## Sponsor

Novartis

## Generic Drug Name

Nilotinib (AMN107)

## Therapeutic Area of Trial

Imatinib-resistant gastrointestinal stromal tumors (GIST).

## Approved Indication

- Treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase.
- Philadelphia chromosome positive chronic myeloid leukemia in chronic and accelerated phases resistant to or intolerant to prior therapy including imatinib.

## Study Number

CAMN107A2103 (core) & CAMN107A2103E1 (extension)

## Title

A phase I multicenter, dose escalation study of AMN107 in combination with imatinib on a continuous daily dosing schedule in adult patients with imatinib-resistant GIST.

## Phase of Development

Phase I

## Study Start/End Dates

08 Aug 2005 to 27 Jan 2011

## Study Design/Methodology

This was an open-label, multicenter, phase I, dose-escalation study using a 5-parameter adaptive Bayesian logistic model to guide dose escalation. A cohort of patients was initially treated with nilotinib monotherapy at the currently recommended phase II dose for hematologic malignancies (400 mg twice daily (bid)) to evaluate the safety and tolerability of nilotinib monotherapy in patients with GIST. Subsequent cohorts of patients received combination therapy with nilotinib plus imatinib. The final recommended phase II dose for combination therapy was based on considerations of the maximum tolerated dose (MTD) estimated by the Bayesian model and on an overall assessment of safety.

The current study has core and extension parts. The core study consisted of the dose escalation part and had data from the time up to and including when the patients had completed at least 4 cycles of treatment (cut-off date 16-Nov-2006). The extension study was initiated in Nov-2006. It was designed to allow patients responding to nilotinib monotherapy or in combination with imatinib to continue their previously assigned therapy, using an abbreviated safety and efficacy assessment schedule. The current report is an update on the safety and efficacy and includes data up to the last patient in the extension study having completed the study (cut-off date 27-Jan-2011).

## Centers

5 Centers in 4 countries: France (1), Germany (1), Italy (1), United States (2)

## Publication

Demetri G, Casali P, Blay JY et al (2009) A Phase I Study of Single Agent Nilotinib or in Combination with Imatinib in Patients with Imatinib-Resistant Gastrointestinal Stromal Tumors. Clin Cancer Res; 15(18) 5910-16

## Objectives

Primary objective(s) of the core study

- To characterize the safety and tolerability of nilotinib in combination with imatinib in patients with GIST who progressed on previous imatinib therapy
- To determine a phase II dose of nilotinib when given in combination with imatinib.

Secondary objective(s) of the core study

- To characterize the safety and tolerability of nilotinib monotherapy
- To evaluate the pharmacokinetic (PK) profile of nilotinib as monotherapy and in combination with imatinib
- To evaluate tumor response to therapy with nilotinib as monotherapy and in combination with imatinib
- To evaluate the tumor metabolic response by FDG-PET with nilotinib as monotherapy and in combination with imatinib
- To describe the relationship of tumor characteristics as measured in blood and tumor tissue with clinical outcomes.

Objective(s) of the extension study

- To characterize long-term safety and tolerability of nilotinib either as monotherapy or in combination with imatinib in GIST patients showing progression of disease on imatinib.
- To evaluate responses in imatinib-resistant GIST patients treated with nilotinib as monotherapy or in combination of imatinib.

## Test Products, Doses, and Mode of Administration

Nilotinib 50 mg and 200 mg gelatin capsules and imatinib 100 mg and 400 mg tablets were administered orally on a continuous daily schedule.

The dose of nilotinib as a single agent was 400 mg bid. Four combination therapy cohorts were evaluated:

- nilotinib 200 mg qd + imatinib 400 mg bid.
- nilotinib 400 mg qd + imatinib 400 mg bid.
- nilotinib 400 mg bid + imatinib 400 mg bid.
- nilotinib 400 mg bid + imatinib 400 mg qd.

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

Not applicable.

## Criteria for Evaluation

### Primary variables

- Safety assessments consisted of monitoring and recording all AEs, including SAEs, with their severity and relationship to study drug, and regular monitoring of laboratory evaluations, vital signs, physical condition, cardiac function, and pregnancies.
- In addition, evaluation of dose-limiting toxicity (DLT) was used to determine the MTD. Cardiac function was monitored by assessing blood pressure, pulse, ECG, cardiac enzymes, and MUGA or ECHO.

### Secondary variables

- Serum samples from all patients were analyzed to determine nilotinib, imatinib, and N-desmethyl imatinib metabolite concentrations using a validated method of liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification of approximately 10 ng/mL for both nilotinib and imatinib.
- Tumor response was evaluated based on the RECIST criteria. Tumor evaluations were based on computed tomography (CT)/magnetic resonance imaging (MRI) and clinical findings.
- As an assessment of early treatment efficacy, change in fluorodeoxyglucose positron emission tomography (FDG-PET) uptake was also assessed (at baseline, Day 6/7, and Day 28).

### Safety and tolerability

Described as Primary variables

### Pharmacology

Described as Secondary variables

### Others

Biomarker Studies: Tumor mutational analyses were conducted on tumor samples to evaluate kinase mutations (PDGFR and KIT).

## Statistical Methods

A 5-parameter Bayesian logistic regression model was used for dose escalation and MTD determi-

nation. After each cohort of patients, the estimated MTD was the one with the highest posterior probability of DLT in the target interval [20%,35%), given that there was less than 5% chance that the posterior probability of DLT exceeded 60% (unacceptable toxicity) and less than 25% chance of either excessive (35%,60%) or unacceptable toxicity. The MTD estimated by the model at completion of a cohort was regarded as dose recommendation, which was integrated with a clinical assessment of the toxicity profiles observed up to that time in determining the next dose.

The efficacy analysis was based on the efficacy population. The definition of response follows the modified RECIST criteria. For the patients recruited during the study, tumor response data were listed by dose cohort. For patients in each cohort, best overall response rates were analyzed and Kaplan-Meier estimates were computed for progression-free survival, time to progression, time-to-response, and duration of response, with 95% confidence intervals (CIs) for medians. In addition, 95% CIs were computed for stable disease or better (complete response, partial response, and stable disease) after 4 months and 6 months.

Those MTD determining patients who experienced DLT were listed individually by dose cohort and reason for the DLT. The DLT rate was summarized by dose cohort using the MTD determining population.

Safety data were summarized mainly on the frequency and severity of AEs by dose cohort and on the number of laboratory values that fell outside of pre-determined ranges. AEs were summarized by dose cohort, body system, relationship to drug, and maximum grade. Other safety data (e.g. ECG, vital signs, and special tests) were considered as appropriate.

## Study Population: Inclusion/Exclusion Criteria and Demographics

### Inclusion criteria

- Males or females aged ≥ 18 years with a World Health Organization (WHO) performance status of 0 to 1.
- Histologically-confirmed, unresectable, or metastatic GIST not amenable to surgery or combined modality with curative intent.
- Radiological confirmation of disease progression during previous imatinib therapy at a daily dose of 800 mg. Patients intolerant to imatinib 800 mg/day but fulfilling all other inclusion criteria and able to tolerate at least 600 mg/day were permitted enrollment into the nilotinib monotherapy cohort after discussion with the Sponsor.
- Patients who received previous treatment with KIT, PDGFR, vascular endothelial growth factor receptor (VEGFR), or tyrosine kinase inhibitors were eligible provided that they were currently on treatment with imatinib and had fully recovered from toxicity attributed to such agents. If imatinib therapy was discontinued to allow treatment with such agents, imatinib must have been reintroduced for the first three combination cohorts at a dose of 400 mg bid for a minimum of 2 weeks before entering the study to allow obtainment of steady state concentrations. For all subsequent combination cohorts, imatinib must have been reintroduced at the cohort-specific dose (400 mg qd, 600 mg qd, or 400 mg bid) for a minimum of 2 weeks before entering the study to allow obtainment of steady state concentrations. In cases where there was concern about early clinical progression, the patient was allowed to pre-start imatinib at a dose of 400 mg bid for 7 days and then switch to the new dose for the remaining 7 days.
- Normal organ and bone marrow function:

- Absolute neutrophil count (ANC) ≥ 1500/µL
- Platelets ≥ 100,000 /µL
- Potassium ≥ lower limit of normal (LLN) or corrected to within normal limits (WNL) with supplements prior to the first dose of study medication
- Total calcium (corrected for serum albumin) ≥ LLN or corrected to WNL with supplements prior to the first dose of study medication
- Magnesium ≥ LLN or corrected to WNL with supplements prior to the first dose of study medication
- Phosphorus ≥ LLN or corrected to WNL with supplements prior to the first dose of study medication
- Alanine aminotransferase (ALT) and aspartate aminotransferase (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 secondary to tumor
- Serum bilirubin, serum amylase, and serum lipase ≤ 1.5 x ULN
- Serum creatinine ≤ 1.5 x ULN or 24-hour creatinine clearance ≥ 50 mL/min
- Provided written informed consent.

**Extension study**

- Documented CR, PR, or SD at the time of entry to extension study and/or possible benefit from continuing treatment in the view of the investigator.
- Normal organ and bone marrow function as defined in the core study protocol
- Provided written informed consent for the extension study.

## Exclusion criteria

- Treatment with any cytotoxic or investigational drug ≤ 4 weeks (6 weeks for nitrosurea or mitomycin C) prior to beginning study drug, with the exception of KIT, PDGFR, VEGFR, or tyrosine kinase inhibitors.
- Prior or concomitant malignancies other than GIST, with the exception of previous or concomitant basal cell skin cancer or cervical carcinoma in situ.
- Previous intolerance to the cohort-specific imatinib dose if the patient is to be included in one of the combination cohorts.
- Impaired cardiac function, including any one of the following:
  - Left ventricular ejection fraction (LVEF) < 45% or below the institutional LLN (whichever is higher) as determined by multiple uptake gated acquisition (MUGA) scan or echocardiogram (ECHO)
  - Complete left bundle branch block
  - Use of a cardiac pacemaker
  - ST depression > 1 mm in two or more leads or T wave inversions in two or more contiguous leads
  - Congenital long QT syndrome
  - History or presence of significant ventricular or atrial tachyarrhythmias

  - Clinically significant resting bradycardia (< 50 beats per minute)
  - QTc > 450 msec on screening electrocardiogram (ECG) (using the QTcF formula)
  - Right bundle branch block plus left anterior hemiblock, bifascicular block
  - 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 (CHF), uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- Severe or uncontrolled concurrent medical disease that, in the opinion of the investigator, could cause unacceptable safety risks or compromise compliance with the protocol (e.g., impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of nilotinib, uncontrolled diabetes).
- Use of therapeutic coumarin derivatives (i.e., warfarin, acenocoumarol, phenprocoumon).
- Concomitant treatment with any medication known to prolong the QT interval as well as CYP3A4 inhibitors if the treatment cannot be either discontinued or switched to a different medication prior to starting study drug administration.
- Major surgery ≤ 2 weeks prior to starting study drug or lack of recovery from side effects from previous surgery.
- Receipt of wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation < 2 weeks prior to starting drug, or patients who have not recovered from the side effects of such therapy.
- Known diagnosis of human immunodeficiency virus (HIV) infection.
- History of noncompliance to medical regimens or inability or unwillingness to return for scheduled visits.
- Pregnancy or lactation, or adults of reproductive potential not employing an effective method of birth control. Women of childbearing potential must have had a negative serum pregnancy test within 48 hours prior to administration of study drugs. Post menopausal women must have been amenorrheic for at least 12 months to be considered of non-childbearing potential. Male and female patients were required to use an effective method of birth control throughout the study and for 3 months following discontinuation of study drugs.
- Unwillingness or inability to comply with the protocol.
- Known ongoing alcohol or drug abuse.
- Any of the following contraindications to FDG-PET:
  - Uncontrolled diabetes
  - Inability to lie down for approximately 1 hour

**Extension study**

- Inability to swallow the medication
- Any unresolved AEs due to participation in the core study.
- A history of noncompliance to medical regimens or inability or unwillingness to return for all scheduled visits.

## Number of Subjects

### Patient disposition by treatment group (ITT population)

| | AMN 400 mg bid | AMN 200 mg qd / IM 400 mg bid | AMN 400 mg qd / IM 400 mg bid | AMN 400 mg bid / IM 400 mg bid | AMN 400 mg bid / IM 400 mg qd | Total |
|---|---|---|---|---|---|---|
| | N=18 | N=7 | N=7 | N=5 | N=16 | N=53 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Enrolled core study | 18 (100.0) | 7 (100.0) | 7 (100.0) | 5 (100.0) | 16 (100.0) | 53 (100.0) |
| Completed core study | 1 (5.6) | 0 (0.0) | 2 (28.6) | 2 (40.0) | 9 (56.3) | 14 (26.4) |
| Discontinued core study | 17 (94.4) | 7 (100.0) | 5 (71.4) | 3 (60.0) | 7 (43.8) | 39 (73.6) |
| Primary reason for discontinuation | | | | | | |
| Adverse event(s) | 2 (11.1) | 0 | 0 | 1 (20.0) | 0 | 3 (5.7) |
| Withdrew consent | 1 (5.6) | 1 (14.3) | 0 | 0 | 0 | 2 (3.8) |
| Death | 1 (5.6) | 0 | 1 (14.3) | 0 | 0 | 2 (3.8) |
| Disease progression | 13 (72.2) | 6 (85.7) | 4 (57.1) | 2 (40.0) | 7 (43.8) | 32 (60.4) |
| Enrolled extension study | 1 (5.6) | 0 | 2 (28.6) | 2 (40.0) | 9 (56.3) | 14 (26.4) |
| Discontinued extension study | 1 (5.6) | 0 | 2 (28.6) | 2 (40.0) | 9 (56.3) | 14 (26.4) |
| Primary reason for discontinuation | | | | | | |
| Adverse event(s) | 1 (5.6) | 0 | 0 | 0 | 1 (6.3) | 2 (3.8) |
| Withdrew consent | 0 | 0 | 0 | 0 | 1 (6.3) | 1 (1.9) |
| Disease progression | 0 | 0 | 2 (28.6) | 2 (40.0) | 7 (43.8) | 11 (20.8) |

Abbreviations: AMN = AMN107 (nilotinib), bid = Twice daily, IM = Imatinib, ITT = Intent to treat, qd = Once daily.

## Demographic and Background Characteristics

### Demographic summary by treatment group (ITT population)

| | AMN 400 mg bid | AMN 200 mg qd / IM 400 mg bid | AMN 400 mg qd / IM 400 mg bid | AMN 400 mg bid / IM 400 mg bid | AMN 400 mg bid / IM 400 mg qd | Total |
|---|---|---|---|---|---|---|
| | N=18 | N=7 | N=7 | N=5 | N=16 | N=53 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Age, years** | | | | | | |
| Mean | 51.5 | 50.4 | 58.1 | 52.4 | 60.4 | 55.0 |
| SD | 12.40 | 14.81 | 8.45 | 6.35 | 11.91 | 12.07 |
| Median | 47.5 | 45.0 | 57.0 | 50.0 | 63.0 | 57.0 |
| Range | 24-74 | 40-83 | 49-74 | 46-61 | 38-77 | 24-83 |
| **Gender, n (%)** | | | | | | |
| Male | 7 (38.9) | 5 (71.4) | 6 (85.7) | 4 (80.0) | 9 (56.3) | 31 (58.5) |
| Female | 11 (61.1) | 2 (28.6) | 1 (14.3) | 1 (20.0) | 7 (43.8) | 22 (41.5) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Race, n (%)** | | | | | | |
| Caucasian | 16 (88.9) | 7 (100) | 7 (100) | 4 (80.0) | 16 (100) | 50 (94.3) |
| Black | 1 (5.6) | 0 | 0 | 0 | 0 | 1 (1.9) |
| Asian | 1 (5.6) | 0 | 0 | 1 (20.0) | 0 | 2 (3.8) |
| **Ethnicity, n (%)** | | | | | | |
| Hispanic/Latino | 1 (5.6) | 0 | 0 | 0 | 0 | 1 (1.9) |
| Indian (Indian | 0 | 0 | 0 | 1 (20.0) | 0 | 1 (1.9) |
| subcontinent) | | | | | | |
| Other | 17 (94.4) | 7 (100) | 7 (100) | 4 (80.0) | 16 (100) | 51 (96.2) |
| **Weight, kg** | | | | | | |
| Mean | 69.4 | 77.9 | 83.2 | 67.8 | 72.4 | 73.1 |
| SD | 16.94 | 17.68 | 12.27 | 14.27 | 16.22 | 16.22 |
| Median | 70.2 | 75.0 | 80.1 | 73.0 | 69.5 | 73.0 |
| Range | 47.5-102.4 | 53.0-102.0 | 71.7-108.9 | 42.5-76.6 | 48.0-118.0 | 42.5-118.0 |
| **Height, cm** | | | | | | |
| N | 18 | 7 | 7 | 5 | 15 | 52 |
| Mean | 170.6 | 173.3 | 177.4 | 170.2 | 169.1 | 171.4 |
| SD | 8.45 | 14.76 | 6.29 | 12.56 | 6.75 | 9.30 |
| Median | 169.0 | 180.0 | 174.0 | 175.0 | 170.0 | 172.5 |
| Range | 156.0- | 150.0- | 173.0- | 152.0- | 155.0- | 150.0- |
| | 191.0 | 187.0 | 188.0 | 183.0 | 178.0 | 191.0 |
| **BMI, kg/m2** | | | | | | |
| N | 18 | 7 | 7 | 5 | 15 | 52 |
| Mean | 23.6 | 25.8 | 26.4 | 23.2 | 25.9 | 24.9 |
| SD | 3.87 | 4.61 | 3.00 | 3.12 | 5.38 | 4.35 |
| Median | 23.3 | 24.5 | 26.8 | 23.7 | 24.7 | 24.2 |
| Range | 17.4-30.2 | 21.7-35.3 | 21.6-30.8 | 18.4-27.1 | 20.4-40.8 | 17.4-40.8 |
| **WHO PS, n (%)** | | | | | | |
| Grade 0 | 9 (50.0) | 3 (42.9) | 4 (57.1) | 5 (100) | 8 (50.0) | 29 (54.7) |
| Grade 1 | 9 (50.0) | 4 (57.1) | 3 (42.9) | 0 | 7 (43.8) | 23 (43.4) |
| Grade 2 | 0 | 0 | 0 | 0 | 1 (6.3) | 1 (1.9) |

Abbreviations: AMN = AMN107 (nilotinib), bid = Twice daily, BMI = Body mass index, IM = Imatinib, ITT = Intent to treat, qd = Once daily, SD = Standard deviation, WHO PS = World Health Organization performance status.

## Primary Objective Results

Safety assessment was the primary variable.

Safety and tolerability

## Serious Adverse Events and Deaths

**Deaths, other serious and clinically significant adverse events or related discontinuations (Safety population)**

| | AMN 400 mg bid | AMN 200 mg qd / IM 400 mg bid | AMN 400 mg qd / IM 400 mg bid | AMN 400 mg bid / IM 400 mg bid | AMN 400 mg bid / IM 400 mg qd | Total |
|---|---|---|---|---|---|---|
| | N=18 | N=7 | N=7 | N=5 | N=16 | N=53 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Deaths reported within 28 days of last dose of study drug | 1 (5.6) | 0 | 1 (14.3) | 0 | 0 | 2 (3.8) |
| Death reported as primary reason for discontinuation | 1 (5.6) | 0 | 1 (14.3) | 0 | 0 | 2 (3.8) |
| SAEs (fatal or non-fatal) | 8 (44.4) | 3 (42.9) | 3 (42.9) | 1 (20.0) | 8 (50.0) | 23 (43.4) |
| Study drug-related SAEs | 0 | 0 | 0 | 0 | 1 (6.3) | 1 (1.9) |
| AEs leading to discontinuation | 4 (22.2) | 1 (14.3) | 1 (14.3) | 1 (20.0) | 1 (6.3) | 8 (15.1) |
| Study drug-related AEs leading to discontinuation | 2 (11.1) | 0 | 0 | 1 (20.0) | 0 | 3 (5.7) |
| AEs leading to dose adjustment/ interruption | 8 (44.4) | 3 (42.9) | 4 (57.1) | 4 (80.0) | 12 (75.0) | 31 (58.5) |
| Study drug-related AEs leading to dose adjustment/ interruption | 3 (16.7) | 1 (14.3) | 2 (28.6) | 4 (80.0) | 10 (62.5) | 20 (37.7) |
| Abbreviations: AEs = Adverse events, AMN = AMN107 (nilotinib), bid = Twice daily, IM = Imatinib, qd = Once daily, SAEs = Serious adverse events. | | | | | | |

**Adverse events regardless of study drug relationship by primary system organ class and treatment group (Safety population)**

| | AMN 400 mg bid | AMN200 mg qd / IM 400 mg bid | AMN 400 mg qd / IM 400 mg bid | AMN 400 mg bid / IM 400 mg bid | AMN 400 mg bid / IM 400 mg qd | Total |
|---|---|---|---|---|---|---|
| | n=18 | n=7 | n=7 | n=5 | n=16 | N=53 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Any primary system organ class | 18 (100.0) | 7 (100.0) | 7 (100.0) | 5 (100.0) | 16 (100.0) | 53 (100.0) |
| Gastrointestinal disorders | 18 (100.0) | 5 (71.4) | 5 (71.4) | 4 (80.0) | 14 (87.5) | 46 (86.8) |
| General disorders and administration site conditions | 13 (72.2) | 5 (71.4) | 5 (71.4) | 4 (80.0) | 15 (93.8) | 42 (79.2) |
| Skin and subcutaneous tissue disorders | 13 (72.2) | 5 (71.4) | 6 (85.7) | 5 (100.0) | 13 (81.3) | 42 (79.2) |
| Musculoskeletal and connective tissue disorders | 12 (66.7) | 4 (57.1) | 4 (57.1) | 4 (80.0) | 7 (43.8) | 31 (58.5) |
| Investigations | 12 (66.7) | 2 (28.6) | 3 (42.9) | 1 (20.0) | 6 (37.5) | 24 (45.3) |
| Psychiatric disorders | 11 (61.1) | 2 (28.6) | 3 (42.9) | 3 (60.0) | 5 (31.3) | 24 (45.3) |
| Nervous system disorders | 8 (44.4) | 3 (42.9) | 3 (42.9) | 2 (40.0) | 7 (43.8) | 23 (43.4) |
| Metabolism and nutrition dis- | 11 (61.1) | 2 (28.6) | 3 (42.9) | 2 (40.0) | 4 (25.0) | 22 (41.5) |

| | | | | | | |
|---|---|---|---|---|---|---|
| orders | | | | | | |
| Respiratory, thoracic, and mediastinal disorders | 10 (55.6) | 2 (28.6) | 3 (42.9) | 1 (20.0) | 5 (31.3) | 21 (39.6) |
| Infections and infestations | 9 (50.0) | 1 (14.3) | 3 (42.9) | 1 (20.0) | 5 (31.3) | 19 (35.8) |
| Blood and lymphatic system disorders | 2 (11.1) | 3 (42.9) | 3 (42.9) | 1 (20.0) | 6 (37.5) | 15 (28.3) |
| Eye disorders | 3 (16.7) | 1 (14.3) | 3 (42.9) | 0 | 3 (18.8) | 10 (18.9) |
| Renal and urinary disorders | 4 (22.2) | 1 (14.3) | 2 (28.6) | 0 | 3 (18.8) | 10 (18.9) |
| Vascular disorders | 2 (11.1) | 2 (28.6) | 1 (14.3) | 2 (40.0) | 2 (12.5) | 9 (17.0) |
| Hepatobiliary disorders | 4 (22.2) | 0 | 1 (14.3) | 0 | 3 (18.8) | 8 (15.1) |
| Injury, poisoning, and procedural complications | 3 (16.7) | 1 (14.3) | 1 (14.3) | 1 (20.0) | 2 (12.5) | 8 (15.1) |
| Cardiac disorders | 4 (22.2) | 0 | 0 | 0 | 3 (18.8) | 7 (13.2) |
| Reproductive system and breast disorders | 3 (16.7) | 0 | 3 (42.9) | 0 | 1 (6.3) | 7 (13.2) |
| Ear and labyrinth disorders | 1 (5.6) | 0 | 0 | 0 | 3 (18.8) | 4 (7.5) |
| Neoplasms benign, malignant, and | 0 | 0 | 1 (14.3) | 0 | 3 (18.8) | 4 (7.5) |
| unspecified | | | | | | |
| Social circumstances | 0 | 0 | 0 | 0 | 1 (6.3) | 1 (1.9) |

AMN = AMN107 (nilotinib), bid = Twice daily, IM = Imatinib, qd = Once daily.

A patient with multiple occurrences of an adverse event under one treatment is counted only once in that adverse event category.

A patient with multiple occurrences of an adverse event under one treatment is counted only once in that adverse event category.

**Most frequent adverse events occurring in at least 10% of patients by preferred term (Safety population)**

| | **AMN 400 mg bid** | **AMN200 mg qd / IM 400 mg bid** | **AMN 400 mg qd / IM 400 mg bid** | **AMN 400 mg bid / IM 400 mg bid** | **AMN 400 mg bid / IM 400 mg qd** | **Total** |
|---|---|---|---|---|---|---|
| | **N=18** | **N=7** | **N=7** | **N=5** | **N=16** | **N=53** |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Any event | 18 (100.0) | 7 (100.0) | 7(100.0) | 5(100.0) | 16(100.0) | 53(100.0) |
| Abdominal pain | 11 (61.1) | 2 ( 28.6) | 3( 42.9) | 1( 20.0) | 7( 43.8) | 24( 45.3) |
| Nausea | 7 (38.9) | 1 (14.3) | 4( 57.1) | 2( 40.0) | 8( 50.0) | 22( 41.5) |
| Rash | 3 (16.7) | 2 (28.6) | 3( 42.9) | 3( 60.0) | 11( 68.8) | 22( 41.5) |
| Vomiting | 7 (38.9) | 2 (28.6) | 3( 42.9) | 2( 40.0) | 8( 50.0) | 22( 41.5) |
| Diarrhea | 6 (33.3) | 2 (28.6) | 2( 28.6) | 2( 40.0) | 9( 56.3) | 21( 39.6) |
| Fatigue | 13 (72.2) | 2 (28.6) | 2( 28.6) | 1( 20.0) | 3( 18.8) | 21( 39.6) |
| Constipation | 8 (44.4) | 1 (14.3) | 1( 14.3) | 0 | 6( 37.5) | 16( 30.2) |
| Pruritus | 4 (22.2) | 1(14.3) | 2( 28.6) | 0 | 9( 56.3) | 16( 30.2) |
| Pyrexia | 6 (33.3) | 2(28.6) | 1( 14.3) | 0 | 7( 43.8) | 16( 30.2) |
| Anemia | 2 (11.1) | 3(42.9) | 3( 42.9) | 1( 20.0) | 6( 37.5) | 15( 28.3) |
| Edema peripheral | 1 (5.6) | 3(42.9) | 3( 42.9) | 1( 20.0) | 7( 43.8) | 15( 28.3) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Asthenia | 3 (16.7) | 1(14.3) | 3( 42.9) | 0 | 6( 37.5) | 13( 24.5) |
| Anorexia | 8 (44.4) | 1(14.3) | 2( 28.6) | 1( 20.0) | 0 | 12( 22.6) |
| Headache | 3 (16.7) | 3(42.9) | 2( 28.6) | 1( 20.0) | 3( 18.8) | 12( 22.6) |
| Muscle spasms | 2 (11.1) | 2(28.6) | 3( 42.9) | 1( 20.0) | 3( 18.8) | 11( 20.8) |
| Abdominal pain upper | 3 (16.7) | 2(28.6) | 2( 28.6) | 0 | 3( 18.8) | 10( 18.9) |
| Back pain | 3 (16.7) | 0 | 2( 28.6) | 3( 60.0) | 2( 12.5) | 10( 18.9) |
| Flatulence | 3 (16.7) | 0 | 2( 28.6) | 3( 60.0) | 2( 12.5) | 10( 18.9) |
| Myalgia | 6 (33.3) | 0 | 1( 14.3) | 2( 40.0) | 1( 6.3) | 10( 18.9) |
| Depression | 3 (16.7) | 1(14.3) | 2( 28.6) | 2( 40.0) | 1( 6.3) | 9( 17.0) |
| Pain in extremity | 4 (22.2) | 1(14.3) | 2( 28.6) | 2( 40.0) | 0 | 9( 17.0) |
| Dyspepsia | 3 (16.7) | 1(14.3) | 2( 28.6) | 0 | 2( 12.5) | 8( 15.1) |
| Eczema | 3 (16.7) | 1(14.3) | 3( 42.9) | 1( 20.0) | 0 | 8( 15.1) |
| Weight decreased | 2 (11.1) | 1(14.3) | 1( 14.3) | 1( 20.0) | 3( 18.8) | 8( 15.1) |
| Erythema | 0 | 1(14.3) | 3( 42.9) | 1( 20.0) | 2( 12.5) | 7( 13.2) |
| Alopecia | 2 (11.1) | 1(14.3) | 0 | 0 | 3( 18.8) | 6( 11.3) |
| Dry skin | 3 (16.7) | 1(14.3) | 0 | 1( 20.0) | 1( 6.3) | 6( 11.3) |
| hyperbilirubinemia | 4 (22.2) | 0 | 1( 14.3) | 0 | 1( 6.3) | 6( 11.3) |
| Hypokalemia | 3 (16.7) | 0 | 1( 14.3) | 1( 20.0) | 1( 6.3) | 6( 11.3) |
| Sleep disorder | 6 (33.3) | 0 | 0 | 0 | 0 | 6( 11.3) |

Abbreviations: AMN = AMN107 (nilotinib), bid = Twice daily, IM = Imatinib, qd = Once daily.

A patient with multiple occurrences of an adverse event under one treatment is counted only once in the adverse event category for that treatment.

**Most frequent CTC grade 3 and 4 adverse events occurring in more than one patient by preferred term and treatment group (Safety population)**

| | AMN 400 mg bid | AMN200 mg qd / IM 400 mg bid | AMN 400 mg qd / IM 400 mg bid | AMN 400 mg bid / IM 400 mg bid | AMN 400 mg bid / IM 400 mg qd | Total |
|---|---|---|---|---|---|---|
| | N=18 | N=7 | N=7 | N=5 | N=16 | N=53 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Any grade 3/4 | 9 (50.0) | 3 (42.9) | 3 (42.9) | 4 (80.0) | 11 (68.8) | 30 (56.6) |
| event | | | | | | |
| Abdominal pain | 4 (22.2) | 1 (14.3) | 0 | 0 | 3 (18.8) | 8 (15.1) |
| Rash | 0 | 0 | 1 (14.3) | 2 (40.0) | 2 (12.5) | 5 (9.4) |
| Anemia | 1 (5.6) | 2 (28.6) | 0 | 0 | 0 | 3 (5.7) |
| Diarrhea | 2 (11.1) | 0 | 0 | 1 (20.0) | 0 | 3 (5.7) |
| Hyperbilirubinemia | 2 (11.1) | 0 | 1 (14.3) | 0 | 0 | 3 (5.7) |
| Edema peripheral | 0 | 0 | 0 | 0 | 3 (18.8) | 3 (5.7) |
| Vomiting | 2 (11.1) | 0 | 0 | 0 | 1 (6.3) | 3 (5.7) |
| Abdominal pain lower | 2 (11.1) | 0 | 0 | 0 | 0 | 2 (3.8) |
| Cerebrovascular accident | 1 (5.6) | 0 | 0 | 0 | 1 (6.3) | 2 (3.8) |
| Anorexia | 2 (11.1) | 0 | 0 | 0 | 0 | 2 (3.8) |
| Flank pain | 2 (11.1) | 0 | 0 | 0 | 0 | 2 (3.8) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Hypoglycemia | 2 (11.1) | 0 | 0 | 0 | 0 | 2 (3.8) |
| Nausea | 2 (11.1) | 0 | 0 | 0 | 0 | 2 (3.8) |

Abbreviations: AMN = AMN107 (nilotinib), bid = Twice daily, CTC = Common Terminology Criteria, IM = Imatinib, qd =Once daily.

A patient with multiple occurrences of an adverse event under one treatment is counted only once in the adverse event category for that treatment. A patient with multiple grade ratings for an adverse event while on a treatment is only counted under the maximum rating.

**Dose-limiting toxicities during Cycle 1 by treatment (MTD-determining population)**

| | **AMN 400 mg bid** | **AMN 400 mg bid / IM 400 mg bid** | **AMN 400 mg bid / IM 400 mg qd** | **Total** |
|---|---|---|---|---|
| | **n=16** | **n=5** | **n=16** | **N=50** |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Rash | 0 | 2 (40.0) | 3 (18.8) | 5 (10.0) |
| Hyperbilirubinemia | 1 (6.3) | 0 | 0 | 1 (2.0) |

AMN = AMN107 (nilotinib), bid = Twice daily, IM = Imatinib, MTD = Maximum tolerated dose, qd = Once daily.

## Secondary Objective Results

Pharmacokinetics

**Summary statistics of nilotinib pharmacokinetic parameters at steady-state (Day 8 or 15) (PK population)**

| Study cohort | Imatinib dose | Nilotinib dose | $T_{max}$ (h) median (range) | $C_{max}$ (ng/mL) mean ± SD | $T_{last}$ (h) median (range) | $C_{avg}$ (ng/mL) mean ± SD | $AUC_{last}$ (ng.h/mL) mean ± SD | CL/F (L/h) mean ± SD |
|---|---|---|---|---|---|---|---|---|
| 1 (n=15) | 0 mg | 400 mg bid | 2.8 (0-9.8) | 1644 ± 828 | 11.8 (9.9-12.0) | 1172 ± 587 | 13636 ± 6617 | 35.6 ± 16.7[b] |
| 2 (n=6) | 400 mg bid | 200 mg qd | 4.0 (2.9-6.3) | 655 ± 277 | 23.9 (23.3-25.4) | 438 ± 150 | 10474 ± 3491 | 21.5 ± 9.3[a] |
| 3 (n=6) | 400 mg bid | 400 mg qd | 6.4 (1.9-23.8) | 1236 ± 705 | 23.8 (23.5-24.0) | 863 ± 472 | 20498 ± 11135 | 25.6 ± 13.8[a] |
| 4 (n=5) | 400 mg bid | 400 mg bid | 2.1 (0-12.5) | 2160 ± 756 | 12.2 (8.1-12.5) | 1617 ± 610 | 18717 ± 8516 | 24.8 ± 10.0[a] |
| 5 (n=12) | 400 mg qd | 400 mg bid | 0 (0-5.0) | 2509 ± 1266 | 10.9 (6.5-12.1) | 1642 ± 701 | 16760 ± 9450 | 19.1 ± 6.1[b] (n=3) |

bid = Twice daily, PK = Pharmacokinetic, qd = Once daily, SD = Standard deviation.

Study cohorts were as follows: 1 = nilotinib monotherapy group, 2 = nilotinib 200 mg qd + imatinib 400 mg bid group, 3 = nilotinib 400 mg qd + imatinib 400 mg bid group, 4 = nilotinib 400 mg bid + imatinib 400 mg bid group, 5 = nilotinib 400 mg bid + imatinib 400 mg qd group.

aCL/F was estimated as: Dose/ AUC0-t

bCL/F was estimated as: Dose/AUC0-$\tau$

Efficacy

**Best overall response by treatment group (Efficacy population)**

| | AMN 400 mg bid | AMN 200 mg qd / IM 400 mg bid | AMN 400 mg qd / IM 400 mg bid | AMN 400 mg bid / IM 400 mg bid | AMN 400 mg bid / IM 400 mg qd | Total |
|---|---|---|---|---|---|---|
| | **N=18** | **N=7** | **N=7** | **N=5** | **N=16** | **N=53** |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| **Response, n (%)** | | | | | | |
| Complete response (CR) | 0 | 0 | 0 | 0 | 0 | 0 |
| Partial response (PR) | 1 (5.6) | 0 | 0 | 0 | 1 (6.3) | 2 (3.8) |
| Stable disease (SD) | 13 (72.2) | 7 (100.0) | 5 (71.4) | 4 (80.0) | 9 (56.3) | 38 (71.7) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Progressive disease (PD) | 2 (11.1) | 0 | 1 (14.3) | 0 | 6 (37.5) | 9 (17.0) |
| Unknown | 1 (5.6) | 0 | 0 | 0 | 0 | 1 (1.9) |
| Not assessed | 1 (5.6) | 0 | 1 (14.3) | 1 (20.0) | 0 | 3 (5.7) |
| **Overall response (CR or PR), n (%)** | 1 (5.6) | 0 | 0 | 0 | 1 (6.3) | 2 (3.8) |
| **Duration of response (DOR)-overall response** | | | | | | |
| Median DOR, days | 197.0 | | | | 379.0 | 288.0 |
| 95% CI[#] | | | | | | (197.0, 379.0) |
| Range | 197.0-197.0 | | | | 379.0-379.0 | 197.0, 379.0 |
| **Disease control (CR, PR, or SD)** | | | | | | |
| n (%) with disease control | 14 (77.8) | 7 (100.0) | 5 (71.4) | 4 (80.0) | 10 (62.5) | 40 (75.5) |
| 95% CI[#] | | | | | | (61.7, 86.2) |
| Median duration of response, days | 158.5 | 87.5 | 115.0 | 414.0 | 259.0 | 148.0 |
| 95% CI[#] | | | | | | (78.0, 259.0) |
| Range | 29.0-450.0 | 57.0 – 172.0 | 56.0 - 1317 | 16.0 – 876.0 | 50.0 - 1233 | 16.0 - 1317 |
| **Clinical benefit, n (%)** | | | | | | |
| SD or better after 4 months | 9 (50.0) | 0 | 3 (42.9) | 2 (40.0) | 7 (43.8) | 21 (39.6) |
| 95% CI[#] | | | | | | (26.5, 54.0) |
| SD or better after 6 months | 5 (27.8) | 0 | 2 (28.6) | 2 (40.0) | 7 (43.8) | 16 (30.2) |
| 95% CI[#] | | | | | | (18.3, 44.3) |
| **Observed death and progression** | | | | | | |
| Within 4 months | 7 (38.9) | 1 (14.3) | 4 (57.1) | 2 (40.0) | 7 (43.8) | 21 (39.6) |
| Within 6 months | 9 (50.0) | 5 (71.4) | 5 (71.4) | 2 (40.0) | 8 (50.0) | 29 (54.7) |
| **Progression free survival (PFS) (Kaplan-Meier estimates)** | | | | | | |
| PFS rate at 4 months | 58.8% | 83.3% | 42.9% | 50.0% | 56.3% | 58.2% |
| PFS rate at 6 months | 47.1% | 16.7% | 28.6% | 50.0% | 50.0% | 42.2% |
| Median (days) | 168.0 | 142.5 | 112.0 | 468.5 | 191.5 | 168.0 |
| 95% CI for median (days) | ------- | ------- | ------- | ------- | ------- | (112.0, 223.0) |
| Minimum (days) | 12.0 | 112.0 | 22.0 | 69.0 | 27.0 | 12.0 |
| Maximum (days) | 505.0 | 223.0 | 1372.0 | 932.0 | 1289.0 | 1372.0 |
| **Time to response (TTR) (days)-overall response** | | | | | | |
| Median | | | | | | |

| | | | |
|---|---|---|---|
| 95% CI for median | ---------- | ---------- | ( , ) |
| Minimum | 27.0 | 62.0 | 27.0 |
| Maximum | 27.0 | 62.0 | 62.0 |

Abbreviations: AMN = AMN107 (nilotinib), bid = Twice daily, CI = Confidence interval, CR = Complete response, DOR = Duration of response, IM = Imatinib, NA = Not applicable, NR = Not yet reportable, PD = Progressive disease, PFS = Progression-free survival, PR = Partial response, qd = Once daily, SD = Stable disease, TTP = Time to progression.

*Best overall response was calculated according to RECIST criteria based on all overall lesion responses up to the last treatment date (also counting discontinuation due to progressive disease as a response on the last treatment date). “Unknown” was assigned when the best response could not be classified as complete response, partial response, stable disease, or progressive disease. “Not assessed” was assigned when there was no response assessment for the patient.

#95% CIs provided for Total column only.

### Metabolic and anatomic imaging responses

| Imaging response | Lesions Week 1 | Lesions Week 4 | Patients Week 1 | Patients Week 4 |
|---|---|---|---|---|
| Metabolic PR | 51/133 (38%) | 47/123 (38%) | 13/37 (35%) | 9/33 (27%) |
| Metabolic SD | 69/133 (52%) | 54/123 (44%) | 22/37 (59%) | 19/33 (58%) |
| Metabolic PD | 13/133 (10%) | 22/123 (18%) | 2/37 (5%) | 5/33 (15%) |
| Anatomic PR | 6/97 (6%) | 11/118 (9%) | 0/27 (0%) | 0/34 (0%) |
| Anatomic SD | 85/97 (88%) | 93/118 (79%) | 27/27 (100%) | 30/34 (88%) |
| Anatomic PD | 6/97 (6%) | 14/118 (12%) | 0/27 (0%) | 4/34 (12%) |

PD = Progressive disease, PR = Partial response, SD = Stable disease.

## Safety Results

## Adverse Events by System Organ Class

Described under primary results.

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

Described under primary results.

## Serious Adverse Events and Deaths

Described under primary results

## Other Relevant Findings

**Newly occurring or worsening from baseline to CTC grade 3 or 4 hematology abnormalities by treatment group (Safety population)**

| | AMN 400 mg bid | AMN 200 mg qd / IM 400 mg bid | AMN 400 mg qd / IM 400 mg bid | AMN 400 mg bid / IM 400 mg bid | AMN 400 mg bid / IM 400 mg qd | Total |
|---|---|---|---|---|---|---|
| | n=18 | n=7 | n=7 | n=5 | n=16 | n=53 |
| | n/N* (%) | n/N* (%) | n/N* (%) | n/N* (%) | n/N* (%) | n/N* (%) |
| **Hemoglobin (hypo)** | | | | | | |
| Grade 3 | 2/18 (11.1) | 0/7 (0.0) | 0/7 (0.0) | 1/5 (20.0) | 0/16 (0.0) | 3/53 (5.7) |
| Grade 4 | 0/18 (0.0) | 0/7 (0.0) | 0/7 (0.0) | 0/5 (0.0) | 0/16 (0.0) | 0/53 (0.0) |
| **White blood cells (hypo)** | | | | | | |
| Grade 3 | 0/18 (0.0) | 0/7 (0.0) | 0/7 (0.0) | 0/5 (0.0) | 0/16 (0.0) | 0/53 (0.0) |
| Grade 4 | 0/18 (0.0) | 1/7 (14.3) | 0/7 (0.0) | 0/5 (0.0) | 0/16 (0.0) | 1/53 (1.9) |
| **Neutrophils (hypo)** | | | | | | |
| Grade 3 | 0/18 (0.0) | 0/7 (0.0) | 0/7 (0.0) | 0/5 (0.0) | 0/16 (0.0) | 0/53 (0.0) |
| Grade 4 | 0/18 (0.0) | 1/7 (14.3) | 0/7 (0.0) | 0/5 (0.0) | 0/16 (0.0) | 1/53 (1.9) |

Abbreviations: AMN = AMN107 (nilotinib), bid = Twice daily, CTC = Common Toxicity Criteria, IM = Imatinib, qd = Once daily.

n = number of subjects who had less than grade 3 at baseline and worsened to grade 3 post-baseline, or who had less than grade 4 at baseline and worsened to grade 4 post-baseline. N* = total number of subjects evaluable post-baseline who had less than grade x at baseline.

**Newly occurring or worsening from baseline to CTC grade 3 or 4 biochemistry abnormalities by treatment group (Safety population)**

| | AMN 400 mg bid | AMN 200 mg qd / IM 400 mg bid | AMN 400 mg qd / IM 400 mg bid | AMN 400 mg bid / IM 400 mg bid | AMN 400 mg bid / IM 400 mg qd | Total |
|---|---|---|---|---|---|---|
| | n=18 | n=7 | n=7 | n=5 | n=16 | n=53 |
| | n/N* (%) | n/N* (%) | n/N* (%) | n/N* (%) | n/N* (%) | n/N* (%) |
| Phosphate (hypo) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Grade 3 | 2/17 (11.8) | 2/7 (28.6) | 0/4 (0.0) | 1/4 (25.0) | 1/15 (6.7) | 6/47 (12.8) |
| Grade 4 | 1/18 (5.6) | 0/7 (0.0) | 0/6 (0.0) | 0/4 (0.0) | 0/16 (0.0) | 1/51 (2.0) |
| Bilirubin (total) (hyper) | | | | | | |
| Grade 3 | 2/18 (11.1) | 0/7 (0.0) | 1/7 (14.3) | 0/5 (0.0) | 0/16 (0.0) | 3/53 (5.7) |
| Grade 4 | 0/18 (0.0) | 1/7 (14.3) | 0/7 (0.0) | 0/5 (0.0) | 0/16 (0.0) | 1/53 (1.9) |
| Sodium (hypo) | | | | | | |
| Grade 3 | 2/18 (11.1) | 0/6 (0.0) | 0/7 (0.0) | 0/5 (0.0) | 2/16 (12.5) | 4/52 (7.7) |
| Calcium (hypo) | | | | | | |
| Grade 4 | 1/18 (5.6) | 1/7 (14.3) | 0/6 (0.0) | 0/5 (0.0) | 0/16 (0.0) | 2/52 (3.8) |
| Glucose (hyper) | | | | | | |
| Grade 3 | 1/18 (5.6) | 0/7 (0.0) | 0/7 (0.0) | 1/5 (20.0) | 0/16 (0.0) | 2/53 (3.8) |
| Grade 4 | 0/18 (0.0) | 0/7 (0.0) | 0/7 (0.0) | 0/5 (0.0) | 1/16 (6.3) | 1/53 (1.9) |
| Bicarbonate (hypo) | | | | | | |
| Grade 4 | 0/16 (0.0) | 0/4 (0.0) | 1/5 (20.0) | 0/2 (0.0) | 0/12 (0.0) | 1/39 (2.6) |
| Magnesium (hyper) | | | | | | |
| Grade 3 | 0/15 (0.0) | 0/7 (0.0) | 0/6 (0.0) | 0/4 (0.0) | 1/16 (6.3) | 1/48 (2.1) |
| Grade 4 | 0/15 (0.0) | 0/7 (0.0) | 1/6 (16.7) | 0/4 (0.0) | 1/16 (6.3) | 2/48 (4.2) |
| Alkaline phosphatase (hyper) | | | | | | |
| Grade 3 | 1/18 (5.6) | 0/7 (0.0) | 0/7 (0.0) | 1/5 (20.0) | 0/16 (0.0) | 2/53 (3.8) |
| ALT (hyper) | | | | | | |
| Grade 3 | 1/18 (5.6) | 0/7 (0.0) | 0/7 (0.0) | 1/5 (20.0) | 0/16 (0.0) | 2/53 (3.8) |
| AST (hyper) | | | | | | |
| Grade 3 | 0/18 (0.0) | 1/7 (14.3) | 0/7 (0.0) | 0/5 (0.0) | 0/16 (0.0) | 1/53 (1.9) |
| Lipase (hyper) | | | | | | |
| Grade 3 | 0/18 (0.0) | 1/7 (14.3) | 0/6 (0.0) | 1/5 (20.0) | 0/16 (0.0) | 2/52 (3.8) |

Abbreviations: ALT = Alanine aminotransferase, AMN = AMN107 (nilotinib), AST = aspartate aminotransferase, bid = Twice daily, CTC = Common Toxicity Criteria, IM = Imatinib, qd = Once daily.

n = number of subjects who had less than grade x at baseline and worsened to grade x post-baseline. N* = total number of subjects evaluable post-baseline who had less than grade x at baseline

**Newly occurring or worsening from baseline cardiac enzyme abnormalities by treatment group (Safety population)**

| | AMN 400 mg bid | AMN 200 mg qd / IM 400 mg bid | AMN 400 mg qd / IM 400 mg bid | AMN 400 mg bid / IM 400 mg bid | AMN 400 mg bid / IM 400 mg qd | Total |
|---|---|---|---|---|---|---|
| | n=18 | n=7 | n=7 | n=5 | n=16 | n=53 |
| | n/N* (%) | n/N* (%) | n/N* (%) | n/N* (%) | n/N* (%) | n/N* (%) |
| **CK** | | | | | | |
| > ULN to ≤ 2.5 x ULN | 2/15 (13.3) | 2/4 (50.0) | 1/6 (1 .7) | 2/5 (40.0) | 2/11 (18.2) | 9/41 (22.0) |
| > 2.5 x ULN to ≤ 5 x ULN | 0/17 (0.0) | 1/6 (16.7) | 0/6 (0.0) | 0/5 (0.0) | 0/11 (0.0) | 1/45 (2.2) |
| **CK-MB** | | | | | | |
| > ULN to ≤ 1.5 x ULN | 1/9 (11.1) | 0/3 (0.0) | 0/5 (0.0) | 0/3 (0.0) | 2/14 (14.3) | 3/34 (8.8) |
| > 1.5 x ULN to ≤ 2 x ULN | 0/9 (0.0) | 0/3 (0.0) | 1/5 (20.0) | 0/3 (0.0) | 1/14 (7.1) | 2/34 (5.9) |
| **Trop nin I** | | | | | | |
| > ULN to ≤ 1.5 x ULN | 1/9 (11.1) | 0/3 (0.0) | 0/5 (0.0) | 0/3 (0.0) | 0/15 (0.0) | 1/35 (2.9) |
| > 1.5 x ULN to ≤ 2 x ULN | 0/9 (0.0) | 1/3 (33.3) | 0/5 (0.0) | 0/3 (0.0) | 0/15 (0.0) | 1/35 ( .9) |

Abbreviations: AMN = AMN107 (nilotinib), bid = Twice daily, CK= Creatinine kinase, CK-MB= Creatinine kinase isoenzyme (muscle brain dimeric form), IM = Imatinib, qd = Once daily, ULN = Upper limit of the normal range, n = number of patients who had less than grade x at baseline and worsened to grade x postbasleine. N*= total number of subjects evaluable post-baseline who had less than grade x at baseline.

## Biomarker assessments

The archival tumors were micro-dissected and processed for DNA extraction. Exon 9, 11, 13, and 17 of the C-KIT gene and the exon 12 and 18 of the PDGFRA gene were PCR-amplified. These regions were then screened for any mutations by Denatured High Performance Liquid Chromatography (D-HPLC). Bi-directional sequencing was used to confirm any mutations identified during the D-HPLC analyses. Mutational data was available for 15 patients and was analyzed.

C-KIT mutations were found in tumors from 19/23 (83%) patients, five of whom had mutation in exon 9 (5/23, 22%) and 14 in exon 11 (14/23, 61%). Tumor from one patient showed double mutations in exon 11 and exon 13. None of the tumors analyzed were found to have mutations in the PDGFRA gene.

Three of the five patients whose tumor carries exon 9 C-KIT mutation showed stable disease, one progressive disease, and one unknown. One of the 14 patients whose tumor had exon 11 C-KIT mutation achieved partial response, nine stable disease, three progressive disease, and one not assessable. Four patients without detectable C-KIT mutation in their tumors all achieved stable disease.

| |
|---|
| **Date of Clinical Trial Report**<br>20 Jun 2008 (core)<br>11 Aug 2011 (extension) |
| **Date Inclusion on Novartis Clinical Trial Results Database**<br>21 Apr 2010 (core) |
| **Date of Latest Update**<br>11 Jan 2012 (Core + Extension) |