloid Leukemia (AML), Adolescents, Children, Initial / Newly diagnosed

Outcome measures

Primary outcome

Primary Objective (efficacy):

To assess the clinical benefit of quizartinib as measured by the MRD-negativity rate (defined as <0.1% using flow-cytometry) after up to two courses of conventional chemotherapy plus quizartinib, in newly diagnosed pediatric de novo AML with a FLT3-ITD and without a concurrent NPM1 mutation.

Endpoint: The percentage of patients with MRD levels <0.1% (MRD negativity) after up to 2 courses of induction chemotherapy plus quizartinib, as measured in the bone marrow using multiparameter flow cytometry (MFCM) before start of consolidation therapy, in the evaluable population for response.

Primary Objective (safety):

During the safety run-in, the co-primary objective will be to determine the Recommended Phase 2 Dose (RP2D) of quizartinib for newly diagnosed pediatric AML patients with a FLT3-ITD and without a concurrent NPM1 mutation, based on the safety and tolerability profile of quizartinib observed at dose levels.

Endpoint: Incidence of Dose-Limiting Toxicities (DLTs) assessed during Induction course 1 and 2 (until day 56 of each course) for the DLTs evaluable patients.

Secondary outcome

Secundary Objectives:

- Efficacy

To explore the added anti-leukemic effect of quizartinib based on other measures of response, as defined as secondary endpoints, including morphological overall response rate (ORR), MRD by MFCM, event free survival (EFS), overall survival (OS), disease free survival (DFS), duration of response, cumulative incidence of relapse (CIR), number and percentage of patients actually being treated with hematopoietic stem cell transplantation (HSCT), number of patients starting and completing continuation treatment post-HSCT.

Endpoints:

Other measurements of treatment response:

- Proportion of subjects with a complete remission (CR) rate without evidence of MRD after 1 and after 2 induction courses (including CR and remission with

incomplete blood count or platelet recovery)

- Bone marrow blast counts by morphology and MFCM after induction course 1 and induction course 2 and before allo-SCT; CRc (CR and CRi) and morphologic leukemia-free state (MLFS) rates after induction course 1 and 2; MRD negativity (<0.1%), after course 1 and 2 and before allo-HSCT; Absolute MRD levels after induction course 1 and 2, and before allo-HSCT;
- Bone marrow blast counts by morphology and MFCM at other timepoints (The disease assessments at other time-points (e.g., After consolidation course 2, 3, before/during continuation treatment)
- Event-free survival (EFS) probability, at least at 1, 2 and 3 years

(Time from the start of treatment until an event, defined as 1) not achieving CR/CRi because of early death or with refractory disease (ie: treatment failure); 2) morphological relapse; 3) second malignancy; 4) death in complete remission due to any cause.

- Overall survival (OS) probability, at least at 1, 2 and 3 years

(Time from the start of treatment until death, due to any cause.)

- Disease free survival (DFS) probability, at least at 1, 2 and 3 years

(Time from CR/CRi until morphological relapse or death due to any cause)

- Duration of complete response

(Time from CR until morphological relapse or death due to any cause)

- Cumulative incidence of morphological relapse (CIR) probability, at least at 1,2 and 3 years
- Number and percentage of patients proceeding to HSCT
- Number of patients starting and completing continuation treatment post-HSCT

- Safety

To describe the safety and tolerability of combining quizartinib with conventional treatment and quizartinib given as single-agent after HSCT.

Endpoints:

- Adverse events (AEs), as characterized by type, frequency, severity (as graded using CTCAE, v5.0).
- Laboratory abnormalities (including time to recovery of ANC and PLT), electrocardiograms and changes in vital signs as characterized by type, frequency, severity and timing will be tabulated, and reported as AEs when considered clinically significant by the investigator.
- The cumulative incidence of non-relapse mortality, defined as the cumulative probability of non-relapse mortality, with time calculated between start of study treatment and death due to other causes than relapsed or refractory leukemia, accounting for competing events.

- Pharmacokinetics (PK)

To characterize the pharmacokinetics of quizartinib and its main circulating active metabolite AC886

Endpoint:

Population PK analysis to estimate AUC (tau) and Cmax for quizartinib and AC886, clearance (CL/F) and volume of distribution (Vss/F) for quizartinib.

- Palatability of quizartinib formulations

To assess the palatability of quizartinib formulations.

Endpoint:

Patients and/or parents or legal guardians will answer using a Hedonic scale

for the taste and ability to swallow the medicine.

Study description

Background summary

In some AML patients, a genetic change called *FLT3-ITD* is present in the AML cells, while the so-called NPM1 gene is normal. FLT3-ITD is a protein in leukemia cells that allows AML cells to grow and survive. Patients with this change in AML cells combined with a normal NPM1 generally have a poorer prognosis.
Quizartinib is a drug that can inhibit the growth of AML cells. The drug quizartinib is therefore not chemotherapy but an FLT3 protein inhibitor. Quizartinib is not yet approved for use.
The drug quizartinib has already been studied in adults with relapsed AML. In this case, quizartinib was given alone or in combination with chemotherapy. A better response was seen compared to standard chemotherapy. The drug quizartinib is also being studied in children with relapsed AML. No results are known yet.
In this study, the drug quizartinib is combined with standard chemotherapy as given according to the CHIP-AML22 protocol (CHIP-AML22/Master).

Study objective

This study has been transitioned to CTIS with ID 2023-505000-27-01 check the CTIS register for the current data.

To investigate the safety and efficacy of quizartinib in children and adolescents with newly diagnosed FLT3-ITD positive AML with normal NPM1.

Study design

This is a single-arm, open label, multinational, multicenter phase II study, with a safety run-in.

This study is linked to the CHIP-AML22 Master protocol.

Intervention

Induction chemotherapy will consist of MEC (mitoxantrone, etoposide, cytarabine) plus quizartinib as first induction course, followed by ADE (cytarabine, daunorubicin, etoposide) plus quizartinib as second induction course. All patients in CR1 (including CRi) after these 2 induction courses will receive HAM (high-dose cytarabine, mitoxantrone) plus quizartinib as 3rd course (consolidation course 1). These 3 courses together are standard of care chemotherapy. The intervention that is studied in this protocol consists of adding quizartinib for 14 days to each course of chemotherapy.
Patients will subsequently be transplanted as per standard of care, with a matched allogeneic donor (allo-SCT). After an allo-SCT, patients will receive continuation treatment with quizartinib for six 28-day courses, which is part of the intervention in this trial, except in patients who were MRD-negative (defined as leukemic cells <0.1% in BM) after induction course 1 (in BM1) and who remained MRD-negative afterwards. Patients with >5% leukemic cells in bone marrow after induction course 2 are considered to have resistant disease (RD), and will go off treatment of this trial but will continue to be followed for survival and will be treated according to the CHIP-AML22 master protocol.

If an allo-SCT is not done for whatever reason (lack of suitable donor, lack of informed consent, too poor clinical condition), such (rare) patients will receive up to two more courses of chemotherapy, consisting of HA3E (high-dose cytarabine, etoposide) plus quizartinib and FLA (fludarabine, cytarabine) plus quizartinib, unless they are transplanted before these courses after all. Such patients will also receive continuation treatment with quizartinib as described above, except in patients who were MRD-negative (defined as leukemic cells <0.1% in BM) after induction course 1 (in BM1) and who remained MRD-negative afterwards.

Study burden and risks

The extra burden compared to standard treatment consists of:
- ECGs, maximum of 49 x 3 ECGs
- Extra blood sampling, maximum of 38x (but will be combined as much as possible with regular blood sampling)
- Pregancy tests, maximum of 20x (but will be combined as much as possible with regular blood sampling)
- Extra bone marrow aspirates maximum of 3x (After SCT)
- Extra questionnaires: maximum of 3x
- Completing diary: maximally for 238 days

Risks:
The following side effects were reported by mostly older patients with AML who

were taking similar doses of quizartinib to those used in this study. Some of these side effects were serious, some required hospitalization, were life threatening, or were fatal.

QT interval prolongation/Torsade de pointes
Quizartinib is known to cause changes in electrical activity in the heart called QT interval prolongation. It may cause irregularities of the heartbeat, called arrhythmia. These can be life-threatening or fatal. A type of heart arrhythmia which can be due to prolonged QT interval is Torsade de pointes; it is serious and can be life threatening or can even cause cardiac arrest (or sudden loss of heart function) or sudden death.
In a large quizartinib study in AML patients who received prior AML therapy, 3.3% of patients (8 out of 241 patients) had a degree of QT prolongation that was clinically important. Among 724 AML patients treated with quizartinib alone, there was 1 event of Torsade de pointes (0.1%) and 1 event of cardiac arrest (0.1%) where arrhythmia cannot be excluded.
Additionally, in an ongoing study in adults where quizartinib is given in combination with chemotherapy (QuANTUM-First, AC220-A-U302), among an estimated 265 patients who received quizartinib therapy, 2 adult patients experienced cardiac arrest (heart stopping beating) (1 fatal and 1 non-fatal) with a serious arrhythmia known as ventricular fibrillation (an irregular, serious and potentially fatal very rapid heartbeats) recorded on ECG, and 1 patient died in sleep with no specific cause identified.

The risk of QT prolongation is higher for patients:
- With a condition known as long QT syndrome. Quizartinib should not be used in subjects with long QT syndrome.
- With low blood minerals such as potassium and magnesium
- With pre-existing heart disease or previous history of arrhythmia (irregular heartbeat)

Taking other medications or supplements that are known to cause QT interval prolongation may increase your child*s risk of QTc prolongation, so the study doctor may advise that your child not take these medicines at the same time as quizartinib.
In addition, some medications may increase the levels of study drug in the blood; and require a dose decrease of the study drug by the study doctor.
Because of these risks, the study doctor will do blood tests and ECGs before your child starts and during treatment with the study drug. In addition, the study doctor may tell you to decrease your child*s dose, temporarily stop, or permanently stop taking the study drug if they develop side effects during treatment with the study drug.
It is important to contact the study doctor immediately if your child experiences any of the following:
- Any kind of irregular heartbeat, dizziness, light-headedness, fainting or blackouts. This could be a sign that the study drug, and/or other medications, could be interfering with the way your child*s heart works.

- Diarrhea and/or vomiting or unable to eat or drink fluids in usual amounts. These can lead to abnormal levels of minerals, such as potassium and magnesium, in your child*s blood, which can put your child at a risk of developing abnormal heart rhythm.
It is important that your child does not take any other medications while taking the study drug unless your child*s study doctor tells you it is okay to do so.

Bone marrow suppression
As a drug used for treating AML, quizartinib also can cause bone marrow suppression. While your child is taking part in this study, your child*s blood cell counts will be checked closely, and they may need blood and/or platelet transfusions if they become anemic (they do not have enough red blood cells) or have a low platelet count or are bleeding. If your child is taking quizartinib, the study doctor may choose to lower your child*s dose if they have bone marrow suppression.
Listed below are common side effects linked to bone marrow suppression from quizartinib:
- Anemia (decrease in the number of red blood cells) (in more than 50% of subjects)
- Low platelets (thrombocytopenia) (in more than 50% of subjects) which will decrease the ability of your child*s body to stop bleeding
- Low white blood cells (neutropenia) (in more than 50% of subjects) which will decrease the ability to fight infection and can result in sepsis, lung infections, urinary tract infections, gastrointestinal infections, sinus infections, and skin infections, oral thrush and oral herpes infections
- Fever with a decrease in the number of white blood cells (febrile neutropenia) (in 30% of subjects), which is associated with an increased risk of infection
- Lymphopenia - reduced numbers of lymphocytes (a type of white blood cells) (in 80% of subjects) which help your child*s body*s immune system
- Pancytopenia (in less than 5% of subjects) - reduced numbers of all types of blood cells (red blood cells, platelets and white blood cells) at the same time

Infections
Because quizartinib may cause bone marrow suppression, which can cause decrease in the number of the normal blood cells that help fight infection (white blood cells), your child may develop infections while receiving treatment with quizartinib. These can range from mild to severe, life-threatening or even fatal infections. The most common infections linked to quizartinib therapy are listed below, but other (including rare) infections can also occur:
- Pneumonia (>10% of subjects)
- Sepsis, (> 10% of subjects), a severe, sometimes life-threatening, infection that has spread by the bloodstream. One or more of your child*s body organs may stop working properly or fail. Organs affected can include their heart, lungs, kidneys, liver and or their blood clotting system. Sepsis may occur in association with neutropenia (neutropenic sepsis).

- Septic shock (in 1% of subjects), a severe life-threating sepsis, with low blood pressure which reduces the amount of blood and oxygen that reaches the body's organs, stopping them from working properly
- Other infections caused by fungi or viruses, infections of the upper airways

Bleeding
Because quizartinib may cause bone marrow suppression, which can cause decrease in the number of the normal blood cells that help blood to clot (platelets), your child may develop bleeding while receiving treatment with quizartinib. This can range from mild to severe, life-threatening or even fatal bleeding. While bleeding can occur anywhere, nose bleeds, bruises, bleeding from the mouth, stomach or intestines are the most common. Less common is bleeding from the vagina, lungs or into the brain/tissues around the brain. Bleeding into the brain can be fatal or result in permanent disability.

Differentiation syndrome
Quizartinib may cause a condition called differentiation syndrome, which may be life-threatening or lead to death if not treated. Differentiation syndrome occurs when leukemic cells in your child*s blood mature (or change). These newly changed cells can cause various signs and symptoms (described below) and damage various organs of the body.
Differentiation syndrome has been observed in patients taking quizartinib for an AML that has relapsed or become refractory (unresponsive) to treatment. When quizartinib is given together with chemotherapy, the chemotherapy helps to clear away the leukemic cells. Therefore differentiation syndrome is not likely to occur when your child is receiving treatment with quizartinib.

Symptom

Contacts

Public
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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) Enrollment on CHIP-AML22/Master:
Patients must be enrolled on the CHIP-AML22/Master prior to enrolment on CHIP-AML/Quizartinib linked-trial, and may have received a diagnostic work-up according to the master protocol. Induction treatment can be started as standard of care.

2) FLT3-ITD+ and wild-type NPM1:
Presence of FLT3-ITD+ and NPM1 wild type in bone marrow or peripheral blood provided by the local laboratories, as part of standard of care diagnostics.
The results of FLT3-ITD testing must be obtained prior to the first dose of quizartinib (e.g., Induction course 1, Day 10).

3) Age:
Patients must be from 1 month to <= 18 years old at initial diagnosis

4) Performance status
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.

5) Organ function criteria:
These criteria must be met based on the results before start of any chemotherapy (e.g., MEC)
a. Adequate Renal Function Defined as:
• Calculated eGFR >= 50 mL/min/1.73 m2 using the Schwartz formula.

b. Adequate Liver Function Defined as:
• Total or direct (conjugated) bilirubin < 5xULN for age (<= 5xULN if related to leukemic
involvement), AND
• Aspartate transaminase (AST) and alanine transaminase (ALT) <5xULN (<10×ULN if related to leukemic involvement)

6) Life expectancy: > 6 weeks

7) Pregnancy test:
Serum/urine pregnancy test (for all girls >= age of menarche) negative within 2 weeks prior to enrollment on the quizartinib linked-trial.

8) Taking quizartinib:
Patients must be able to reliably swallow or administer quizartinib by NG tube.

9) Informed consent:
Written informed consent/assent for the quizartinib linked trial from patients and/or from parents or legal guardians for minor patients, according to local law and regulations.

Exclusion criteria

General exclusion criteria
a. Patients with only extramedullary disease
b. Uncontrolled or significant cardiovascular disease, including
i. Diagnosed or suspected congenital long QT syndrome
ii. History of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de Pointes); any history of arrhythmia will be discussed with sponsor, the national coordinator and C.I. the prior to subject*s entry into the study.
iii. QT interval corrected >450 ms:
- QTc interval corrected with Fridericia*s formula (QTcF) for subjects >= 6 years of age at the time of enrollment.
iv. Left ventricular systolic dysfunction (LVSD), defined as ejection fraction (EF) below 55% during the screening for the CHIP-AML22/Master protocol.
v. History of uncontrolled angina pectoris or myocardial infarction within 6 months.
vi. 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).
vii. Heart rate <50 beats/minute on ECG during the screening for the CHIP-AML22/Master protocol (In case, adolescents with a normal sinusoidal rhythm and no evidence of other cardiac dysfunction will be discussed with sponsor, the national coordinator and C.I. the prior to subject*s entry into

the study.)
viii. Uncontrolled hypertension (e.g., systolic blood pressure and /or diastolic blood pressure that is, on repeated measurement, at or above the 95th percentile for sex, age, and height).
ix. History of complete left bundle branch block.
x. History of New York Heart Association Class 3 or 4 heart failure.
c. Known history of HIV or active clinically relevant liver disease (e.g., active hepatitis B or active hepatitis C)
d. Underlying GI disease that may affect absorption of study drug
e. Use of strong or moderate CYP3A inducers will be prohibited throughout the duration of the study. Strong CYP3A4 inhibitors will be allowed with a concomitant dose reduction of quizartinib with the exception during the safety run-in.
f. History of hypersensitivity to any of the study medications or their excipients.
g. Other serious illnesses or medical conditions, that will likely make it impossible to complete treatment according to protocol (e.g., patients who should not be given any of the study medications based on the SmPC)
h. Currently participating in other investigational interventional procedures, if it interferes with any endpoints of the quizartinib trial.

Note: Patients may be enrolled in either SCRIPT-AML or Pro-Teico study (i.e., conditioning regimen for allo-SCT or infection prophylaxis) as
a) The endpoints of the quizartinib trials are not influenced
b) These trials are evaluating approved agents
c) The medications being evaluated do not conflict with the mechanism of action of quizartinib

2) Additional exclusion criteria during safety run-in
a. Patients with CNS3 disease
b. Using strong CYP3A4 inhibitors (If patient can stop using strong CYP3A4 inhibitors, he/she will be allowed to enroll. In such case, no washout is required for the strong CYP3A4 inhibitor)

Study design

Design

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

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	02-10-2023
Enrollment:	9
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Quizartinib
Generic name:	Quizartinib dihydrochloride

Ethics review

Approved WMO Date:	16-01-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	07-04-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	31-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-11-2023
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	08-11-2023
Application type:	Amendment
Review commission:	METC NedMec

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	CTIS2023-505000-27-01
EudraCT	EUCTR2022-002886-14-NL
CCMO	NL82701.041.22