Sponsor

Novartis

Generic Drug Name

Nilotinib

Therapeutic Area of Trial

Chronic myeloid leukemia and relapsed/refractory Philadelphia chromosome positive acute lymphoblastic leukemia

Approved Indication

Indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in adult patients resistant to or intolerant to at least one prior therapy including imatinib.

Study Number

CAMN107A1101

Title

A phase I/II multicenter, dose-escalation study of oral nilotinib on a continuous daily dosing schedule in adult patients with Glivec®(imatinib)-resistant or Glivec®(imatinib)-intolerant CML, or relapsed/refractory Ph+ ALL.

Phase of Development

Phase I

Study Start/End Dates

25 Aug 2005 to 8 May 2006

Study Design/Methodology

This was an open-label, multicenter, phase I study of nilotinib designed to evaluate the tolerability/safety and DLT (dose-limiting toxicity) of nilotinib up to the dose levels (400 mg b.i.d.) being used in the ongoing global Phase II study (CAMN107A2101) and to characterize the safety, tolerability, PK profile and preliminary anti-leukemic activity of nilotinib when administered orally on a continuous once-daily or twice-daily dosing schedule, in 28-day cycles, to adult patients with either imatinib-resistant or imatinib-intolerant, or relapsed/refractory Ph+ ALL (dose-escalation cohorts).

Centers

16 centers in Japan.

Publication

None

Objectives

Primary objective(s)

- To evaluate the tolerability/safety and dose-limiting toxicity (DLT) of nilotinib up to the dose levels (400 mg b.i.d.) being used in the global Phase II study (CAMN107A2101) when administered as a single agent in an oral once-daily dose or twice-daily dosing regimen to adult Japanese patients with imatinib-resistant CML or imatinib-intolerant CML or relapsed/refractory Ph+ ALL.
- To evaluate the PK profile of nilotinib in serum after oral dose administration.

Secondary objective(s)

- To evaluate the safety including acute and chronic toxicities of nilotinib.
- To evaluate the preliminary anti-leukemic activity in imatinib-resistant or imatinibintolerant CML-CP patients, imatinib-resistant or imatinib-intolerant CML-AP patients, imatinib-resistant or imatinib-intolerant CML-BC patients and relapsed/refractory patients with Ph+ ALL.
- To assess changes in the following parameters before, during and after therapy in malignant cells taken from the bone marrow and/or blood: Q-RT-PCR to detect the presence of Bcr-Abl transcript and mutational analysis of Bcr-Abl.

Test Product (s), Dose(s), and Mode(s) of Administration

The starting dose of nilotinib was a flat dose of 200 mg administered continuously on a once daily schedule, repeated in a 28-day cycle. nilotinib was administered on a continuous, once daily schedule or every 12 hours until disease progression, unacceptable toxicity occurs and/or the patient or the physician decided that it was not beneficial for the patient to continue. Patients achieving a complete response/remission received two or more additional cycles for maintenance of their response at the discretion of the investigator.

Reference Product(s), Dose(s), and Mode(s) of Administration

None

Criteria for Evaluation

Primary variables

- DLT: A DLT was clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications, which occurs during cycle 1, and meets any of DLT criteria.
- PK parameters determined
  - The PK variables to be evaluated were trough, maximum concentration of drug (Cmax), time at which Cmax occurs (tmax) and area under the curve (AUC) of nilotinib and its metabolites, if possible.

Secondary variables

Efficacy:

The primary efficacy was hematologic response as evaluated by the investigators, using disease-

specific response-criteria based on peripheral blood, bone marrow, and extramedullary measurements. Cytogenetic response for CML patients was also assessed.

Safety:

Safety assessments consisted of 1) the monitoring and recording all adverse events and serious adverse events, 2) the regular monitoring of hematology, blood chemistry values and urine values, 3) the regular measurement of vital signs, physical examination including weight and performance status, and 4) the regular cardiac assessments. Additionally, chest Xrays were repeated as clinically indicated.

Pharmacology

Pharmacokinetic profile has been evaluated as part of primary variables.

Statistical Methods

Tolerability and DLT up to the dose levels (400 mg b.i.d.) were evaluated. Efficacy, safety, and pharmacokinetic profile were also characterized.

As efficacy evaluation on the ITT population, two efficacy responses (hematologic and cytogenetic response during the first 3 cycles) were investigated by initial dose cohort and disease type. All responses post-baseline based on investigator's evaluation were used in the analysis.

All safety analyses except for the safety evaluation on DLT were performed for the safety population. The assessment of safety was performed by initial dose cohort. The assessment of safety was based mainly on the frequency of adverse events and on the number of patients with abnormal laboratory values based on CTCAE grades. Other safety data such as vital signs and ECG were summarized as appropriate. All safety measurements and observations were listed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Patients with a cytopathologically confirmed diagnosis of Ph+ ALL who were either relapsed after or refractory to standard therapy, or patients with CML-CP, CML-AP or CML-BC who were resistant or intolerant to imatinib
  - Imatinib-resistant or imatinib-intolerant CML-BC was defined as at least 30% blasts in peripheral blood or bone marrow or extramedullary disease other than liver or spleen
  - Imatinib-resistant or imatinib-intolerant CML-AP patients with BC before starting treatment only in dose escalation cohorts
  - Imatinib resistant or intolerant CML-CP patients with BC or AP before starting treatment only in dose escalation cohorts
  - Relapse or refractory Ph+ ALL
    - Patients with Ph+ ALL who have minimal residual disease (MRD) were eligible only if there was indication of evolving relapse defined as a > 2 log increased of Bcr-Abl transcript level (as reported by local laboratories), as compared to the minimum level achieved with prior therapy in peripheral blood
    - Patients with Ph+ ALL whose disease exhibit features of biphenotypic acute leukemia was eligible

- Patients with Ph+ ALL who relapsed after achieving complete remission with previous medication or diagnosed as refractory without achieving complete remission. Prior Glivec therapy for patients with Ph+ALL was permitted but was not required.

- Age = 20 years old
- Able to agree to hospitalization for at least 2 weeks to participate in this study
- WHO Performance Status (PS) = 2
- Patients must have the following laboratory values:
  - Potassium = LLN or corrected to within normal limits with supplements prior to the first dose of study medication
  - Magnesium = LLN or corrected to within normal limits with supplements prior to the first dose of study medication
  - Total calcium (corrected for serum albumin) = LLN or correctable with supplements
  - Magnesium = LLN or correctable with supplements
  - Phosphorus = LLN or correctable with supplements
  - ALT and AST = 2.5 x upper limit of normal (ULN) or = 5.0 x ULN if considered due to tumor
  - Alkaline phosphatase = 2.5 x ULN unless considered due to tumor
  - Serum bilirubin = 1.5 x ULN
  - Serum creatinine = 1.5 x ULN or 24 hours creatinine clearance= 50 mL/min
  - Serum amylase = 1.5 x ULN and serum lipase = 1.5 x ULN
- Written informed consent prior to any study procedures being performed

Exclusion criteria

- Cytopathologically confirmed central nervous system (CNS) infiltration (in absence of suspicion of CNS involvement, lumbar puncture was not required)
- Impaired cardiac function, including any one of the following
  - LVEF < 45% or below institutional lower limit of the normal range (which ever was higher) as determined by echocardiogram
  - Complete left bundle branch block
  - Use of a cardiac pacemaker
  - ST depression of > 1 mm in 2 or more leads and/or T-wave inversions in 2 or more contiguous leads
  - Congenital long QT syndrome
  - History of or presence of significant ventricular or atrial tachyarrhythmias
  - Clinically significant resting bradycardia (< 50 beats per minute)
  - QTc > 450 msec on screening ECG (using the QTcF formula)
  - Right bundle branch block plus left anterior hemibloc, bifascicular book
  - Myocardial infarction within 12 months prior to starting nilotinib

- Unstable angina diagnosed or treated during the past 12 months
- Other clinically significant heart disease (e.g., congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- Impairment of gastrointestinal function or gastrointestinal disease that may have significantly altered after the absorption of nilotinib (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
- Use of therapeutic warfarin
- Acute or chronic liver or renal disease considered unrelated to tumor (e.g., hepatitis, cirrhosis, renal insufficiency, etc.)
- Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol.
- Treatment with any hematopoietic colony-stimulating growth factors (e.g., Glanulocyte colony-stimulating factor, G-CSF) = 1 week prior to starting study drug.
- Patients who were currently receiving treatment with any of the medications listed and that could not be either discontinued or switched to a different medication prior to starting study drug.
- Patients who had received chemotherapy = 1 week or who were within 5 half-lives of their last dose chemotherapy (6 weeks for nitrosurea or mitomycin-C) prior to starting studydrug or who have not recovered from side effects of such therapy. Hydroxyurea was permitted at the investigator's discretion prior to enrollment.
- Patients who had received imatinib = 1 week or who had not recovered from side effects of such therapy.
- Patients who had received immunotherapy = 1 week prior to starting study drug or who had not recovered from side effects of such therapy.
- Patients who had received any investigational drug (excluding STI571/Glivec®) = 4 weeks or investigational cytotoxic agent within 1 week (or who were within 5 half-lives of a previous investigational cytotoxic agent) prior to starting study drug or who had not recovered from side effects of such therapy.
- Patients who had received wide field radiotherapy = 4 weeks or limited field radiation for palliation = 2 week prior to starting study drug or who had not recovered from side effects of such therapy.
- Patients who had received imatinib = 5 days or who had not recovered from side effects of such therapy.
- Patients who were pregnant or breast feeding, or adults of reproductive potential not employing an effective serum pregnancy test. (Women of childbearing potential must have had a negative serum pregnancy test at baseline evaluation). Post-menopausal women must have been amenorrheic for at least 12 months to be considered of non-childbearing potential. Male and female patients must have agreed to employ an effective barrier method of birth control throughout the study and for up to 3 months following discontinuation of study drug.
- Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing was notmandatory).

- Patients with a history of another primary malignancy that was currently clinically significant or currently required active intervention.
- Patients unwilling or unable to comply with the protocol.

Number of Subjects

Patient disposition by initial dose cohort (ITT population)

	200 mg q.d. N = 4 n (%)	400 mg q.d. N = 4 n (%)	400 mg b.i.d. N = 3 n (%)	Total N = 11 n (%)
Completed the study	1 (25.0)	4 (100.0)	3 (100.0)	8 (72.7)
Discontinued the study	3 (75.0)	0 (0.0)	0 (0.0)	3 (27.3)
Adverse event(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject withdrew consent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disease progression	3 (75.0)	0 (0.0)	0 (0.0)	3 (27.3)

Approximately 9 patients were planned to be enrolled in the dose escalation (Phase I component) of the study; 11 patients (5 CML-CP, 2 CML-AP, 2 CML-BC, and 2 Ph+ ALL) were enrolled and treated with nilotinib; 11 patients were analyzed.

Three of 4 patients in the 200 mg q.d. cohort discontinued the study due to disease progression. All patients in the 400 mg q.d. cohort and the 400 mg b.i.d. cohort completed the study.

Demographic and Background Characteristics

Demographic summary by initial dose cohort (ITT population)

Demographic variable	200 mg q.d. N = 4	400 mg q.d. N = 4	400 mg b.i.d. N = 3	Total N = 11
Age (years)				
n	4	4	3	11
mean ± s.d.	61.3 ± 12.69	52.3 ± 12.53	50.7 ± 15.01	55.1 ± 12.83
Sex - n				
Female	1	0	0	1
Male	3	4	3	10
Weight (kg)				
n	4	4	3	11
mean ± s.d.	60.8 ± 8.59	75.7 ± 14.30	65.0 ± 6.78	67.3 ± 11.81
WHO performance status - n (%)				
Grade 0	1 (25.0)	4 (100.0)	3 (100.0)	8 (72.7)
Grade 1	3 (75.0)	0 (0.0)	0 (0.0)	3 (27.3)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade > 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

For all patients, the median age was 56 years (range 38 - 80 years), and 90.9% (10/11) of patients were male. The median body weight was 66.8 kg (range 48.1 - 86.1 kg). Eight of 11 (72.7%) patients had WHO PS grade 0, and the others had PS grade 1.

There was no apparent difference in demographic characteristics amongst the 3 cohorts.

Primary Objective Result(s)

DLT:

Dose limiting toxicities (DLTs) during Cycle 1 by initial dose cohort MTD-determining population

DLTs	200mg QDN=3	400mg QDN=3	400mg bidN=3	Total N=9
	n (%)	n (%)	n (%)	n (%)
There are no patients with Dose limiting toxicities				

Pharmacokinetics results:

Pharmacokinetic parameters of nilitinib (ITT population)

	Cohort	N	tmax (hr)	Cmax (ng/mL)	AUC0-12 (ng*hr/mL)	AUC0-24 (ng*hr/mL)
Day 1	200 mg q.d.	4	3.1 [3.0 - 4.0]	491 ± 174	-	6410 ± 2680
	400 mg q.d.	4	3.5 [1.9 - 7.0]	818 ± 420	-	11600 ± 5600
	400 mg b.i.d.	3	4.0 [4.0 - 7.0]	909 ± 300	7330 ± 2160	-
Day 15	200 mg q.d.	3	3.0 [3.0 - 7.0]	727 ± 170	-	11000 ± 800
	400 mg q.d.	4	3.0 [2.0 - 7.1]	1600 ± 510	-	21200 ± 9300
	400 mg b.i.d.	3	5.0 [3.0 - 5.0]	2760 ± 1730	26000 ± 18900	52000 ± 37800 [a)]

Median [min - max] for tmax, and mean ± SD for Cmax and AUC.

a): AUC0-24 for b.i.d dosing was calculated as AUC0-12 multiplied by 2.

Secondary Objective Result(s)

Efficacy results:

Hematologic response

Best hematologic response during the first three cycles by initial dose cohort and disease type (ITT population)

Disease type	Hematologic response category	200 mg q.d. N = 4 n (%)	400 mg q.d. N = 4 n (%)	400 mg b.i.d. N = 3 n (%)	Total N = 11 n (%)
CML-CP (N = 5)	Evaluable	1 (100.0)	1 (50.0)	0 (0.0)	2 (40.0)
	Not evaluable	0 (0.0)	1 (50.0)	2 (100.0)	3 (60.0)
	Evaluable Patients				
	CHR	0 (0.0)	1 (100.0)	0 (0.0)	1 (50.0)
	SD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	PD	1 (100.0)	0 (0.0)	0 (0.0)	1 (50.0)
	Not assessable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CML-AP (N = 2)	Hematologic response	0 (0.0)	2 (100.0)	0 (0.0)	2 (100.0)
	CHR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	MR/NEL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	RTC	0 (0.0)	2 (100.0)	0 (0.0)	2 (100.0)
	SD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	PD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Not assessable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CML-BC (N = 2)	Hematologic response	0 (0.0)	0 (0.0)	1 (100.0)	1 (50.0)
	CHR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	MR/NEL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	RTC	0 (0.0)	0 (0.0)	1 (100.0)	1 (50.0)
	SD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	PD	1(100.0)	0 (0.0)	0 (0.0)	1 (50.0)
	Not assessable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ph+ ALL (NOT MRD) (N = 2)	Hematologic response	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)
	CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	CRp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	PR	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)
	HI	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	SD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	PD	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)
	Not assessable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Cytogenetic response

Best cytogenetic response during the first three cycles in Ph+ CML patients by initial dose cohort and disease type (Ph+ CML patients in the ITT population)

Disease type	Cytogenetic response category	200 mg q.d. N = 2 n (%)	400 mg q.d. N = 4 n (%)	400 mg b.i.d. N = 3 n (%)	Total N = 9 n (%)
CML-CP (N = 5)	Evaluable	1 (100.0)	2 (100.0)	2 (100.0)	5 (100.0)
	Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Evaluable Patients				
	Major response	0 (0.0)	1 (50.0)	1 (50.0)	2 (40.0)
	Complete	0 (0.0)	1 (50.0)	0 (0.0)	1 (20.0)
	Partial	0 (0.0)	0 (0.0)	1 (50.0)	1 (20.0)
	Minor	0 (0.0)	0 (0.0)	1 (50.0)	1 (20.0)
	Minimal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Not assessable	1 (100.0)	1 (50.0)	0 (0.0)	2 (40.0)
CML-AP (N = 2)	Major response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Complete	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Partial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Minor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Minimal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	None	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)
	Not assessable	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)
CML-BC (N = 2)	Major response	0 (0.0)	0 (0.0)	1 (100.0)	1 (50.0)
	Complete	0 (0.0)	0 (0.0)	1 (100.0)	1 (50.0)
	Partial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Minor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Minimal	1 (100.0)	0 (0.0)	0 (0.0)	1 (50.0)
	None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Not assessable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Safety Results

Adverse events, regardless of study drug relationship, by system organ class

System organ class	200 mg q.d. N = 4 n (%)	400 mg q.d. N = 4 n (%)	400 mg b.i.d. N = 3 n (%)	Total N = 11 n (%)
Any system organ class	4 (100.0)	4 (100.0)	3 (100.0)	11 (100.0)
Blood and lymphatic system disorders	4 (100.0)	2 (50.0)	1 (33.3)	7 (63.6)
Cardiac disorders	1 (25.0)	0 (0.0)	1 (33.3)	2 (18.2)
Eye disorders	0 (0.0)	1 (25.0)	2 (66.7)	3 (27.3)
Gastrointestinal disorders	4 (100.0)	1 (25.0)	2 (66.7)	7 (63.6)
General disorders and administration site conditions	3 (75.0)	3 (75.0)	2 (66.7)	8 (72.7)
Hepatobiliary disorders	1 (25.0)	0 (0.0)	2 (66.7)	3 (27.3)
Immune system disorders	1 (25.0)	1 (25.0)	0 (0.0)	2 (18.2)
Infections and infestations	2 (50.0)	1 (25.0)	1 (33.3)	4 (36.4)
Investigations	3 (75.0)	3 (75.0)	2 (66.7)	8 (72.7)
Metabolism and nutrition disorders	3(75.0)	1 (25.0)	3 (100.0)	7 (63.6)
Musculoskeletal and connective tissue disorders	2 (50.0)	2 (50.0)	2 (66.7)	6 (54.5)
Nervous system disorders	3 (75.0)	3 (75.0)	2 (66.7)	8 (72.7)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	3 (75.0)	0 (0.0)	3 (27.3)
Skin and subcutaneous tissue disorders	3 (75.0)	2 (50.0)	3 (100.0)	8 (72.7)

Most Frequently Reported AEs Overall by Preferred Term n (%)

Preferred term	Total N = 11 n (%)
Neutropenia	6 (54.5)
Pyrexia	6 (54.5)
Headache	6 (54.5)
Anaemia	4 (36.4)
Leukopenia	4 (36.4)
Thrombocytopenia	4 (36.4)
Rash	4 (36.4)
Lymphopenia	3 (27.3)
Eye disorders	3 (27.3)

Nausea	3 (27.3)
Vomiting	3 (27.3)
Blood creatine phosphokinase increased	3 (27.3)
Blood creatinine increased	3 (27.3)
Blood lactate dehydrogenase increased	3 (27.3)
Blood phosphorus decreased	3 (27.3)
Anorexia	3 (27.3)
Hypokalaemia	3 (27.3)
Myalgia	3 (27.3)

Serious Adverse Events and Deaths

	Nilotinib
No. (%) of subjects studied	11
No. (%) of subjects with AE(s)	11 (100)
Number (%) of subjects with serious or other significant events	n (%)
Death	0
SAE(s)[1]	4 (36.36)
Discontinued due to SAE(s)	0

1 Thrombocytopenia, 1 cardiac failure, 1 sepsis, 1 hypercalcemia

Other Relevant Findings

The pharmacokinetics parameters have been described under Primary Objective Result(s).

Date of Clinical Trial Report

21 May 2007

Date Inclusion on Novartis Clinical Trial Results Database

7 May 2010

Date of Latest Update

14 May 2008