Sponsor

Novartis

Generic Drug Name

Nilotinib

Therapeutic Area of Trial

Chronic Myeloid Leukemia

Approved Indication

Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia resistant to or intolerant to imatinib.

Study Number

CAMN107A2109

Title

An open-label, multicenter, expanded access study of oral AMN 107 in adult patients with Imatinib (Glivec®/Gleevec®) - resistant or -intolerant chronic myeloid leukemia in blast crisis, accelerated phase or chronic phase

Phase of Development

Phase III

Study Start/End Dates

13-Jan-2006 (FPFV) to 12-Nov-2008 (LPLV)

Study Design/Methodology

Multicenter, open-label, non-randomized study of oral nilotinib (400 mg b.i.d.) in patients with imatinib-resistant or -intolerant Philadelphia chromosome positive (Ph+) CML-BC, CML-AP, or CML-CP.

A total of 1793 patients were asked to attend the clinic for the screening visit, twice during the first month of the trial, once during the second month and third month, then once every 3 months thereafter until study completion. As per protocol, all patients were to receive nilotinib 400 mg orally b.i.d, provided there were no safety concerns. All dose reductions were based on the worst graded toxicity during the previous cycle. Dose re-escalation to nilotinib 400 mg b.i.d. following prior nilotinib reduction due to AEs, was permitted after resolution of the associated adverse event/s to grade = 1. Treatment with nilotinib was continued until the patient experienced unacceptable toxicity that precluded any further treatment, disease progression, and/or as long as the patient was benefiting, at the discretion of the Investigator. The objectives of the trial were to evaluate the safety profile of nilotinib in a large number of patients and to provide patients with life-threatening conditions, imatinib resistant/intolerant CML in BC, AP, and CP, with expanded access to nilotinib until such time as the product was commercially available. In the event where nilotinib did not become commercially available by the aforementioned Last Patient Last Visit (LPLV) date then each pertinent participating country had a plan in place to ensure that patients

still being treated at the global LPLV date could continue to receive nilotinib. Efficacy was not considered part of the objectives, however, to quantify the benefit to patients, efficacy data on disease response and progression based on the Investigator's assessment were collected.

Centers

375 in total – 284 recruited patients

USA (60 centers), Germany (55), Italy (48), Spain (28), France (22), Belgium (21), United Kingdom (11),Brazil (9), Taiwan (9), Canada (8), Russia (8), China (7), Korea (7), Austria (6), Netherlands (6), Turkey (6), Australia (5), Czech Republic (5), Malaysia (5), Poland (5), Sweden (5), Switzerland (5), Thailand (5), Greece (4), Mexico (3), South Africa (3), Denmark (2), New Zealand (2), Slovakia (2), Argentina (1), Egypt (1), Hong Kong (1), Hungary (1), Ireland (1), Lebanon (1), Jordan (1), Norway (1), Singapore (1), Saudi Arabia (1), United Arab Emirates (1), and Venezuela (1)

Publication

None

Objectives

- To evaluate the safety profile of nilotinib in a large number of patients.
- To provide patients with life-threatening conditions; imatinib-resistant or –intolerant Chronic Myeloid Leukemia – in Blast Crisis (BC), Accelerated Phase (AP) and Chronic Phase (CP) with expanded access to nilotinib until such time as the prduct was commercially available or as defined by local regulations for patient transition to compassionate use or local study.

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

Nilotinib was supplied as a 200 mg hard gelatin capsule. Patients receive nilotinib 400 mg orally b.i.d. as per protocol.

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

Not applicable

Criteria for Evaluation

Safety:

- Monitoring all AEs, SAEs;
- Cardiac assessments including MUGA/ECHO, chest X-ray, and ECG monitoring;
- Monitoring of hematology, blood chemistry, and urine values;
- Measurement of vital signs, physical examination including body weight, and performance status;
- Monitoring of pregnancies.

Efficacy:

- Efficacy assessments were not part of the objectives for this study. However, to quantify the benefit to patients, efficacy data on disease response and progression based on the Investigator's assessment were collected. Therefore it was recommended the sites performed, as a minimum, 6 monthly Aspirate and cytogenetic analysis of bone marrow, evaluation of extra medullary disease, cancer-related symptoms according to the defined standard response criteria for each stage of the disease: BC, AP, and CP, to assess response and disease progression.

Statistical Methods

Two analysis populations, (i) ITT population, included all patients who received at least one dose of the study medication. Patients who were screened but never started treatment were listed, but not included in the ITT population; (ii) Safety population included all patients who received at least one dose of study medication and had at least one post-baseline safety assessment.

The data were summarized descriptively. Continuous variables: summarized by mean, SD, median, minimum, maximum (25% and 75% quartiles, as appropriate) and number of patients with non-missing data. Categorical variables were summarized by absolute frequencies and percentages. For the efficacy analyses, The number and % of responders were presented as well as the associated 95% CI. Analyses were performed for the best responses within 6 months of treatment and during the entire study. All safety analyses were performed using the safety population. The assessment of safety was based mainly on the frequency of AEs. ECG data were summarized and listed as appropriate. Laboratory data were not collected nor analyzed by the sponsor, except that abnormal laboratory values or test results might be recorded and analyzed as AEs. Notably abnormal vital sign values, LVEF data, and overall interpretation for cardiac imaging and chest x-ray evaluations were listed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Males or females = 18 years of age.
- WHO performance status = 2.
- IM-resistant or -intolerant Ph+ CML in BC defined as at least 30% blasts in peripheral blood and/or bone marrow or extramedullary disease excluding liver and spleen.

- Imatinib-resistant or -intolerant Ph+ CML patients in AP defined with one or more of the following criteria present within 4 weeks prior to beginning treatment:
  - = 15% but < 30% blasts in blood or bone marrow
  - = 30% blasts plus promyelocytes in peripheral blood or bone marrow (providing that < 30% blasts present in bone marrow)
  - Peripheral basophils = 20%
  - Thrombocytopenia <100 x 10^9/L unrelated to therapy
- Imatinib-resistant or -intolerant Ph+ CML in CP defined with the following criteria:
  - < 15% blasts in peripheral blood and bone marrow
  - < 30% blasts plus promyelocytes in peripheral blood and bone marrow
  - < 20% basophils in the peripheral blood
  - = 50 x 10^9/L (= 50,000/mm^3) platelets
  - No evidence of extramedullary leukemic involvement, with the exception of liver and spleen
- CML patients who had been treated with an investigational TKI who otherwise meet the definition of imatinib-resistance or intolerance are eligible
- Patients who had received dasatinib provided that they had at least one day (24 hours) washout from their last dose of medication and have recovered from side effects of such therapy prior to starting study drug.
- Potassium, total calcium, magnesium, and phosphorus within normal limits or correctable to WNL with supplements.
- ALT & AST = 2.5 x ULN or = 5.0 x ULN if due to tumor; Alkaline phosphatase = 2.5 x ULN unless due to tumor.
- Serum bilirubin = 1.5 x ULN; Serum creatinine = 1.5 x ULN or 24-hour creatinine clearance = 50 mL/min; Serum amylase and serum lipase = 1.5 x ULN.

Exclusion criteria

- Cytopathologically confirmed CNS infiltration. (in absence of suspicion of CNS involvement, lumbar puncture is not required)
- Impaired cardiac function, including any one of the following:
  - LVEF < 45% or below the institutional lower limit of the normal range (whichever is higher) as determined by MUGA scan or echocardiogram
  - Complete left bundle branch block
  - Use of a ventricular-paced pacemaker
  - Congenital long QT syndrome
  - History of or presence of clinically significant ventricular or atrial tachyarrhythmias
  - Clinically significant resting bradycardia (< 50 beats per minute)
  - QTc > 450 msec on screening and on day 1 ECG (using the QTcF formula). If QTc >450 msec and electrolytes are not within normal ranges before AMN107 dosing, electrolytes should be corrected and then the patient rescreened for QTc criterion
  - Right bundle branch block plus left anterior hemiblock, bifascicular block
  - Myocardial infarction within 12 months prior to starting AMN107

- Other clinically significant heart disease (e.g., unstable angina, congestive heart failure, uncontrolled hypertension)

- Use of therapeutic coumarin derivatives (i.e., warfarin, acenocoumarol, phenprocoumon) up to the day before study drug administration
- Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection, acute or chronic liver disease considered unrelated to tumor, impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of AMN107 that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol)
- Patients who are currently receiving treatment with any of the medications that have the potential to prolong the QT interval or are strong CYP3A4 inhibitors or who are within 5 half-lives of the last dose of this medication prior to starting study drug.
- Patients who have received chemotherapy = 1 week or who are within 5 half-lives of their last dose of chemotherapy (6 weeks for nitrosurea or mitomycin-C) prior to starting study drug or who have not recovered from side effects of such therapy. Hydroxyurea is permitted as clinically indicated at the investigators discretion prior to enrollment Patients who have received imatinib within 3 days prior to beginning of study drug or who have not recovered from side effects of such therapy.
- Patients who have received immunotherapy =1 week prior to starting study drug or who have not recovered from side effects of such therapy
- Patients who have received any investigational drug = 4 weeks or investigational drug /cytotoxic agent within 1 week (or who are within 5 half-lives of a previous investigational cytotoxic agent) prior to starting study drug or who have not recovered from side effects of such therapy
- Patients who have undergone major surgery = 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy known diagnosis of human deficiency virus (HIV) infection (HIV testing is not mandatory)
- Patient with a history of another malignancy that is currently clinically significant or currently requires active intervention.
- Patients who are pregnant or breast feeding, or adults of reproductive potential not employing an effective method of birth control. (Women of childbearing potential must have a negative serum pregnancy test within 48 hrs prior to administration of AMN107). Post menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Male and female patients must agree to employ a highly effective method of birth control throughout the study and for 6 months following discontinuation of study drug. A highly effective method of birth control is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomised partner. The effect of AMN107 on female and male fertility and spermogenesis is unknown. Male patients should be counseled on the risks of an irreversible infertility and the option of sperm cryopreservation.
- Patients unwilling or unable to comply with the protocol
- Prior treatment with nilotinib

Results:

Patient disposition – n (%) of patients (All patients)

	CML-CP N=1422 n (%)	CML-AP N=181 n (%)	CML-BC N=190 n (%)	Total N=1793 n (%)
Completed the Study	857 (60.3)	65 (35.9)	19 (10.0)	941 (52.5)
Discontinued	565 (39.7)	116 (64.1)	171 (90.0)	852 (47.5)
Primary reason for discontinuation				
Adverse event(s)	204 (14.3)	27 (14.9)	24 (12.6)	255 (14.2)
Abnormal laboratory value(s)	26 (1.8)	2 (1.1)	5 (2.6)	33 (1.8)
Abnormal test procedure result(s)	3 (0.2)	0	0	3 (0.2)
Unsatisfactory therapeutic effect	222 (15.6)	63 (34.8)	100 (52.6)	385 (21.5)
Subject's condition no longer requires study drug	9 (0.6)	3 (1.7)	4 (2.1)	16 (0.9)
Protocol violation	16 (1.1)	3 (1.7)	2 (1.1)	21 (1.2)
Subject withdrew consent	46 (3.2)	6 (3.3)	5 (2.6)	57 (3.2)
Lost to follow-up	18 (1.3)	2 (1.1)	4 (2.1)	24 (1.3)
Administrative problems	6 (0.4)	0	1 (0.5)	7 (0.4)
Death*	15 (1.1)	10 (5.5)	26 (13.7)	51 (2.8)

* Death includes only those patients for whom death was reported as the primary reason for discontinuation of study drug on the End of Study CRF.

Analysis populations (All patients)

Populations	CML-CP N=1422 n (%)	CML-AP N=181 n (%)	CML-BC N=190 n (%)	Total N=1793 n (%)
Intent-to-treat (ITT)	1422 (100.0)	181 (100.0)	190 (100.0)	1793 (100.0)
Safety	1422 (100.0)	181 (100.0)	190 (100.0)	1793 (100.0)

Demographic and Background Characteristics

Demographic summary by disease classification (ITT population)

Demographic Variable	CML-CP N=1422	CML-AP N=181	CML-BC N=190	Total N=1793
Age (years)				
Mean	52.0	50.0	48.6	51.4
SD	14.10	14.74	15.04	14.31
Median	53.0	50.0	50.0	52.0
Min -Max	17-85	18-86	19-83	17-86
Sex – n (%)				
Female	726 (51.1)	77 (42.5)	68 (35.8)	871 (48.6)
Male	696 (48.9)	104 (57.5)	122 (64.2)	922 (51.4)
Race – n (%)				
Asian	277 (19.5)	46 (25.4)	63 (33.2)	386 (21.5)
Black	47 (3.3)	9 (5.0)	10 (5.3)	66 (3.7)
Caucasian	1029 (72.4)	113 (62.4)	108 (56.8)	1250 (69.7)
Native American	9 (0.6)	2 (1.1)	1 (0.5)	12 (0.7)
Other	57 (4.0)	10 (5.5)	8 (4.2)	75 (4.2)
Pacific islander	2 (0.1)	1 (0.6)	0	3 (0.2)
Ethnicity – n (%)				
Chinese	132 (9.3)	28 (15.5)	42 (22.1)	202 (11.3)
Hispanic/Latino	186 (13.1)	24 (13.3)	24 (12.6)	234 (13.1)
Indian (Indian subcontinent)	12 (0.8)	0	1 (0.5)	13 (0.7)
Japanese	1 (0.1)	0	0	1 (0.1)
Mixed Ethnicity	6 (0.4)	0	0	6 (0.3)
Other	1085 (76.3)	129 (71.3)	123 (64.7)	1337 (74.6)
Weight (kg)				
n	1403	173	188	1764
Mean	75.0	74.0	71.8	74.6
SD	17.31	18.68	17.73	17.52
Median	73.0	71.0	69.0	72.3
Min -Max	40.1-165.0	43.0-167.2	43.0-156.1	40.1-167.2
Height (cm)				
n	1383	172	185	1740
Mean	167.1	168.6	168.8	167.4
SD	9.83	9.28	10.30	9.84
Median	166.0	168.0	170.0	167.0
Min -Max	140-198	145-196	142-195	140-198
WHO Performance Status – n (%)				
Grade 0	1043 (73.3)	77 (42.5)	66 (34.7)	1186 (66.1)
Grade 1	296 (20.8)	78 (43.1)	62 (32.6)	436 (24.3)
Grade 2	29 (2.0)	17 (9.4)	57 (30.0)	103 (5.7)
Grade > 2	0	0	1 (0.5)	1 (0.1)
Missing	54 (3.8)	9 (5.0)	4 (2.1)	67 (3.7)

Safety Results

Adverse events regardless of study drug relationship by system organ class (Safety population)

Primary system organ class	CML-CP N=1422 n (%)	CML-AP N=181 n (%)	CML-BC N=190 n (%)	Total N=1793 n (%)
Any system organ class	1372 (96.5)	173 (95.6)	186 (97.9)	1731 (96.5)
Blood and lymphatic system disorders	630 (44.3)	120 (66.3)	142 (74.7)	892 (49.7)
Cardiac disorders	156 (11.0)	19 (10.5)	30 (15.8)	205 (11.4)
Congenital, familial and genetic disorders	10 (0.7)	1 (0.6)	1 (0.5)	12 (0.7)
Ear and labyrinth disorders	47 (3.3)	8 (4.4)	6 (3.2)	61 (3.4)
Endocrine disorders	17 (1.2)	1 (0.6)	0	18 (1.0)
Eye disorders	142 (10.0)	15 (8.3)	13 (6.8)	170 (9.5)
Gastrointestinal disorders	696 (48.9)	92 (50.8)	108 (56.8)	896 (50.0)
General disorders and administration site conditions	577 (40.6)	88 (48.6)	120 (63.2)	785 (43.8)
Hepatobiliary disorders	336 (23.6)	43 (23.8)	49 (25.8)	428 (23.9)
Immune system disorders	20 (1.4)	5 (2.8)	2 (1.1)	27 (1.5)
Infections and infestations	540 (38.0)	73 (40.3)	100 (52.6)	713 (39.8)
Injury, poisoning and procedural complications	77 (5.4)	14 (7.7)	17 (8.9)	108 (6.0)
Investigations*	623 (43.8)	82 (45.3)	93 (48.9)	798 (44.5)
Metabolism and nutrition disorders	525 (36.9)	76 (42.0)	78 (41.1)	679 (37.9)
Musculoskeletal and connective tissue disorders	583 (41.0)	65 (35.9)	77 (40.5)	725 (40.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	34 (2.4)	9 (5.0)	17 (8.9)	60 (3.3)
Nervous system disorders	519 (36.5)	59 (32.6)	60 (31.6)	638 (35.6)
Pregnancy, puerperium and perinatal conditions	1 (0.1)	0	0	1 (0.1)
Psychiatric disorders	151 (10.6)	20 (11.0)	24 (12.6)	195 (10.9)
Renal and urinary disorders	75 (5.3)	13 (7.2)	17 (8.9)	105 (5.9)
Reproductive system and breast disorders	86 (6.0)	9 (5.0)	11 (5.8)	106 (5.9)
Respiratory, thoracic and mediastinal disorders	355 (25.0)	63 (34.8)	76 (40.0)	494 (27.6)
Skin and subcutaneous tissue disorders	728 (51.2)	83 (45.9)	99 (52.1)	910 (50.8)
Social circumstances	1 (0.1)	0	0	1 (0.1)
Surgical and medical procedures	4 (0.3)	0	1 (0.5)	5 (0.3)
Vascular disorders	145 (10.2)	23 (12.7)	32 (16.8)	200 (11.2)

* For further clarification of AEs under Investigation, see MedDRA terminology (version 11.1).

Frequent AEs (occurring in = 10% of patients overall) were thrombocytopenia (31.6%), rash (27.4%),headache (23.8%), hyperbilirubinemia (20.2%), neutropenia (19.4%), anemia (19.1%), nausea(17.2%), pyrexia (17.2%), increased ALT (15.3%), pruritus (14.8%), fatigue (13.2%), vomiting (12.8%),constipation (12.6%), diarrhea (12.4%), increased lipase (12.3%), myalgia (12.0%), cough (11.7%), and asthenia (10.2%).

Frequent serious adverse events regardless of study drug relationship by preferred term (at least 2% in any group) and CTC severity grade (Safety population)

Preferred term	All grades				Grade 3 or 4			
	CML-CP N=1422 n (%)	CML-AP N=181 n (%)	CML-BC N=190 n (%)	Total N=1793 n (%)	CML-CP N=1422 n (%)	CML-AP N=181 n (%)	CML-BC N=190 n (%)	Total N=1793 n (%)
Pyrexia	25 (1.8)	14 (7.7)	21 (11.1)	60 (3.3)	7 (0.5)	4 (2.2)	10 (5.3)	21 (1.2)
Thrombocytope-nia	32 (2.3)	14 (7.7)	14 (7.4)	60 (3.3)	31 (2.2)	14 (7.7)	14 (7.4)	59 (3.3)
Febrile neutrope-nia	14 (1.0)	6 (3.3)	14 (7.4)	34 (1.9)	10 (0.7)	4 (2.2)	10 (5.3)	24 (1.3)
Neutropenia	16 (1.1)	6 (3.3)	11 (5.8)	33 (1.8)	15 (1.1)	5 (2.8)	10 (5.3)	30 (1.7)
Anemia	12 (0.8)	7 (3.9)	12 (6.3)	31 (1.7)	10 (0.7)	6 (3.3)	10 (5.3)	26 (1.5)
Pneumonia	16 (1.1)	5 (2.8)	10 (5.3)	31 (1.7)	12 (0.8)	3 (1.7)	8 (4.2)	23 (1.3)
Dyspnea	16 (1.1)	4 (2.2)	4 (2.1)	24 (1.3)	12 (0.8)	4 (2.2)	3 (1.6)	19 (1.1)
Leukocytosis	9 (0.6)	3 (1.7)	6 (3.2)	18 (1.0)	7 (0.5)	3 (1.7)	6 (3.2)	16 (0.9)
Diarrhea	8 (0.6)	2 (1.1)	4 (2.1)	14 (0.8)	5 (0.4)	0	0	5 (0.3)
Septic shock	3 (0.2)	2 (1.1)	8 (4.2)	13 (0.7)	3 (0.2)	2 (1.1)	8 (4.2)	13 (0.7)
White blood cell count increased	2 (0.1)	1 (0.6)	6 (3.2)	9 (0.5)	2 (0.1)	1 (0.6)	5 (2.6)	8 (0.4)
Cardiac failure	1 (0.1)	3 (1.7)	4 (2.1)	8 (0.4)	1 (0.1)	3 (1.7)	3 (1.6)	7 (0.4)
Cerebral hemorrhage	1 (0.1)	1 (0.6)	5 (2.6)	7 (0.4)	1 (0.1)	1 (0.6)	5 (2.6)	7 (0.4)
Sepsis	1 (0.1)	0	6 (3.2)	7 (0.4)	1 (0.1)	0	6 (3.2)	7 (0.4)
Blast cell count increased	0	0)	5 (2.6)	5 (0.3)	0	0	5 (2.6)	5 (0.3)
Lower respiratory tract infection	1 (0.1)	4 (2.2)	0	5 (0.3)	0	3 (1.7)	0	3 (0.2)

Preferred terms are presented in descending frequency in the Total group with all grades.

- In total, 26.2% of patients experienced at least one SAE of any grade and 21.7% experienced a grade 3/4 SAE. The most commonly affected primary System Organ Class (SOC) of SAEs was blood and lymphatic system disorders (8.3%), mainly consisting of thrombocytopenia (3.3%), febrile neutropenia (1.9%), neutropenia (1.8%), and anemia (1.7%),
- Other frequently affected primary SOCs were infections and infestations (6.9%) such as pneumonia (1.7%), gastrointestinal disorders (5.1%) such as diarrhea (0.8%), and general disorders and administration site conditions (4.8%) such as pyrexia (3.3%), cardiac disorders (3.0%) such as cardiac failure (0.4%), and respiratory, thoracic and mediastinal disorders (3.2%) such as dyspnea (1.3%).
- Out of 469 patients who experienced SAEs, 194 (10.8%) had SAEs suspected of being re-

lated to nilotinib. SAEs most commonly suspected of being related to nilotinib were thrombocytopenia (2.6%), neutropenia (1.4%), febrile neutropenia (1.2%), anemia (1.1%), pyrexia (0.6%), and vomiting (0.5%). All other SAEs suspected of being related to nilotinib occurred in <0.5% of patients in the total group, with no meaningful differences between CML groups.

Dose reduction and dose interruption (Safety population)

Parameter	**CML-CP N=1422 n (%)**	**CML-AP N=181 n (%)**	**CML-BC N=190 n (%)**	**Total N=1793 n (%)**
Patients with dose reduction				
Yes	678 (47.7)	71 (39.2)	79 (41.6)	828 (46.2)
No	744 (52.3)	110 (60.8)	111 (58.**4)**	965 (53.8)
Reason for dose reduction				
Adverse Event	311 (21.9)	42 (23.2)	43 (22.6)	396 (22.1)
Dosing Error	80 (5.6)	8 (4.4)	10 (5.3)	98 (5.5)
Lab Test Abnormality	43 (3.0)	12 (6.6)	11 (5.8)	66 (3.7)
Scheduling Conflict	33 (2.3)	9 (5.0)	16 (8.4)	58 (3.2)
Missing	307 (21.6)	16 (8.8)	8 (4.2)	331 (18.5)
No response assessment**				
Discontinued	207 (14.6)	35 (19.3)	40 (21.1)	282 (15.7)
Ongoing	45 (3.2)	3 (1.7)	2 (1.1)	50 (2.8)
Patients with Dose interruption				
Yes	745 (52.4)	94 (51.9)	85 (44.7)	924 (51.5)
No	677 (47.6)	87 (48.1)	105 (55.3)	869 (48.5)
Reason for Dose Interruption				
Adverse Event	626 (44.0)	79 (43.6)	73 (38.4)	778 (43.4)
Dosing Error	50 (3.5)	8 (4.4)	5 (2.6)	63 (3.5)
Lab Test Abnormality	111 (7.8)	11 (6.1)	13 (6.8)	135 (7.5)
Scheduling Conflict	33 (2.3)	6 (3.3)	1 (0.5)	40 (2.2)
Missing	1 (0.1)	0	0	1 (0.1)

- A patient with multiple dose reductions or dose interruptions is counted only once in the respective “Yes” category. Multiple episodes of the same reason for a patient are counted only once. A patient with multiple reasons is counted once in each of the reason category.
- Dose reduction refers to dose decrease from previous dose record to a lower dose equal to 0.
- Dose interruption refers to dose decrease to 0.

- Blood and lymphatic system disorders were the most commonly reported affected primary SOC causing discontinuation, occurring in 162 patients (9.0%) overall and with comparable frequency across all CML groups (8.8%, 9.4% and 10.5% for CML-CP, CML-AP and CMLBC, respectively).
- Other frequent hematological AEs leading to discontinuation were anemia leukocytosis (0.6%), leukopenia (0.4%), increased white blood cell count (0.3%), pancytopenia (0.1%) Most of the anemia AEs and all of the leukopenia causing discontinuation were suspected of being related to study drug.

Deaths, other serious or clinically significant adverse events (Safety population)

Deaths and serious or significant events	CML-CP N=1422 n (%)	CML-AP N=181 n (%)	CML-BC N=190 n (%)	Total N=1793 n (%)
Deaths on study or within 28 days of last dose*	17 (1.2)	10 (5.5)	27 (14.2)	54 (3.0)
Deaths due to progressive disease**	2 (0.1)	3 (1.7)	7 (3.7)	12 (0.7)
Patients with SAE(s)	284 (20.0)	71 (39.2)	114 (60.0)	469 (26.2)
SAE(s) related to study drug	127 (8.9)	31 (17.1)	36 (18.9)	194 (10.8)
SAE(s) leading to discontinuation	61 (4.3)	18 (9.9)	35 (18.4)	114 (6.4)
Patients with AE(s)	1372 (96.5)	173 (95.6)	186 (97.9)	1731 (96.5)
AE(s) related to study drug	1249 (87.8)	153 (84.5)	147 (77.4)	1549 (86.4)
AE(s) leading to discontinuation	256 (18.0)	40 (22.1)	59 (31.1)	355 (19.8)
AE(s) requiring dose adjustment or interruption	780 (54.9)	105 (58.0)	99 (52.1)	984 (54.9)
Grade 3 or 4 AE(s)	872 (61.3)	137 (75.7)	162 (85.3)	1171 (65.3)

* Death count includes only 51 deaths which occurred on study and 3 additional deaths which occurring within 28 days of last dose and were imputed manually.

**Progressive disease = CML (chronic myeloid leukemia)

Primary cause of death as recorded in the clinical database (n=54) by preferred term (Safety population)

Preferred term	CML-CP N=1422 n (%)	CML-AP N=181 n (%)	CML-BC N=190 n (%)	Total N=1793 n (%)
Any death [1]	17 (1.2)	10 (5.5)	27 (14.2)	54 (3.0)
Progressive disease [2]	2 (0.1)	3 (1.7)	7 (3.7)	12 (0.7)
Cerebral hemorrhage	1 (0.1)	1 (0.6)	2 (1.1)	4 (0.2)
Respiratory failure	1 (0.1)	1 (0.6)	2 (1.1)	4 (0.2)
Septic shock	1 (0.1)	0	3 (1.6)	4 (0.2)
Cardiac failure	0	1 (0.6)	2 (1.1)	3 (0.2)
Death [3]	2 (0.1)	0	0	2 (0.1)
Intracranial hemorrhage	1 (0.1)	0	1 (0.5)	2 (0.1)
Multi-organ failure	1 (0.1)	1 (0.6)	0	2 (0.1)
Sepsis	0	2 (1.1)	2 (1.1)	0 2 (1.1) 2 (0.1)
Acute coronary syndrome	1 (0.1)	0	0	1 (0.1)
Cerebrovascular accident	0	0	1 (0.5)	1 (0.1)
Circulatory collapse	1 (0.1)	0	0	1 (0.1)
Hemorrhagic stroke	0	0	1 (0.5)	1 (0.1)
Intra-abdominal hemorrhage	0	1 (0.6)	0	1 (0.1)
Klebsiella sepsis	0	0	1 (0.5)	1 (0.1)
Lobar pneumonia	0	1 (0.6)	0	1 (0.1)
Lung infection	1 (0.1)	0	0	1 (0.1)
Meningitis	1 (0.1)	0	0	1 (0.1)
Meningorrhagia	0	0	1 (0.5)	1 (0.1)
Myeloid leukemia	0	0	1 (0.5)	1 (0.1)

Myocardial infarction	1 (0.1)	0	0	1 (0.1)
Pneumonia	0	0	1 (0.5)	1 (0.1)
Pulmonary edema	0	0	1 (0.5)	1 (0.1)
Pulmonary hemorrhage	0	0	1 (0.5)	1 (0.1)
Sinus bradycardia	1 (0.1)	0	0	1 (0.1)
Subdural hemorrhage	1 (0.1)	0	0	1 (0.1)
Sudden death	1 (0.1)	0	0	1 (0.1)
Thrombocytopenia	0	1 (0.6)	0	1 (0.1)

Abbreviations: AP = accelerated phase, BC = blast crisis, CML = chronic myelogenous leukemia, CP = chronic phase.

[1] Includes only those patients for whom death was reported as the primary reason for discontinuation from the study.

[2] Progressive disease = chronic myeloid leukemia

[3] Causes of death of two patients were unknown

- Fifty-four patients (3.0%) died during the study or = 28 days after the last dose of nilotinib. Of the 54 deaths, 51 (2.8%) were reported on the End of Study CRF as the primary reason for discontinuation. The other three patients had a different reason for study discontinuation as reported on the End of Study CRF or AE CRF.
- The most common reported primary cause of death among these 54 patients was progressive disease, i.e. CML, which occurred in 12 patients (0.7%) overall, the majority of whom had CML-BC (7 patients). Three patients in the CML-CP group died due to unspecified causes: two deaths were of unknown causes and one death was reported as sudden death. Hemorrhagic events were responsible for a number of deaths: cerebral hemorrhage, four deaths (0.2%); intracranial hemorrhage, two deaths (0.1%); hemorrhagic stroke, intra-abdominal hemorrhage, meningorrhagia, pulmonary hemorrhage, and subdural hemorrhage, 1 death each. One CMLAP patient died due to thrombocytopenia. There were no apparent trends in the causes of deaths between the CML groups, with the exception, as expected, of the higher number of CML-BC patients who died from progressive disease.

Efficacy Results – Investigator's assessment

Best hematologic response within 6 months of treatment and during the study for all patients (ITT population)

Parameter	**CML-CP N=1422 n (%)**	**CML-AP N=181 n (%)**	**CML-BC N=190 n (%)**	**Total N=1793 n (%)**
Month 6				
Hematologic responders	828 (58.2)	76 (42.0)	40 (21.1)	944 (52.6)
95% CI	55.7 - 60.8	34.8 - 49.2	15.3 - 26.8	50.3 - 55.0
Complete hematologic response (CHR)	519 (36.5)	38 (21.0)	13 (6.8)	570 (31.8)
Marrow response/No evidence of leukemia	309 (21.7)	23 (12.7)	15 (7.9)	347 (19.4)
Return to chronic phase (RTC)	n/a	15 (8.3)	12 (6.3)	27 (1.5)
Stable disease	221 (15.5)	28 (15.5)	39 (20.5)	288 (16.1)
Not adequate for response	61 (4.3)	13 (7.2)	11 (5.8)	85 (4.7)

Non-responders *	312 (21.9)	64 (35.4)	100 (52.6)	476 (26.5)
Progressive disease	60 (4.2)	26 (14.4)	58 (30.5)	144 (8.0)
No response assessment**	252 (17.7)	38 (21.0)	42 (22.1)	332 (18.5)
Discontinued	207 (14.6)	35 (19.3)	40 (21.1)	282 (15.7)
Ongoing	45 (3.2)	3 (1.7)	2 (1.1)	50 (2.8)
Overall study				
Hematologic responders	900 (63.3)	78 (43.1)	44 (23.2)	1022 (57.0)
95% CI	60.8 - 65.8	35.9 - 50.3	17.2 - 29.2	54.7 - 59.3
Complete hematologic response (CHR)	611 (43.0)	40 (22.1)	16 (8.4)	667 (37.2)
Marrow response/No evidence of leukemia	289 (20.3)	23 (12.7)	17 (8.9)	329 (18.3)
Return to chronic phase (RTC)	n/a	15 (8.3)	11 (5.8)	26 (1.5)
Stable disease	186 (13.1)	27 (14.9)	39 (20.5)	252 (14.1)
Not adequate for response	47 (3.3)	13 (7.2)	8 (4.2)	68 (3.8)
Non-responders*	289 (20.3)	63 (34.8)	99 (52.1)	451 (25.2)
Progressive disease	64 (4.5)	26 (14.4)	59 (31.1)	149 (8.3)
No response assessment**	225 (15.8)	37 (20.4)	40 (21.1)	302 (16.8)
Discontinued	225 (15.8)	37 (20.4)	40 (21.1)	302 (16.8)

* Patients with progressive disease as their best response or had no response assessment were considered non-responders.

** Patients who did have any post-baseline hematologic assessment (discontinued or ongoing) by this time point.

Best cytogenetic response within 6 months and during the study for all patients (ITT population)

	CML-CP N=1422 n (%)	CML-AP N=181 n (%)	CML-BC N=190 n (%)	Total N=1793 n (%)
Month 6				
Major cytogenetic response (CR, PR)	550 (38.7)	23 (12.7)	34 (17.9)	607 (33.9)
95% CI	36.1 - 41.2	7.9 - 17.6	12.4 - 23.3	31.7 - 36.0
Complete response	381 (26.8)	9 (5.0)	21 (11.1)	411 (22.9)
Partial response	169 (11.9)	14 (7.7)	13 (6.8)	196 (10.9)
Minor cytogenetic response	69 (4.9)	8 (4.4)	8 (4.2)	85 (4.7)
Minimal cytogenetic response	119 (8.4)	19 (10.5)	13 (6.8)	151 (8.4)
None cytogenetic response *	269 (18.9)	53 (29.3)	45 (23.7)	367 (20.5)
No response assessment **	415 (29.2)	78 (43.1)	90 (47.4)	583 (32.5)
Discontinued	284 (20.0)	60 (33.1)	83 (43.7)	427 (23.8)
Ongoing	131 (9.2)	18 (9.9)	7 (3.7)	156 (8.7)
Overall study				
Major cytogenetic response (CR, PR)	641 (45.1)	35 (19.3)	37 (19.5)	713 (39.8)
95% CI	42.5 - 47.7	13.6 -25.1	13.8 - 25.1	37.5 - 42.0
Complete response	486 (34.2)	20 (11.0)	24 (12.6)	530 (29.6)

Partial response	155 (10.9)	15 (8.3)	13 (6.8)	183 (10.2)
Minor cytogenetic response	65 (4.6)	7 (3.9)	10 (5.3)	82 (4.6)
Minimal cytogenetic response	115 (8.1)	20 (11.0)	12 (6.3)	147 (8.2)
None cytogenetic response*	254 (17.9)	47 (26.0)	43 (22.6)	344 (19.2)
No response assessment**	347 (24.4)	72 (39.8)	88 (46.3)	507 (28.3)
Discontinued	347 (24.4)	72 (39.8)	88 (46.3)	507 (28.3)

* Patients with 'None cytogenetic response' or had no response assessment were considered non-responders.

**Patients who did have any post-baseline cytogenetic assessment (discontinued or ongoing) by this time point.

Other Relevant Findings

Pharmacokinetics

An additional pharmacokinetic sub-study was conducted, a total of 23 Chinese CML patients (one with CML-AP and 22 with CML-CP) were enrolled. Of these, 21 patients completed the pharmacokinetic assessment. The results are reported in a separate Pharmacokinetics Sub-Study Report.

Date of Clinical Trial Report

15 Sept 2009

Date Inclusion on Novartis Clinical Trial Results Database

29 June 2010

Date of Latest Update