A phase III randomized, open-label, multi-center study of nilotinib versus imatinib in adult patients with philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP) who have suboptimal cytogenetic response (CyR) ib unatubub

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To evaluate the CCyR rate at 12 months of nilotinib compared to imatinib in adult patients with Ph+ CML in CP who have a suboptimal cytogenetic response on imatinib.

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

Summary

ID

NL-OMON31183

Source
ToetsingOnline

Brief title
CML chronic fase, suboptimal respons on imatinib, imatinib versus nilotinib

Condition

- Leukaemias

Synonym
Chronic myeloid leukemia (CML)

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Spectrum Twente
Source(s) of monetary or material Support: Industrie;nl Novartis Pharma B.V.

Intervention

Keyword: CML-chronic phase, imatinib, nilotinib, suboptimal cytogenetic response

Outcome measures

Primary outcome

To evaluate the CCyR rate at 12 months of nilotinib compared to imatinib in adult patients with Ph+ CML in CP who have a suboptimal cytogenetic response on imatinib.

Secondary outcome

To evaluate the rate of durable CCyR at 24 months (patients who have achieved CCyR by 12 months, and also maintain continuous CCyR until the 24 month time point).

To evaluate the rate of a major molecular response (MMR) of nilotinib compared to imatinib in adult patients with Ph+ CML in CP.

To evaluate the rate of durable CCyR over the initial 24 months of this study in adult patients with Ph+ CM in CP who have a suboptimal cytogenetic response to imatinib. Rate of durable CCyR over 24 months is defined as the proportion of patients who have been in continuous CCyR for a period of at least one year during this 24 month time period.

To evaluate the CCyR rate of nilotinib compared to imatinib in adult patients with Ph+ CML in CP at 24 months.

To evaluate the time to and duration of CCyR of nilotinib compared to imatinib in adult patients with Ph+ CML in CP.

To evaluate the rate of a > 4 log reduction in BCR-ABL transcript levels of nilotinib compared to imatinib in adult patients with Ph+ CML in CP.

To evaluate the time to and duration of a > 4 log reduction in BCR-ABL transcript levels of nilotinib compared to imatinib in adult patients with Ph+ CML in CP.

To describe overall survival, progression free survival, and event-free survival up to 5 years in adult patients with Ph+ CML in CP.

To evaluate the safety profile of nilotinib and imatinib in adult patients with Ph+ CML in CP.

To investigate the presence of BCR-ABL mutations in patients at the initiation of the study and during the course of treatment and correlate the mutations with treatment response to nilotinib and imatinib.

To examine whether individual genetic variation ingenes relating to drug

metabolism,CML, and the drug target pathway confer differential response to

nilotinib and imatinib (pharmacogenetic assessment).

To identify sources of variability in PK parameters for both nilotinib and

imatinib and to investigator PK/PD relationships.

To examine the patient reported outcocmes (PRO) including quality of life (QoL)

between nilotinib and imatinib.

Study description

Background summary

Imatinib mesylate binds to the inactive conformation of BCR-ABL tyrosine kinase suppressing the Ph+ clone in CML. It is effective in CML and is a major advance in therapy. Evidence suggests that in individuals treated with imatinib the achievement of a complete cytogenetic response (CCyR) is a predictor of positive outcome. If a patient has not achieved at least a partial cyctogenetic response (PCyR) by 12 months, achievement of CCyR is unlikely.

Nilotinib is a novel, oral tyrosine kinase inhibitor with improved potency compared with imatinib. Niltinib was also found to have an acceptable tolerability profile. Preliminary results from an ongoing study appear to confirm the efficacy and safety profile of nilotinib. In this study the effect on CCyR of nilotinib will be compared with imatinib.

Study objective

To evaluate the CCyR rate at 12 months of nilotinib compared to imatinib in adult patients with Ph+ CML in CP who have a suboptimal cytogenetic response on imatinib.

Study design

After the screeningperiod patients will be randomized 1:1 between nilotinib and imatinib. Patients will be treated open label.
Patients will be treated until progressive disease, until unacceptable toxicity

or up to 5 years.
Patients who continue on study will be followed for up to 5 years for event free, progression free, and overall survival.

Intervention

After randomization patients will be treated with imatinib 2x400 mg or nilotinib 2x400 mg. A cycle is 28 days, patients take their medication continuously.

Study burden and risks

After the screening period patients will visit the hospital every week first month of treatment. Until 6 months of treatment patients will visit the hospital every month. After 2 years of treatment patients will visit the hospital every 3 months up to 5 years of treatment.

Evaluation of response will be determined by cytogenetics of the bone marrow assessment.
ECG's and ECHO's are performed to monitor the cardiac function.

Possible risks for patients during the course of this study are toxicity from nilotinib and imatinib and the effects of venapuncture and bone marrow assessment.

Mogelijk risico gedurende dit onderzoek zijn de bijwerkingen van imatinib en nilotinib, gevolgen van venapuntie en gevolgen van beenmergafname.

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

Adult patients with suboptimal cytogenetic response to a dose of 400 mg imatinib (first line therapy) defined as:
* 6-12 months of treatment and have 36-95% Ph+ metaphases or
* 12-18 months of treatment and have 1-35% Ph+ metaphases;EOG 0, 1, or 2;Patients must meet the following laboratory criteria:
Total bilirubin <1.5 X ULN
SGOT and SGPT <2.5 X ULN
Creatinine <1.5 X ULN
Serum potassium, phosphorus, magnesium and calcium >LLN or correctable with supplements prior to first dose of study drug.;Written informed consent.

Exclusion criteria

Previously documented T315I mutations;Achieved prior PCyR or CCyR on imatinib and lost that response prior to entering the study;Prior treatment with > 400 mg imatinib;Previous treatment with any other tyrosine kinase inhibitor except imatinib;Impaired cardiac function

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):	01-12-2007
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Gleevec
Generic name:	imatinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tasigna
Generic name:	nilotinib

Ethics review

Approved WMO Date:	26-10-2007
Application type:	First submission
Review commission:	METC Twente (Enschede)
Approved WMO Date:	10-04-2008
Application type:	Amendment

Review commission: METC Twente (Enschede)

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	EUCTR2005-005047-26-NL
CCMO	NL18485.044.07