A multi-center, open-label, pharmacokinetic study of oral nilotinib in pedriatric patients with Gleevec (imatinib)-resistant/intolerant Ph+ CML chronic phase (CP) or accelerated phase (AP) or with refractory/relapsed Ph+ ALL.;Met protocol amendment #03 verandert de titel als volgt: *A multi-center, open-label, pharmacokinetic study of oral nilotinib in pediatric patients with newly diagnosed chronic phase (CP) Ph+ CML, with CP or accelerated phase (AP) Ph+ CML resistant/intolerant to imatinib

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Primary: To characterize the PK of nilotinib in pediatric patients with newly diagnosed CP Ph+ CML, with CP or AP Ph+ CML resistant / intolerant to imatinib and/or dasatinib, or with Ph+ ALL refractory/relapsed.Secondary:• To assess the safety and...

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

Summary

ID

NL-OMON39198

Source
ToetsingOnline

Brief title
AMN107A2120

Condition

- Leukaemias

Synonym
Chronic Myeloid Leukemia and Philadelphia chromosome positive acute Lymphoblastic Leukemia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: CML, Nilotinib, Ph+ ALL, Pharmacokinetics

Outcome measures

Primary outcome

Primary: PK parameters of nilotinib, i.e. AUC0-*, Cmax, Cmin, tmax, t1/2, Vd/F,

AUC0-* and CL/F.

Secondary outcome

Secondary:

• Safety and tolerability: incidence and severity of adverse events and abnormal

laboratory tests.

• Activity: hematologic, cytogenetic, and molecular response.

• Mutational assessments of BCR-ABL

Study description

Background summary

Nilotinib (AMN107) is a novel, oral ATP-competitive inhibitor of BCR-ABL tyrosine kinase with improved potency and greater target selectivity compared to that of imatinib. Nilotinib is currently approved for the treatment of adult patients with Ph+ CML in CP or AP resistant or intolerant to prior therapy including imatinib and for the treatment of adult patients with newly diagnosed Ph+ CML in CP, at 400 mg bid and 300 mg bid, respectively. A Phase I dose-escalation study followed by a Phase II study [CAMN107A2101] in adult patients with imatinib resistant or intolerant Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML), Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), and other hematologic malignancies demonstrated that nilotinib taken at the recommended dose of 400 mg twice daily was effective and well tolerated. A Phase III randomized study [CAMN107A2303]]in newly diagnosed adult patients with Ph+ CML CP showed superiority of nilotinib vs. imatinib. At the 12-month analysis time point: the MMR rate was significantly higher with nilotinib compared to imatinib. By 36 months, the MMR rate as well as the estimated rate of patients free from progression to AP/BC remained higher with nilotinib than with imatinib. Tasigna® is currently approved and marketed as an immediate release hard gelatin capsule at the dose strength of 150 mg and 200 mg.

Despite the success of imatinib used as either a single agent for Ph+ CML or in combination with chemotherapy for Ph+ ALL, resistance or persistence of disease or intolerance to imatinib occurs in many patients. Nilotinib is a TKI that was designed to be a more specific inhibitor of BCR-ABL than imatinib. Adult patients have demonstrated a

benefit from switching to 2nd-generation TKIs such as nilotinib. The positive benefit/risk
profile demonstrated by nilotinib in adult patients with newly diagnosed as well as
imatinib resistant/intolerant Ph+ leukemias may also be demonstrated in pediatric Ph+
leukemia patients as they are also characterized by t(9:22) and expression of the BCRABL
oncoprotein.
The pharmacokinetics (PK) of nilotinib has been characterized previously in adult
patients and healthy volunteers. However, limited information/data has been obtained
regarding the PK profiles of nilotinib in patients of ages less than 18 years. The
metabolism of nilotinib has been shown to be primarily mediated by cytochrome P450
3A4 (CYP3A4), and to a very minor extent, by CYP2C8. Based on literature reportreports, the CYP3A4 expression and activity reaches its adult level at 1-2 years
after birth (Johnson, et al 2006). Therefore no significant difference in the metabolism of
nilotinib is expected between the pediatric (>=1 year) and adult populations.
The current study is proposed to evaluate the PK of nilotinib in pediatric patients with
newly diagnosed CP Ph+ CML, with CP or AP Ph+ CML resistant / intolerant to imatinib
and/or dasatinib, or with Ph+ ALL refractory /relapsed to standard therapy.

Study objective

Primary: To characterize the PK of nilotinib in pediatric patients with newly diagnosed CP Ph+ CML, with CP or AP Ph+ CML
resistant / intolerant to imatinib and/or dasatinib, or with Ph+ ALL refractory/relapsed.

Secondary:
• To assess the safety and tolerability of nilotinib.
• To assess the pharmacodynamics of nilotinib by its activity (hematologic, cytogenetic and molecular responses).
• To assess mutations in BCR-ABL at baseline and at the end of study.

Study design

This is a PK study with the assessment of nilotinib safety and activity as

secondary endpoints.

Intervention

The approved adult dose of nilotinib for the treatment of imatinib resistant / intolerant CML is 400mg twice daily. The equivalent dose, based on an average BSA of 1.73 m2 in adults, is 230 mg/m2 twice daily which will be investigated in this trial.

Study burden and risks

Extra procedures compared to standard treatment are:
Hospitalisation/stay in the institute will be extended on the day of pharmacokinetic sampling.
18 x ECG
1 x MUGA
28 x blood sampling (1.5 ml each time)

Common side effects of nilotinib are: nausea, constipation, diarrhoea, headache, tiredness, muscle pain, itching, rash, hives and hair loss ,vomiting, abdominal pain, stomach discomfort after meals, flatulence, bone pain, pain in joints, muscle spasms, pain in extremity, back pain, flank pain, skin reddening, dry skin, acne, skin wart, decreased skin sensitivity, weight decrease or increase, decreased appetite, insomnia, night sweats, excessive sweating, hot flushes, voice disorder, eye itching and dry eyes.

Contacts

Public
Novartis

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Scientific
Novartis

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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. Male or female patients less than 18 years and more than 1 year of age at study entry.
2. Patients must have one of the following: newly diagnosed CP Ph+ CML, CP or AP Ph+ CML resistant/-intolerant to imatinib and/or dasatinib, or Ph+ ALL either relapsed after or refractory to standard therapy.
a.
• Imatinib or dasatinib resistance in Ph+ CML is defined as:
• Increasing WBC or platelet count while on imatinib or dasatinib therapy indicative of a hematological relapse or primary resistance to imatinib or dasatinib
• Cytogenetic or molecular response consistent with suboptimal response or failure criteria adapted from ELN (European Leukemia Net) recommendations
• Progression to accelerated phase or blast crisis while on imatinib or dasatinib therapy.
• Reappearance of Ph+ bone marrow cells after a complete cytogenetic response to Imatinib or dasatinib.
• A greater than 30% increase in Ph+ cells in peripheral blood or bone marrow cytogenetics while on
imatinib or dasatinib therapy.
• Loss of molecular response on imatinib or dasatinib therapy.
b.
• Imatinib/dasatinib intolerance (at any dose or duration) is defined as the development of AEs
requiring discontinuation of imatinib or dasatinib therapy.
c.
Newly diagnosed CP Ph+ CML is defined as:
• Patients with Ph+ CML-CP within 6 months of diagnosis (date of initial diagnosis is the date of first cytogenetic analysis).
• Diagnosis of chronic myelogenous leukemia in chronic phase with cytogenetic confirmation of Philadelphia chromosome with (9;22) translocation (to confirm the presence of BCR-ABL and review of a

minimum 20 metaphases is required). Standard conventional cytogenetic
analysis must be done on bone marrow. FISH cannot be used for study purposes.
3. Performance status: Karnofsky >= 50% for patients > 10 years of age, and Lansky >= 50 for
patients <= 10 years of age.
4. Patients must have adequate renal, hepatic and pancreatic function and normal electrolytes
defined as:
• Creatinine clearance or radioisotope GFR >= 70 ml/min/1.73 m2, or
a serum creatinine based on age as follows:
Age (Years) Maximum Serum Creatinine (mg/dL)
1 < age <= 5 0.8
5 < age <= 10 1.0
10< age <= 15 1.2
> 15 1.5
• Total bilirubin (sum of conjugated + unconjugated) <= 1.5 x upper limit of normal (ULN) for age.
• Serum amylase and lipase <= 1.5 x ULN
• SGPT (ALT) and SGOT (AST) <= 2 x upper limit of normal (ULN) for age.
5. Patients must have the following laboratory values (>=LLN (lower limit of normal) or corrected to within normal limits with supplements prior to the first dose of study medication):
• Potassium >= LLN
• Magnesium >= LLN
• Phosphorus >= LLN
• Total calcium (corrected for serum albumin) >= LLN

Exclusion criteria

Patients meeting any of the following criteria will be excluded from entry into or continuation in the study:
1. Patients actively receiving therapy with strong CYP3A4 inhibitors and the treatment cannot be either discontinued or switched to a different medication at least 14 days prior to starting study
drug.
2. Patients who are currently receiving treatment with any medications that have a known risk or potential risk to prolong the QT interval and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug.
3. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug(e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, mal-absorption, small bowel resection, or gastric bypass surgery).
4. Acute or chronic liver, pancreatic or severe renal disease considered unrelated to CML or ALL.
5. History of pancreatitis within 12 months of study entry or past medical history of chronic pancreatitis.

6. No active or systemic bacterial, fungal, or viral infection as documented by positive cultures, radiological imaging techniques, or septic shock syndrome
7. Impaired cardiac function including any one of the following:
• Inability to determine the QT interval on ECG
• Complete left bundle branch block
• Use of a ventricular-paced pacemaker
• Congenital long QT syndrome or a known family history of long QT syndrome.
• History of or presence of clinically significant ventricular or atrial tachyarrhythmias
• Clinically significant resting brachycardia (<50 beats per minute)
• QTcF > 450 msec on baseline ECG (using the QTcF formula). If QTcF >450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-screened for QTcF
• History of clinically documented myocardial infarction within 12 months of study entry
• History of unstable angina within 12 months of study entry
• Other clinically significant heart disease (e.g. congestive heart failure or uncontrolled hypertension).
8. Patients who have received dasatinib therapy within the past 3 days.
9. Patients who have received imatinib therapy within the past 5 days.
10. a) Patients who have received myelosuppressive chemotherapy within 14 days prior to first dose of study drug.
b) Patients who have not recovered from all acute toxicities from all prior myelosuppressive chemotherapy to <= Grade 1 (except alopecia) prior to starting study drug.
11. Patients receiving greater than 14 days of hydroxyurea for the treatment of Ph+ CML or corticosteroids for the treatment of
Ph+ ALL and has not been discontinued at least one week prior to initiation of nilotinib (see section 6.6.4 for details on permitted concomitant use of hydroxyurea and corticosteroids).
12. Patients who have received hematopoietic growth factors within 7 days of study start or Pegfilgrastim (Neulasta®) within 14 days of study start.
13. Stem Cell Transplant (SCT) or Rescue without total body irradiation (TBI): Evidence of active graft vs. host disease and < 3 months since SCT.
14. External beam radiation therapy (XRT):
• < 2 weeks after local palliative XRT (small port)
• < 3 months after prior total body irradiation, or craniospinal radiation, or >= 50% radiation of pelvis
• < 6 weeks after other substantial BM irradiation
15. Patients with a known T315I mutation in BCR-ABL.
16. Patients with known Hepatitis B, Hepatitis C, or HIV infection.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-05-2011
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tasigna
Generic name:	Nilotinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-01-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-05-2011
Application type:	First submission
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:	19-10-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-06-2015
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-06-2015
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	EUCTR2010-018419-14-NL
ClinicalTrials.gov	NCT01077544
CCMO	NL33920.078.10