Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Nilotinib

Trial Indication(s)

Newly diagnosed chronic phase (CP)-Ph+ chronic myeloid leukemia (CML); CP or accelerated phase (AP)-Ph+ CML resistant / intolerant to imatinib and/or dasatinib; refractory / relapsed Ph+ acute lymphoblastic leukemia (ALL)

Protocol Number

CAMN107A2120

Protocol Title

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 and/or dasatinib, or with refractory/relapsed Ph+ ALL

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase IV

Study Start/End Dates

Study Start Date: April 2011 (Actual)
Study Completion Date: July 2015 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This is a multi-center, open-label study to characterize the PK of nilotinib in the study population administered as 230 mg/m^2 twice daily (bid) to pediatric patients.

The planned study population was 14 pediatric patients (maximum of 24 patients): 7 patients ages 1 year to < 10 years (Group 1) and 7 patients ages ≥ 10 years to < 18 years (Group 2) with imatinib/dasatinib resistant/intolerant Ph$^+$ CML in CP or AP, or Ph$^+$ ALL refractory/relapsed to standard therapy.

Upon completion of a minimum of 12 cycles (28 days per cycle) of treatment, patients who were benefiting from the treatment with nilotinib, as determined by the Investigator, were offered the option to receive extended therapy with nilotinib. Four patients were enrolled in a rollover study and a fifth patient was enrolled in a compassionate use study. Patients reaching age 18 years at end of the study were eligible for commercial nilotinib (Tasigna®).

Centers

30 centers in 10 countries: United States(8), Netherlands(2), Italy(4), United Kingdom(4), France(5), Germany(1), Brazil(3), Russia(1), Thailand(1), Korea, Republic of(1)

Objectives:

The primary objective of the study was to characterize the PK of nilotinib in pediatric patients with newly diagnosed CP-Ph+ CML, **or** CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib, **or** refractory/relapsed Ph+ ALL to standard therapy.

The study had the following secondary objectives:

- 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 treatment.

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

Nilotinib was labeled as AMN107 and supplied by Novartis as 200 mg, 150 mg, and 50 mg hard gelatin capsules. Patients were administered nilotinib 230 mg/m^2 bid, orally, rounded to the nearest 50 mg (max single dose 400 mg) for 28 days (1 cycle) for up to 12 cycles prior to protocol amendment 3 and up to 24 cycles post amendment 3.

Statistical Methods

Following the completion of the last ongoing patient, this CSR included the evaluation of all efficacy, safety, and PK parameters. The statistical analysis of data was performed by Novartis. Efficacy was analyzed using the Full analysis set which included all patients who passed the screening and are enrolled into the study. Patients may or may not have taken study drug. The FAS was used for all demographic and baseline characteristics summaries and all Section 16 listings, unless otherwise specified. Pharmacokinetic Analysis Set (PAS) consisted of all patients who received the nilotinib dose on Day 1, had an evaluable Day 1 PK profile or provided at least one evaluable steady state trough concentration. The PAS was used for all the concentration summaries and plots, and all the PK parameter summaries and analyses unless otherwise specified. Safety was analyzed for all patients who received at least one dose of nilotinib. The Safety set was used for all core safety summaries and all Section 14 listings, unless otherwise specified.

Pharmacokinetic assessment

The primary objective was to characterize single and multiple dose PK of nilotinib in pediatric patients. The PK parameters after the first dose on Cycle 1 Day 1 were estimated by non-compartmental analysis using Phoenix WinNonlin (Pharsight, Mountain View, CA). Due to the limitation of 24-hr sampling, the terminal phases of the Cycle 1 Day 1 PK concentration-time profiles were not attainable in any patient for the calculation of single dose PK parameters such as AUCinf, t1/2, Vd/F and clearance (CL/F), and therefore those parameters were either calculated but flagged for exclusion, or not possible to be calculated and therefore not reported. Instead, PK parameters, AUC0-12h and AUClast (last = 24 hours), for Cycle 1 Day 1 were reported.

Given that the study had no full concentration-time profiles at steady state or after single dose, AUCinf was not possible to be reliably calculated, and the steady-state PK exposure AUCtau and CL/F could not be calculated by non-compartmental analysis. Instead, the study analysis adopted the assessment of steady-state PK using drug accumulation ratio based on trough concentrations. The steady-state AUC was computed using the following formula:

AUCtau = AUCss = (C12h,ss/C12h,1st dose) × AUC0-12h,1st dose,

where C12h,ss is computed as the average of the steady-state trough concentrations available on or after Day 8.

Steady-state CL/F is then calculated based on the computed AUCtau as follows:

Steady-state CL/F = dose/AUCtau

The steady-state CL/F is then scaled by body surface area to calculate the body surface area-adjusted CL/F at steady state.

Efficacy analysis

Using the Full analysis set, clinical activity was presented descriptively and no statistical tests were conducted. Hematological, cytogenetic, and molecular responses were the major efficacy endpoints summarized by descriptive statistics. By-patient listings including time to response, progression, lumbar puncture, survival, and FISH records were provided.

Biomarker analysis

Biomarker analysis was conducted using the Full analysis set for patients enrolled prior to amendment 3. Molecular monitoring of peripheral blood by reverse transcription quantitative polymerase chain reaction was performed by central lab at Baseline, Cycles 1, 3, 6, 9 and 12/ EOT. Patients enrolled after protocol amendment 2 and before amendment 3 may also have had assessments at Cycles 15, 18 and 21. Molecular monitoring of bone marrow by reverse transcription quantitative polymerase chain reaction was performed for CML patients at Baseline, Cycles 1 (Day 28), 6, and 12/EOT. For Ph+ ALL patients, molecular monitoring of bone marrow by reverse transcription quantitative polymerase chain reaction was performed at Baseline, Cycles 1 (Day 28), 3, 6, 9 and 12/EOT. Raw data were listed for each patient.

Safety analysis

All the safety analyses were based on the safety set and summarized by age group and overall.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
-Must have one of the following: newly diagnosed CP Ph+CML, CP or AP resistant/ intolerant to imatinib and/or dasatinib, or Ph+ ALL either relapsed after or refractory to standard therapy
- adequate renal, hepatic and pancreatic function

Exclusion Criteria:
- patients receiving therapy with strong CYP3A4 inhibitors and/or inducers and treatments cannot be stopped or changed to a different medication at least 14 days prior to starting study drug
- patients receiving therapy with any medications with a known risk or possible risk to prolong the QT interval and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug.
- gastrointestinal impairment or disease that may interfere with drug absorption
- liver, pancreatic or severe renal disease unrelated to disease under study
- impaired cardiac function
- patients who received dasatinib within 3 days of starting study drug
- patients who received imatinib within 5 days of starting study drug
- patients receiving hydroxyurea or corticosteroids that has not been discontinued at least 1 week after initiation of nilotinib
- patients who received hematopoietic growth factors within 7 days of starting study drug or Pegfilgrastim (Neulasta®) within 14 days of starting study drug
- patients with Stem Cell Transplant (SCT) or Rescue without TBI: Evidence of active graft vs. host disease and < 3 months since SCT

Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Overall Study

	Group 1	Group 2
Started	8	7
Completed	5	2
Not Completed	3	5
New Cancer Therapy	3	3
Adverse	0	1

Event		
Disease Progression	0	1

Baseline Characteristics

	Group 1	Group 2	Total
Number of Participants [units: participants]	8	7	15
Age Continuous (units: Years) Mean ± Standard Deviation	6.8±1.16	13.7±2.81	10.0±4.12
Gender, Male/Female (units: Participants)			
Female	3	4	7
Male	5	3	8
Weight (units: kg) Mean ± Standard Deviation	24.60±4.739	48.89±17.533	35.93±17.328
Height (units: cm) Mean ± Standard Deviation	119.9±7.49	158.0±16.32	137.7±23.02
Body Mass Index (BMI) (units: kg/m^2) Mean ± Standard Deviation	16.962±1.7654	18.944±3.4563	17.887±2.7795

Summary of Efficacy

Primary Outcome Result(s)

Summary of nilotinib non-compartmental PK parameters: Cmax

	Group 1	Group 2
Number of Participants Analyzed [units: participants]	7	7
Summary of nilotinib non-compartmental PK parameters: Cmax (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)	405.111 (42.5%)	402.715 (35.2%)

Summary of nilotinib non-compartmental PK parameters: Tmax

	Group 1	Group 2
Number of Participants Analyzed [units: participants]	7	7
Summary of nilotinib non-compartmental PK parameters: Tmax (units: h) Median (Full Range)	2.000 (1.02 to 7.08)	3.000 (2.00 to 7.88)

Summary of nilotinib non-compartmental PK parameters: AUClast (last = 24h)

	Group 1	Group 2
Number of Participants Analyzed [units:	7	7

participants]		
Summary of nilotinib non-compartmental PK parameters: AUClast (last = 24h) (units: ng*h/mL) Geometric Mean (Geometric Coefficient of Variation)	4160.969 (38.5%)	5707.368 (51.2%)

Summary of nilotinib non-compartmental PK parameters: AUC0-12h

	Group 1	Group 2
Number of Participants Analyzed [units: participants]	7	7
Summary of nilotinib non-compartmental PK parameters: AUC0-12h (units: ng*h/mL) Geometric Mean (Geometric Coefficient of Variation)	2795.782 (35.7%)	3393.296 (30.4%)

Summary of nilotinib steady-state PK parameters: AUCss

	Group 1	Group 2
Number of Participants Analyzed [units: participants]	7	7
Summary of nilotinib steady-state PK parameters: AUCss (units: ng*h/mL) Geometric Mean (Geometric Coefficient of	15129.182 (38.0%)	14383.076 (33.6%)

Variation)

Summary of nilotinib steady-state PK parameters: CLF (body surface area (BSA) adjusted)

	Group 1	Group 2
Number of Participants Analyzed [units: participants]	7	7
Summary of nilotinib steady-state PK parameters: CLF (body surface area (BSA) adjusted) (units: L/h/m^2)) Geometric Mean (Geometric Coefficient of Variation)	15.356 (38.7%)	15.922 (37.0%)

Summary of nilotinib steady-state PK parameters: Cmin

	Group 1	Group 2
Number of Participants Analyzed [units: participants]	7	7
Summary of nilotinib steady-state PK parameters: Cmin (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)	804.791 (33.7%)	1072.850 (20.5%)

Secondary Outcome Result(s)

Number of Ph+ CML participants with confirmed complete hematologic response (CHR)

	Group 1	Group 2
Number of Participants Analyzed [units: participants]	5	6
Number of Ph+ CML participants with confirmed complete hematologic response (CHR) (units: Participants)		
Yes	5	5
No	0	1

Number of Ph+ CML participants with cytogenic response

	Group 1	Group 2
Number of Participants Analyzed [units: participants]	5	6
Number of Ph+ CML participants with cytogenic response (units: Participants)		
Complete cytogenic response (CCyR)	2	2
Partial cytogenic response (PCyR)	0	1
Minor cytogenic response (mCyR)	0	1
Minimal	0	0
None	0	0

Absence of Ph+ at baseline	3	1

Number of Ph+ CML participants with major molecular response (MMR)

	Group 1	Group 2
Number of Participants Analyzed [units: participants]	5	6
Number of Ph+ CML participants with major molecular response (MMR) (units: Participants)		
Yes	1	2
No	4	4

Efficacy endpoints for Ph+ ALL patients

	Group 1	Group 2
Number of Participants Analyzed [units: participants]	3	1
Efficacy endpoints for Ph+ ALL patients (units: Participants)		
Complete Remission with platelet recovery	2	1
Complete Remission w/incomplete platelet recovery	0	0
Partial remission	0	0
Stable disease	1	0

Progressive disease	0	0

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

	Group 1 N = 8	Group 2 N = 7
Total participants affected	2 (25.00%)	3 (42.86%)
Blood and lymphatic system disorders		
Neutropenia[1, †]	0 (0.00%)	2 (28.57%)
Gastrointestinal disorders		
Appendix disorder[1, †]	1 (12.50%)	0 (0.00%)
General disorders and administration site conditions		
Influenza like illness[1, †]	1 (12.50%)	0 (0.00%)
Pyrexia[1, †]	1 (12.50%)	0 (0.00%)
Renal and urinary disorders		
Renal failure[1, †]	0 (0.00%)	1 (14.29%)

† Systematic Assessment
1 MedDRA

Other Adverse Events by System Organ Class

Frequent Event Reporting Threshold 5%

	Group 1 N = 8	Group 2 N = 7
Total participants affected	8 (100.00%)	7 (100.00%)
Blood and lymphatic system disorders		
Haemolytic anaemia[1, †]	0 (0.00%)	1 (14.29%)
Leukopenia[1, †]	0 (0.00%)	1 (14.29%)
Lymphopenia[1, †]	0 (0.00%)	1 (14.29%)
Neutropenia[1, †]	0 (0.00%)	1 (14.29%)
Thrombocytopenia[1, †]	0 (0.00%)	1 (14.29%)
Ear and labyrinth disorders		
Ear pain[1, †]	0 (0.00%)	2 (28.57%)
Gastrointestinal disorders		
Abdominal pain[1, †]	1 (12.50%)	2 (28.57%)
Abdominal pain upper[1, †]	1 (12.50%)	1 (14.29%)
Constipation[1, †]	0 (0.00%)	1 (14.29%)
Diarrhoea[1, †]	1 (12.50%)	3 (42.86%)
Nausea[1, †]	0 (0.00%)	3 (42.86%)
Odynophagia[1, †]	1 (12.50%)	0 (0.00%)
Toothache[1, †]	0 (0.00%)	1 (14.29%)

Vomiting[1, †]	3 (37.50%)	3 (42.86%)
General disorders and administration site conditions		
Asthenia[1, †]	0 (0.00%)	1 (14.29%)
Catheter site pain[1, †]	1 (12.50%)	0 (0.00%)
Fatigue[1, †]	2 (25.00%)	0 (0.00%)
Malaise[1, †]	0 (0.00%)	1 (14.29%)
Mucosal inflammation[1, †]	0 (0.00%)	1 (14.29%)
Pyrexia[1, †]	1 (12.50%)	1 (14.29%)
Xerosis[1, †]	1 (12.50%)	0 (0.00%)
Hepatobiliary disorders		
Hyperbilirubinaemia[1, †]	2 (25.00%)	2 (28.57%)
Infections and infestations		
Bronchitis[1, †]	0 (0.00%)	1 (14.29%)
Device related infection[1, †]	1 (12.50%)	0 (0.00%)
Ear infection[1, †]	1 (12.50%)	0 (0.00%)
Folliculitis[1, †]	0 (0.00%)	2 (28.57%)
Fungal skin infection[1, †]	0 (0.00%)	1 (14.29%)
Hand-foot-and-mouth disease[1, †]	1 (12.50%)	0 (0.00%)
Lip infection[1, †]	0 (0.00%)	1 (14.29%)
Nasopharyngitis[1, †]	4 (50.00%)	0 (0.00%)
Oral candidiasis[1, †]	0 (0.00%)	1 (14.29%)
Otitis media[1, †]	1 (12.50%)	0 (0.00%)

Rhinitis[1, †]	3 (37.50%)	1 (14.29%)
Skin infection[1, †]	0 (0.00%)	2 (28.57%)
Tinea pedis[1, †]	0 (0.00%)	1 (14.29%)
Tonsillitis[1, †]	0 (0.00%)	1 (14.29%)
Upper respiratory tract infection[1, †]	1 (12.50%)	1 (14.29%)
Investigations		
Alanine aminotransferase increased[1, †]	3 (37.50%)	1 (14.29%)
Aspartate aminotransferase increased[1, †]	3 (37.50%)	0 (0.00%)
Bilirubin conjugated increased[1, †]	1 (12.50%)	1 (14.29%)
Blood bilirubin increased[1, †]	2 (25.00%)	3 (42.86%)
Blood bilirubin unconjugated increased[1, †]	0 (0.00%)	1 (14.29%)
Blood creatinine increased[1, †]	0 (0.00%)	2 (28.57%)
Blood phosphorus decreased[1, †]	1 (12.50%)	0 (0.00%)
Blood sodium decreased[1, †]	1 (12.50%)	0 (0.00%)
Blood urea increased[1, †]	0 (0.00%)	2 (28.57%)
Blood uric acid increased[1, †]	0 (0.00%)	2 (28.57%)
Electrocardiogram QT prolonged[1, †]	1 (12.50%)	0 (0.00%)

Haematocrit decreased[1, †]	0 (0.00%)	1 (14.29%)
Haemoglobin decreased[1, †]	0 (0.00%)	1 (14.29%)
Neutrophil count increased[1, †]	0 (0.00%)	1 (14.29%)
Platelet count decreased[1, †]	0 (0.00%)	1 (14.29%)
Red blood cell count decreased[1, †]	0 (0.00%)	1 (14.29%)
Weight decreased[1, †]	1 (12.50%)	0 (0.00%)
White blood cell count decreased[1, †]	0 (0.00%)	1 (14.29%)
White blood cell count increased[1, †]	0 (0.00%)	1 (14.29%)
Metabolism and nutrition disorders		
Hypoalbuminaemia[1, †]	1 (12.50%)	0 (0.00%)
Musculoskeletal and connective tissue disorders		
Arthralgia[1, †]	0 (0.00%)	3 (42.86%)
Back pain[1, †]	1 (12.50%)	0 (0.00%)
Bone pain[1, †]	1 (12.50%)	1 (14.29%)
Muscle spasms[1, †]	1 (12.50%)	0 (0.00%)
Musculoskeletal pain[1, †]	1 (12.50%)	0 (0.00%)
Neck pain[1, †]	1 (12.50%)	1 (14.29%)
Pain in extremity[1, †]	3 (37.50%)	1 (14.29%)
Tendon pain[1, †]	0 (0.00%)	1 (14.29%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Skin papilloma[1, †]	2 (25.00%)	0 (0.00%)
Nervous system disorders		
Headache[1, †]	4 (50.00%)	2 (28.57%)
Paraesthesia[1, †]	0 (0.00%)	1 (14.29%)
Peripheral sensory neuropathy[1, †]	1 (12.50%)	0 (0.00%)
Presyncope[1, †]	0 (0.00%)	1 (14.29%)
Syncope[1, †]	0 (0.00%)	1 (14.29%)
Reproductive system and breast disorders		
Vulvovaginal pruritus[1, †]	1 (12.50%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders		
Cough[1, †]	2 (25.00%)	2 (28.57%)
Oropharyngeal pain[1, †]	0 (0.00%)	1 (14.29%)
Pharyngeal erythema[1, †]	1 (12.50%)	0 (0.00%)
Productive cough[1, †]	0 (0.00%)	1 (14.29%)
Skin and subcutaneous tissue disorders		
Dermatitis atopic[1, †]	1 (12.50%)	0 (0.00%)
Dry skin[1, †]	0 (0.00%)	2 (28.57%)
Dyshidrotic eczema[1, †]	0 (0.00%)	1 (14.29%)
Eczema[1, †]	2 (25.00%)	1 (14.29%)
Exfoliative rash[1, †]	1 (12.50%)	0 (0.00%)

Psoriasis[1, †]	1 (12.50%)	0 (0.00%)
Rash[1, †]	3 (37.50%)	2 (28.57%)
Rash erythematous[1, †]	1 (12.50%)	0 (0.00%)
Rash maculo-papular[1, †]	1 (12.50%)	0 (0.00%)
Rash papular[1, †]	1 (12.50%)	0 (0.00%)
Skin lesion[1, †]	0 (0.00%)	1 (14.29%)

† Systematic Assessment
1 MedDRA

Other Relevant Findings

None

Conclusion:

Of 11 Ph+ CML patients (5 patients in Group 1, 6 patients in Group 2), 10 (90.9%) patients achieved confirmed complete hematological response, and 1 patient had complete hematological response which was not confirmed at another visit within 4 weeks. Of 11 Ph+ CML patients, 4 patients (36.4%) achieved complete cytogenetic response, 2 patients in each age group (Group 1 (2, 40%); Group 2 (2, 33.3%)). One patient in Group 2 (1, 16.7%) achieved partial cytogenetic response and another 1 patient (1, 16.7%) achieved minor cytogenetic response. Three patients in Group 1 and 1 patient in Group 2 had no Ph+ marrow at Baseline. Major cytogenetic response in this study includes complete cytogenetic response or partial cytogenetic response. Major cytogenetic response was achieved in 2 patients in Group 1 (40%) and 3 patients in Group 2 (50.0%). Major Molecular Response was achieved in 3 Ph+ CML patients (27.3%) 1 patient in Group 1 (20%) and 2 patients in Group 2 (33.3%).

In the 4 Ph+ ALL patients, complete remission was achieved in 3 patients (75%): 2 patients in Group 1 (66.7%) and 1 patient in Group 2 (100%). Stable disease was observed in the 1 remaining patient in Group 1 (33.3%).

The safety profile of pediatric patients dosed with nilotinib 230 mg/m^2 bid is consistent with the already well-known safety profile of adult patients treated with nilotinib. There were some low grade shifts in hepatic transaminases as isolated laboratory findings. There was no evidence of vascular morbidities. No deaths were reported.

In conclusion, the final study results confirmed 230 mg/m^2 bid as the recommended dose in pediatric patients (1 year to < 18 years) with newly diagnosed CP-Ph+ CML, or CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or relapsed/refractory Ph+ ALL.

Date of Clinical Trial Report

30-Nov-2015