A phase I/II, open-label, dose-escalating study to evaluate the safety, tolerability and pharmacokinetics of twice daily oral midostaurin and to evaluate the preliminary clinical and pharmacodynamic response in pediatric patients with relapsed or refractory leukemia

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

Summary

ID

NL-OMON39282

Source
ToetsingOnline

Brief title
Midostaurin for relapsed/refractory pediatric leukemia

Condition

- Leukaemias

Synonym
Relapsed/refractory leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma

Intervention

Keyword: leukemia, midostaurin, pediatric, Phase I/II

Outcome measures

Primary outcome

To determine the maximum tolerated dose (MTD) or to identify the recommended dose for expansion (RDE) for two age groups (>=3 months to <=2 years: >2years to <18 years) of pediatric patients with AML or MLL based on the rate of dose-limiting toxicity (DLT) of midostaurin administered orally in dose ranges studied in adults.

Secondary outcome

• To characterize the safety and tolerability of midostaurin, including acute and chronic toxicities

• To characterize the population PK of single and repeated doses of midostaurin and its metabolite(s),

• To determine the response rates, time to relapse and overall survival of patients treated with midostaurin.

Study description

Background summary

The survival of children with refractory or relapsed Mixed Lineage Leukemia (MLL) gene rearranged Acute Lymphoblastic Leukemia (ALL) or with refractory or second relapse of Acute Myeloid Leukemia (AML) is poor, with recovery rates of 10-20%. Further intensification of upfront therapy is not possible because it leads to very high toxic-death rates in these children Thus, there is need to develop new modalities of treatment for these subtypes of leukemia, which may be added to standard chemotherapy, to further reduce relapse rate without increasing toxicity.

FLT3 activation plays a role in the development of leukemias and is related to a poor outcome. The addition of a targeted agent against FLT3 may offer the possibility for significant therapeutic advantage as demonstrated in adult AML patients expressing FLT3. Childhood MLL shows overexpression of FLT3 compared to other types of leukemia, and AML shows activating FLT3 mutations in a significant percentage of patients. Therefore, FLT3 has the potential to be a promising target for therapy in these subtypes of childhood leukemia. So far, no other FLT3 inhibitors have been developed for use in children in Europe. In the United States of America studies are being conducted with CEP701, however results are not known yet.

Midostaurin inhibits a number of tyrosine kinases, such as the class III tyrosine protein kinase FLT3, and has documented antiproliferative and pro-apoptotic activities in cell systems expressing and depending on mutated FLT3 receptor signaling or in wild-type FLT3 over-expressing cells. In vitro cytotoxicity studies on samples derived from pediatric patients showed that cells from MLL patients were significantly ~5 fold more sensitive to midostaurin than cells from children with conventional ALL. In addition to its activity as a single agent, [Study CPKC412A2104], midostaurin can be combined with standard chemotherapeutic agents used in leukemia resulting in synergism or additivity [Study CPKC412A2106].

In order to support dosing pediatric patients a drink solution has been developed. The relative bioavailability of the drink solution was demonstrated to be biocomparable to the oral capsule in [Study CPKC412A2108], with no conversion factor required.

Study objective

This is a phase I/II pediatric dose-ranging study that will evaluate the safety, tolerability and pharmacokinetics of midostaurin in children <18 years of age and >= 3 months who have relapsed or refractory leukemias that may benefit from administration of midostaurin including MLL-rearranged ALL and AML

with FLT3 mutations.

Treatment with single agent midostaurin may have potential therapeutic benefit in pediatric AML patients similar to the response seen in adults with the disease, as was shown in [Study CPKC412A2104], summarized in section 1.3.4.2. of the protocol. A similar effect may be seen in MLL cases, although there are no adult data to support this, as high FLT3-overexpression in the absence of mutations is mainly limited to infant ALL.

Given midostaurin*s limited potential to induce complete remissions in adults with AML, it is anticipated that in future protocols, midostaurin will be used mainly in combination with regular chemotherapy. This will be addressed in future phase II trials in MLL and AML. However, before doing so, sufficient background data are needed on its safety and preliminary evidence of activity/efficacy as a single agent. Therefore in this study, only a limited number of dose-levels will be assessed, based on availability of adult data, and non-efficacious dose-levels will be avoided. Also a Bayesian logistic model is being used to limit the number of patients that has to be included.

Study design

This is a phase I/II, open-label, dose-escalating study to determine the safety, tolerability, and pharmacokinetics of twice daily oral midostaurin and to determine the preliminary clinical and pharmacodynamic response in pediatric patients with relapsed or refractory leukemia. The dose escalation will be stratified into two age groups, patients aged greater than 2 years and less than 18 years, and those 2 years or younger but greater than or equal to 3 months. Besides this MLL-ALL and AML will be analysed separately. The maximum treatment dose administered in the adult population on monotherapy is 100 mg b.i.d., and in combination with chemotherapy 50mg b.i.d., and for this reason the maximum of midostaurin in the pediatric population will not exceed 60 mg/m2, equivalent to 100 mg b.i.d.
Once the Maximum Tolerated Dose (MTD) or the recommended dose for expansion (RDE) has been established in each stratum of the dose-escalation part additional patients might need to be included in order to have a total of 10 patients within each of the two indications (AML/MLL)treated across all dose levels. A minimum of 10 patients per indication have been enrolled and received at least one dose of midostaurin. The eligibility criteria and assessments for patients enrolled in this dose-expansion phase will be the same as those used during the dose-escalation phase.

An exploratory analysis will also be performed (see protocol)

Intervention

Children will be treated orally with midostaurin (25mg/ml). As long as they

experience benefits from treatment with midostaurin, they can continue to take it. De respons evaluation takes place every 2 weeks.

Study burden and risks

Most of the assessments belong to the standard care in child oncology treatment.

Patient can get side effects of midostaurin, in adults the most common side effects were nausea and vomiting. For this reason patients will be treated with antiemetics. Other potential side effects are tiredness, headache, anorexia, indigestion, diarrhea, flatulence and dehydration. Other less frequent side effects are abdominal cramps, constipation, pain, gout, hypertension, viral infection, rash, increased sweating, urinary tract infection, coughing, bad taste in the mouth, itching, indreased dreams, dizziness and pain in the joints.

The extra blooddraws for the study will be taken from the central line which these patients have.

Contacts

Public
Novartis

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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)
Children (2-11 years)

Inclusion criteria

1. Patients must have a documented diagnosis of one of the following leukemias:
• MLL-rearranged ALL, refractory to standard induction treatment or in first or subsequent relapse
• FLT3-mutated AML refractory to standard induction (after failure of at least 2 different induction chemotherapy regimens) or refractory to reinduction at 1st relapse (after failure of the first re-induction course), or in second or greater relapse
2. Patients must be less than 18 years of age and >=3 months of age.
3. Patients must have a Lansky/Karnofsky performance status >= 60.
4. Patients must have the following laboratory values reflecting appropriate organ function:
• AST and ALT <= 5x Upper Limit of Normal (ULN),
• Serum Bilirubin <= 1.5 x ULN,
• Serum Creatinine <= 2 x ULN.
5. Patients must have an expected survival of greater than 8 weeks.
6. Parent or legal guardian and/or patient must give written informed consent, according to local law and regulations

Exclusion criteria

1. Patients with symptomatic leukemic CNS involvement.
2. Patients with isolated extramedullary leukemia.
3. Patients must have recovered from prior cytotoxic chemotherapy, and a minimum wash-out time of previous chemotherapy of 72 hours should be taken into account. For intrathecal chemotherapy, the minimum wash-out time is 48 hours
4. Patients who had prior allogeneic, syngeneic or autologous bone marrow or stem cell transplant less than 2 months from Day 1
5. Patients who have received any investigational agent within 30 days or 5 half lives, whichever is greater, prior to Day 1.
6. Patients who have had prior treatment with a FLT3 inhibiting drug or investigational agent, except for sorafenib
7. Use of CYP3A4/5 enzyme inducing or inhibiting drugs or CYP3A4/5 enzyme inducing or inhibiting herbal supplements while on study treatment
8. The use of corticosteroids while on study drug (exceptions are noted in the protocol

section 6.6.5)
9. Patients who have had any surgical procedure, excluding central venous catheter placement or other minor procedures (e.g. skin or bone marrow biopsy), within 14 days of Day 1.
10. Patients with any other known disease concurrent severe and/or uncontrolled medical condition (e.g. cardiovascular disease including congestive heart failure or active uncontrolled infection) which could compromise participation in the study.
11. Patients with an abnormal chest X-ray and/or any pulmonary infiltrate including those suspected to be of infectious origin. In particular, patients with resolution of clinical symptoms of pulmonary infection but with residual pulmonary infiltrates on chest x-ray are not eligible until pulmonary infiltrates have completely resolved.
12. Patients with known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of midostaurin, including active graft-versus-host disease of the liver or the gut.
13. Patients with a known confirmed diagnosis of HIV infection or active viral hepatitis.
14. Patients with a left ventricular shortening fraction < 27% as determined by MUGA scan or echocardiogram
15. Patients with abnormal ECG including:
• QTcF >= 450 ms, PR >=200 msec, QRS complex >=110 msec, at screening or prior to first dosing
• Any cardiac conduction abnormality
• Any morphologic abnormality
• Any ST/T wave abnormality
• Any atrial or ventricular arrhythmia
16. Female patients who are pregnant or breast feeding or patients of reproductive potential not employing an effective method of birth control. Barrier contraceptives must be used throughout the trial by both sexes, if applicable.
17. Males of reproductive potential unwilling to comply with contraceptive requirements
18. Patients/parents unwilling or unable to comply with the protocol

Study design

Design

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

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-11-2009
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	midostaurin

Ethics review

Approved WMO Date:	07-08-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-10-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-02-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-02-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	15-12-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-08-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-07-2013

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-02-2014
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	EUCTR2008-006931-11-NL
ClinicalTrials.gov	NCT00866281
CCMO	NL28605.078.09