A Phase 3 Open-Label Randomized Study of Quizartinib (AC220) Monotherapy Versus Salvage Chemotherapy in Subjects with FLT3-ITD Positive Acute Myeloid Leukemia (AML) Refractory To or Relapsed After First-line Treatment With or Without Hematopoietic Stem Cell Transplantation(HSCT) Consolidation.

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Quizartinib selectively inhibits survival pathways that block apoptosis by inhibiting FLT3. Quizartinib inhibits proliferation of FLT3-dependent cell lines, and is effective in human leukemia tumor xenograft models of AML. Data from the Phase 1 and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON45222

Source
ToetsingOnline

Brief title
niet van toepassing.

Condition

- Leukaemias

Synonym
cancer of the blood, Leukemia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AML, FLT3-ITD positive, stam cel transplantation

Outcome measures

Primary outcome

4.1 Primary Objective

The primary objective of the study is to determine whether quizartinib monotherapy prolongs overall survival (OS) compared to salvage chemotherapy in subjects with FLT3-ITD(+) AML who are refractory to or have relapsed within 6 months, after first-line AML therapy.

Secondary outcome

4.2 Secondary Objectives

The secondary objective of the study is to determine event-free survival (EFS) with quizartinib versus salvage chemotherapy.

4.3 Exploratory Objectives

Exploratory objectives are:

• to compare the complete remission (CR) rate (Response definitions provided in Section 7.2)

• to compare the composite complete remission (CRc = CR + CRp + CRi) rate

• to compare the transplantation rate

• to determine leukemia-free survival (LFS)

• to determine the QTc prolonging effects of quizartinib in relation to plasma

drug concentrations

• to determine the pharmacokinetics (PK) of quizartinib and its active

metabolite, AC886

• to determine the exposure-response relationship

• to determine resource utilization in this study population

• pharmacoeconomic analyses

• to identify AML-associated mutations and frequencies

• pharmacogenomic and pharmacoproteomic determinations

Study description

Background summary

Quizartinib (AC220) is a novel oral second-generation Class III receptor tyrosine kinase inhibitor with potent activity against FMS-like tyrosine kinase 3 (FLT3) both in vitro and in vivo. It is currently under development for the indication of the treatment of subjects 18 years of age or older with relapsed (including after hematopoietic stem cell transplantation [HSCT])) or refractory FLT3-internal tandem duplication (ITD) positive (+) acute myeloid leukemia (AML), and has been granted Fast Track Status in the United States and an Orphan Drug Indication in the United States and Europe.
FLT3 is expressed in hematopoietic progenitor cells, and signaling through FLT3 promotes these cells* proliferation and differentiation. FLT3 is mutated in approximately 30% of subjects with AML; the mutations include ITD of the juxtamembrane domain of FLT3 and point mutations, usually in the kinase domain. Both types of mutations constitutively activate FLT3 and contribute to leukemic transformation of hematopoietic cells.
There is an unmet medical need for effective treatment for patients with relapsed/refractory AML, and specifically for those with the FLT3-ITD mutation. The FLT3-ITD mutation is associated with a shorter duration of response, a greater cumulative incidence of relapse, and shorter survival after relapse. It

has been identified as the worst single prognostic factor in AML for duration of complete remission (CR) and relapse-free survival].

Study objective

Quizartinib selectively inhibits survival pathways that block apoptosis by inhibiting FLT3. Quizartinib inhibits proliferation of FLT3-dependent cell lines, and is effective in human leukemia tumor xenograft models of AML. Data from the Phase 1 and Phase 2 studies have shown a high response rate even in patients who were refractory to prior chemotherapy.

Study design

This is a Phase 3, randomized, open-label, 2-arm study to compare the effect of quizartinib monotherapy and salvage chemotherapy on overall survival in subjects with FLT3-ITD(+) AML that is refractory or relapsed within 6 months, after first-line therapy with or without consolidating hematopoietic stem cell transplant (HSCT). The control treatment is a limited choice of one of three standard chemotherapy regimens (low dose cytarabine [LoDAC]; mitoxantrone, etoposide, and intermediate-dose cytarabine [MEC]; or fludarabine, cytarabine, and granulocyte-colony stimulating factor (G-CSF) with idarubicin [FLAG-IDA])) which are widely used to treat patients with AML. Prior to randomization, the Investigator will pre-select 1 of the three salvage chemotherapy regimens for each subject; doses and the duration of study treatments are outlined in Section 5.6.4.2.
The initial target sample size will be approximately 326 subjects, randomized in a 2:1 ratio to receive quizartinib monotherapy (217 subjects) or salvage chemotherapy (109 subjects). The study has an adaptive design. One formal interim analysis will be performed by an independent statistical analysis center (SAC) and evaluated by an independent data monitoring committee (DMC), according to statistical procedures defined a priori. Based on the results of the interim analysis, the DMC may recommend that the study be terminated early for futility or for efficacy, or continue as planned. Additionally, the DMC may recommend the enrollment of additional subjects, up to a maximum of 473 subjects. The precise rules for implementing the adaptive change are fully specified in a confidential (Sponsor access restricted) statistical procedures appendix to the DMC charter. The Sponsor will have no involvement in interim data analysis, interpretation, or the adaptive decision. These tasks will be performed by the SAC and DMC and are described in the DMC charter.

Intervention

STUDY TREATMENT Quizartinib
For subjects randomized to quizartinib the starting dose will be 30 mg/day unless the subject is receiving concurrent therapy with a strong CYP3A4 inhibitor, in which case the starting dose will be 20 mg/day. The dose will be

taken without food (at least one hour before or two hours after a meal) over continuous 28-day cycles. If the subject vomits after taking quizartinib, no replacement dose should be given.
CYCLE 1 DAY 16
For subjects not taking a strong CYP3A4 inhibitor the dose of quizartinib will be increased from 30 to 60 mg/day at Day 16 based on the following criteria:
• The subject*s average QT (QT interval corrected with Fridericia*s formula (QTcF)), based on triplicate reading, must be <= 450 msec on and before Day 15.
For subjects taking a strong CYP3A4 inhibitor, the dose of quizartinib will be increased from 20 mg/day to 30 mg/day providing they meet the above QTcF requirements.
CYCLE 2 DAY 1
Subjects who fail to achieve a CR, CRp, or CRi as defined in Section 7.2 after at least one 28-day cycle of therapy (and who were not eligible for dose escalation at Day 16) may be considered for dose escalation if the following criteria are met:
• Subject has not had dose interruption or dose reduction for toxicity, including QTcF prolongation greater than or equal to Grade 3 or an increase in QTcF of more than 60 msec above baseline.
• The subject must not have aplastic bone marrow at the time of the proposed dose escalation.
In addition, subjects who achieved a response (CR, CRi, CRp or PR) at anytime, and who have subsequently relapsed, may be considered for dose escalation provided they meet the same criteria outlined above.
For subjects not taking a strong CYP3A4 inhibitor the dose of quizartinib will be increased to 60 mg/day.
For subjects taking a strong CYP3A4 inhibitor, the dose of quizartinib will be increased to 30 mg/day providing they meet the above requirements. If any of the specified criteria are met (see protocol pages 8-9), the quizartinib dose will be reduced stepwise from 60 mg/day to 30 mg/day or from 30 mg/ day to 20 mg/day or discontinued. No further dose reductions below 20 mg/day will be allowed.

In subjects receiving a reduced dose of quizartinib, the dose may be re-escalated stepwise from 20 mg to 30 mg to 60 mg, except following Grade 3 QTcF prolongation. If the dose was reduced due to toxicity the subject must have received the reduced dose for 1 full cycle, and all events responsible for dose reduction must have resolved to <= Grade 1. If the dose was reduced due to administration of a strong CYP3A4 inhibitor, the prior dose can be resumed when the inhibitor is withdrawn.
If a subject undergoes HSCT, quizartinib should be discontinued 7 days before the start of a conditioning regimen. For a subject who was randomized to and received quizartinib, treatment with quizartinib may be resumed at 30 to 100 days after the transplant. Quizartinib may be restarted if:
• Subject has an absolute neutrophil count (ANC) >109/L and platelet count > 50 ×109/L without platelet transfusion support within 1 week, or a platelet count > 25 ×109/L without platelet transfusion support within 2 weeks prior to first

dose.
• Subject does not have (1) active acute, or >= Grade 3 graft versus host disease (GVHD) or (2) active GVHD therapy (not prophylaxis) initiation within 21 days of HSCT.
Follow-up
After study treatment is discontinued, subjects will be followed for 30 days for safety, and will then enter long term follow-up every 3 months for collection of information on subsequent AML treatment, remission status, and survival, including the cause and date of death.
Salvage Chemotherapy
The Investigator will pre-select the specific salvage chemotherapy regimen before randomization of each subject. All salvage chemotherapy will be administered during 28-day cycles.
Low Dose Cytarabine (LoDAC)
Cytarabine (20 mg) will be administered twice daily by subcutaneous injection for 10 days (Days 1 through 10) over continuous 28-day cycles. A delay of up to 14 days between cycles is allowed for recovery from toxicity.
MEC Chemotherapy
• Mitoxantrone (8 mg/m2/day) will be administered by 5 minute intravenous (IV) injection for 5 days (Days 1 through 5).
• Etoposide (100 mg/m2/day) will be administered by 1 hour IV infusion immediately after mitoxantrone for 5 days (Days 1 through 5).
• Cytarabine (1000 mg/m2/day) will be administered by 1 hour IV infusion immediately after etoposide for 5 days (Days 1 through 5).
FLAG-IDA Chemotherapy
• G-CSF (300 µg/m2/day) will be administered by 2 hour IV infusion for 5 days (Days 1 through 5). Additional G-CSF is recommended 7 days after the completion of chemotherapy, until ANC is >0.5×109/L.
• Fludarabine (30 mg/m2/day) will be administered by 30 minute IV infusion for 5 days (Days 2 through 6).
• Cytarabine (2000 mg/m2/day) will be administered by 4 hour IV infusion, beginning 4 hours after the fludarabine infusion, for 5 days (Days 2 through 6).
• Idarubicin (10 mg/m2/day) will be administered over 5 to 10 minutes in a fast-running saline drip for 3 days (Days 2 through 4).
In subjects receiving quizartinib or LoDAC, treatment should continue until there is no longer clinical benefit from therapy, or until unacceptable toxicity occurs. Subjects receiving MEC or FLAG-IDA will receive 1 cycle of therapy and be assessed for response on Day 15. Subjects achieving complete remission (CR), complete remission with incomplete hematologic recovery (CRi), or complete remission with incomplete platelet recovery (CRp) (per Investigator assessment) may receive a second cycle of the same therapy at the Investigator*s discretion. Treatment should be discontinued if there is no evidence of response or progressive disease (PD).

Study burden and risks

Belasting voor de deelnemers in deze AMl-patiëntenpopulatie is voornamelijk te

vinden in de ziekenhuisopnames die nodig zijn als de patiënt in de controlegroep wordt gerandomiseerd, en met MEC of FLAG-IDA wordt behandeld. De patiënten in de quizartinibgroep zullen hun behandeling zonder opname in het ziekenhuis kunnen voortzetten.
Voor deelnemers in de LoDAC groep zal de plaats van behandeling afhankelijk zijn, in overleg tussen arts en deelnemer zal worden gekozen voor een poliklinische behandeling of zelfmedicatie door de deelnemer na adequate training in het toedienen van subcutane cytarabine.

The burden for participants in this AML-population is to be mainly found in the hospitalizations that are required if the subject has been randomized in the control group and will be treated with either MEC or FLAG-IDA.
Subjects in the quizartinib group will be able to continue their treatment outside the hospital.
For subjects in the LoDAC treatment group, the treatment wil be administered either in an out-patient clinic setting, or through self medication. This will be determined in consultation between subject and investigator, and after adequate training in the administration of subcutaneous cytarabine injections.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provision of written informed consent approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) with privacy language in accordance with national regulations (e.g., HIPAA authorization for US sites) prior to any study-related procedures, including withdrawal of prohibited medications if applicable. ;2. Age >=18 years at the time of informed consent. ;3. Morphologically documented primary AML or AML secondary to myelodysplastic syndrome (MDS), as defined by World Health Organization criteria, as determined by pathology review at the study site.;4.In first relapse (with duration of remission of 6 months or less) or refractory after prior therapy, with or without HSCT. Induction therapy must have included at least 1 cycle of an anthracycline/mitoxantrone containing induction block at a standard dose.
•Refractory is defined as:
•After 1 cycle, a reduction in bone marrow blasts of less than 50% and failure to achieve a CR, CRp or CRi.
•After 2 cycles, lack of achievement of CR, CRp, or CRi
•First relapse (with duration of remission of 6 months or less) is defined as:
•Achievement of CR, CRi, or CRp, as defined by 2003 International Working Group criteria after initial AML therapy with or without consolidation or maintenance, and with or without HSCT
•Duration of CR, CRi or CRp is measured from the date of the bone marrow assessment which confirmed response or the date of allogeneic transplantation to the date of the bone marrow assessment that identified relapse or the appearance of peripheral blasts.;5. Presence of the FLT3-ITD activating mutation in bone marrow or peripheral blood (allelic ratio as determined by a central laboratory with a cutoff of >3% FLT3ITD/total FLT3).;6. Eligibility for pre-selected salvage chemotherapy, according to the Investigator*s assessment. ;7. ECOG performance score 0-2.;8.Discontinuation of prior AML treatment before the start of study treatment (except hydroxyurea or other treatment to control leukocytosis) for at least 2 weeks for cytotoxic agents, or for at least 5 half-lives for non cytotoxic agents.
9. Serum creatinine <=1.5×upper limit of normal (ULN), or glomerular filtration rate >25 mL/min, as calculated with the Cockcroft-Gault formula.;10. Serum potassium, magnesium, and calcium (serum calcium corrected for hypoalbuminemia) within institutional normal limits. Subjects with electrolytes outside the normal range will be eligible if these values are corrected upon retesting following any necessary supplementation. ;11. Total serum bilirubin <=1.5×ULN.;12. Serum aspartate transaminase (AST) and/or alanine transaminase (ALT) <=2.5×ULN.

Exclusion criteria

1. Acute promyelocytic leukemia (AML subtype M3).
2. AML secondary to prior chemotherapy for other neoplasms, except AML secondary to prior MDS.
3. History of another malignancy, unless the candidate has been disease-free for at least 5 years.
• Candidates with treated non-melanoma skin cancer, carcinoma in situ, or cervical intraepithelial neoplasia are eligible regardless of the time spent disease-free, if they have completed definitive treatment.
• Candidates with organ-confined prostate cancer, with no evidence of recurrent or progressive disease, are eligible if hormonal therapy has been begun, or if thetumor has been surgically removed or treated with definitive radiotherapy.
4. Persistent, clinically significant > Grade 1 non-hematologic toxicity from prior AML therapy.
5. Clinically significant GVHD or GVHD requiring initiation of treatment or treatment escalation within 21 days, and/or > Grade 1 persistent or clinically significant nonhematologic toxicity related to HSCT.
6. History of, or current, central nervous system involvement with AML.
7. Clinically significant coagulation abnormality, such as disseminated intravascular coagulation.
8. Prior treatment with quizartinib or participated in a prior quizartinib study.
9. Prior treatment with a FLT3 targeted therapy including sorafenib or investigational FLT3 inhibitors.
10. Major surgery within 4 weeks prior to screening.
11. Radiation therapy within 4 weeks prior to screening.
12. Uncontrolled or significant cardiovascular disease, including:
•QT interval corrected using Fridericia's formula (QTcF) interval >450 msec (average of triplicate determinations).
•Subject has bradycardia of less than 50 BPM (as determined by central read) unless the subject has a pacemaker.
•Diagnosed or suspected long QT syndrome, or known family history of long QT syndrome.
•History of clinically relevant ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or torsade de pointes.
•History of second or third degree heart block. Candidates with a history of heart block may be eligible if they currently have pacemakers, and have no history of fainting or clinically relevant arrhythmia with pacemakers.
•Myocardial infarction within 6 months prior to screening.
•Uncontrolled angina pectoris within 6 months prior to screening.
•New York Heart Association (NYHA) Class 3 or 4 congestive heart failure.
•Left ventricular ejection fraction (LVEF) <=45 % or institutional lower limit of normal.
•Uncontrolled hypertension.
•Complete left or right bundle branch block.
13. Active infection not well controlled by antibacterial, antifungal, and/or antiviral therapy.
14. Known infection with human immunodeficiency virus, or active hepatitis B or C, or other active clinically relevant liver disease.

15. Unwillingness to receive infusion of blood products according to the protocol.;16.In a man whose sexual partner is a woman of childbearing potential, unwillingness or inability of the man or woman to use an highly effective contraceptive method for the entire study treatment period and for at least 3 months after study treatment completion.
•Male subjects must not freeze or donate sperm starting at Screening and throughout the study period and 105 days after the final study drug administration.
17.In a woman of childbearing potential unwillingness or inability to use an highly effective contraceptive method for the entire study treatment period and for at least 3 months after study treatment completion. Additionally, for women randomized to chemotherapy, unwillingness to adhere to the restrictions in the respective locally established guidelines and local approved label
(prescribing information, Summary of Product Characteristics, or US product
insert) from the manufacturer and the Patient Information Leaflet (package insert) as instructed by the Investigator.
•Women are not regarded as of childbearing potential if they are post-menopausal (at least 2 years without menses) or are surgically sterile (at least 1 month before study)
•Highly effective contraception methods include: hormonal methods associated with inhibition of ovulation, intra-uterine device; surgical sterilization (including partner*s vasectomy) or sexual
abstinence if this is the preferred and usual lifestyle of the subject.
•Female subjects must not donate or retrieve, for their own use, ova from the time of Screening an throughout the study treatment period, and for 12 weeks after the final study drug administration.
18.Pregnancy.
19.Female subjects must agree not to breastfeed from the time of Screening and throughout the study period, and for 25 days after the final study drug administration.
20.Medical condition, serious intercurrent illness, or other circumstance that, in the Investigator*s judgment, could jeopardize the candidate*s safety as a study subject, or that could interfere with study objectives.
21.For subjects in the UK only: Refusal of permission to allow the subject*s General Practitioner to be notified of their participation in the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-12-2014
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Eposin
Generic name:	etoposide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Fludara
Generic name:	fludarabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nvt
Generic name:	cytarabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nvt
Generic name:	mitoxantrone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nvt
Generic name:	quizartinib

Ethics review

Approved WMO

Date:	25-04-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-10-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-04-2020
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
EudraCT	EUCTR2013-004890-28-NL
ClinicalTrials.gov	NCT02039726
CCMO	NL48143.078.14