Sponsor

Novartis

Generic Drug Name

Nilotinib

Therapeutic Area of Trial

Gastrointestinal stromal tumors resistant to both imatinib and sunitinib

Approved Indication

- Treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in adult patients resistant to or intolerant to at least one prior therapy including imatinib.
- Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.

Protocol Number

CAMN107A2201 (Core and Extension phase)

Title

A randomized, open-label, multi-center study to evaluate the efficacy of nilotinib versus best supportive care with or without a tyrosine kinase inhibitor (investigator's choice) in adult patients with gastrointestinal stromal tumors resistant to both imatinib and sunitinib

Phase of Development

Phase III

Study Start/End Dates

05-Mar-2007 to 20-Jun-2011

Study Design/Methodology

This was a phase III, randomized, open- label, parallel group, multicenter, two-arm clinical trial. Patients were randomized 2:1 to receive nilotinib 400 mg twice daily (bid) or control (Best Supportive Care (BSC) with or without imatinib or sunitinib at the last tolerated dose or at the investigator's choice). The core study period for each patient was defined as the time from when the patient was first randomized to the time when a progression free survival (PFS) event was observed for the patient, or to the time when the patient discontinued the core study due to other reasons, or to the time at which the required number of PFS events (approximately 144) for the final ana-lysis had been observed. The time point at which the required number of these events had occurred was estimated and the cut-off date for final analysis was determined as 27-Jun-2008. All patients still on the core study at that date were rolled over to the extension study. Data from the core study up to and including the cutoff date (27-Jun-2008) was used for all statistical analyses of safety and efficacy (core study).

At this point, all patients (irrespectively of the treatment allocation) still ongoing in the Core study (n=74) were offered treatment continuation as part of the Extension study. The last patient was transferred to the Extension study on 26-Aug-2008.

The Extension study evaluated the long-term safety and efficacy of nilotinib treatment in the same patient population as the Core study. Patients included in the Extension study had either continued on the randomized therapy to which they were allocated in the Core study or had crossed over to nilotinib therapy after progression on the randomized control treatment. This allowed an evaluation of the long term efficacy and safety of patients randomized to nilotinib and patients randomized to BCS and who then crossed over to nilotinib.

Centres

50 centers in 13 countries: Australia (3), Canada (4), Czech Republic (1), France (4), Germany (10), Italy (6), Korea (2), Netherlands (1), Poland (1), Spain (4), Switzerland (2), Taiwan (2), US (10). One site in Switzerland and one in the US did not enroll patients.

Outcome measures

Core phase:

Primary outcome measures(s)

The primary variable was progression-free survival (PFS) based on the blind central review using modified RECIST criteria.

Secondary outcome measures(s)

Safety and tolerability

- Safety assessments consisted of recording of all AEs, including SAEs, with their severity and relationship to study drug, and regular monitoring of laboratory evaluations, physical conditions including WHO performance status, vital signs, cardiac function, and pregnancies.

Pharmacology

- Pharmacokinetics and bioanalytics: Population pharmacokinetic (PK) analysis was performed on patients in the nilotinib arm. An exploratory modeling analysis was performed to characterize the relationship between nilotinib serum concentration and changes from baseline in QTcF.

Extension phase:

Primary outcome measures(s)

Long-term safety was evaluated on the patients who entered the Core study and remained on the originally assigned treatment, including all the data from the Core and the Extension study if available until end of the randomized treatment.

Efficacy:

- Overall survival (OS) was analyzed for the Core FAS and Treatment Crossover Analysis Set. PFS and best overall response were analyzed for the Treatment Crossover Analysis Set.

Secondary outcome measures(s)

Safety:

- Safety was assessed for the Core Safety Analysis Set and Treatment Crossover Analysis, monitoring the frequency, duration and severity of AEs, clinical evaluations (vitals signs, echocardiography, ECG) throughout the study, as well as clinical laboratory analyses.

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

Nilotinib 400 mg was taken orally bid.

Statistical Methods

Core phase:

All data from the core study (if applicable, including the follow-up phase after treatment

discontinuation) up to the data cut-off date were analyzed and are reported. In addition, all survival data up to the data cut-off date were used in the overall survival analysis, including data from core phase during treatment; follow up period post core treatment, extension phase, as well as survival follow up.

Patients were analyzed according to the treatment arm they were assigned to at randomization. The intent to treat (ITT) population was defined as all randomized patients and was used for all efficacy analyses and baseline characteristics. The per protocol (PP) population, defined as all randomized patients who received at least one dose of study drug or who were randomized to the control arm with BSC only and had no major protocol deviations, was used only for the PP analysis of the primary efficacy variable and key secondary efficacy variables. The safety population was used for all safety analyses and was defined as all patients who received at least one dose of study medication and had at least one post-baseline safety assessment, or patients who were randomized to the control arm with BSC only and had at least one post-baseline safety assessment. The PK population was used for all PK analyses and was defined as all patients who were randomized to the nilotinib arm, received only nilotinib treatment, and had evaluable pharmacokinetic concentration data.

All efficacy analyses (except PP analyses) were based on the ITT population. The blinded central reader's assessments of CT/MRI scans were used in all analyses other than the specified sensitivity analyses.

Time-to-event variables were analyzed using two-sided log rank test. Observed event rate and Kaplan-Meier estimates of median time (with 95% confidence interval) were presented, along with observed minimum and maximum values. Kaplan-Meier estimates at Months 3, 6, and 12 were also displayed.

The primary efficacy variable was PFS, defined as the time from the date of randomization to the date of the first observation of documented disease progression or death due to any cause, which was calculated as:

PFS = date of PFS event – date of randomization + 1 day.

If a PFS event was not observed, the PFS was censored at the date of last adequate tumor assessment during the core study (including tumor assessments during core follow- up phase) prior to or on the date of the data cut-off. The primary efficacy analysis was performed at an overall 5% level of significance based on the two-sided log-rank test.

There were two key secondary efficacy variables – overall survival and confirmed best overall response rate. Overall survival, defined as the time from the date of randomization to the date of death due to any cause, was compared between arms using a two-sided log rank test. Confirmed best overall response rate, defined as the proportion of patients with complete response or partial response, was compared between arms using Fisher's exact test.

Response rates for stable disease, progressive disease, overall clinical benefit, and unconfirmed best overall response were analyzed using Fisher's exact tests. Time-to-event variables (time to tumor response, TTP, duration of response, and TTF) were analyzed using Kaplan-Meier estimates for the ITT population. TTP and TTF were also tested using log-rank test at two-sided 5% significance level. No tests were performed for time-to response and duration of response. Duration of response was analyzed for responders only.

Extension phase:

Overall survival (OS) was compared between treatment arms based on all randomized patients including all the available data from the Core and the Extension study as well as the survival follow-up until the end of the study by K-M method and log-rank test. OS and PFS for treatment crossover patients were calculated by KM method. The best overall response rate for treatment crossover patients was calculated and its 95% CI was presented as well.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria for core phase:

- Age = 18 years with a World Health Organization (WHO) performance status of 0- 2.
- Histologically-confirmed, unresectable, or metastatic GIST not amenable to surgery or combined modality with curative intent.
- Radiological confirmation of disease progression during imatinib therapy at a dose of at least 400 mg and radiological confirmation of disease progression during sunitinib therapy that was started at 50 mg daily dose.
- At least one measurable site of disease on CT/MRI scan at Visit 2, as defined by RECIST criteria.
- Normal organ electrolyte, and bone marrow function:
- Absolute neutrophil count (ANC) = 1.5 x 10^9/L
- Platelets = 100 x 10^9/L
- 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 due to tumor
- Serum bilirubin = 1.5 x ULN
- Serum lipase and amylase = 1.5 x ULN Serum potassium within the normal limits (WNL) or correctable to WLN with supplements by Visit 2
- Total calcium (corrected for serum albumin) WNL or correctable to WNL with supplements by Visit 2
- Serum magnesium WNL or correctable to WNL with supplements by Visit 2
- Serum phosphorous WNL or correctable to WNL with supplements by Visit 2
- Serum creatinine = 1.5 x ULN or 24-hour creatinine clearance = 50 ml/min

Exclusion criteria for Core phase

- Prior treatment with nilotinib or any other tyrosine kinase inhibitors (TKIs) or targeted agents with exception of imatinib and sunitinib
- Treatment with any cytotoxic and/or investigational cytotoxic drug = 4 weeks (6 weeks for nitrosurea or mitomycin C) prior to Visit 1 with the exception of imatinib and sunitinib targeted therapy
- Prior or concomitant malignancies (primary tumor or a relapse diagnosed and treated in the last 5 years) other than GIST with the exception of previous or concomitant basal cell skin

cancer and previous cervical carcinoma in situ

- Impaired cardiac function at Visit 1 or 2, including any one of the following:
- Left ventricular ejection fraction (LVEF) < 45% or below the institutional LLN (whichever is higher) as determined by echocardiogram (ECHO) at Visit 1
- Complete left bundle branch block
- Use of a ventricular paced cardiac pacemaker
- Congenital long QT syndrome or family history of long QT syndrome History of presence of significant ventricular or atrial tachyarrhythmias
- Clinically significant resting bradycardia (< 50 beats per minute)

QTc > 450 msec on screening ECG using the QTcF formula (if QTc was > 450 msec and electrolytes were not within normal ranges, electrolytes were to be corrected and then the patient re-screened for QTc)

- Right bundle branch block plus left anterior hemiblock, bifascicular block
- Myocardial infarction within 12 months prior to Visit 1
- Other clinically significant heart disease (e.g. unstable angina, congestive heart failure (CHF), uncontrolled hypertension)
- 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 the study drugs, uncontrolled diabetes).
- 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 the study drugs, uncontrolled diabetes).
- For patients who underwent FDG-PET:
  - Inability to remain laying down in PET scanner for up to 1 hour
  - Absence of at least one metastatic lesion = 2 cm on pre-dose CT scan or other radiographic imaging as defined by RECIST criteria
- Use of therapeutic coumarin derivatives (i.e., warfarin, acenocoumarol, phenprocoumon).
- Use of any medications that prolong the QT interval and CYP3A4 inhibitors if the treatment cannot be either safely discontinued or switched to a different medication prior to starting study drug administration.
- Patients who had undergone major surgery = 2 weeks prior to Visit 1 or who had not recovered from side effects of such surgery.
- Receipt of wide field radiotherapy = 4 weeks or limited field radiation for palliation < 2 weeks prior to Visit 1, or patients who had not recovered from the side effects of such therapy.
- 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.

Inclusion criteria for Extension phase

Patients with third-line unresectable and/or metastatic gastrointestinal stromal tumors (GIST) were included in the Core study and then had to meet one of the Extension study entry criteria:

- Patients whose tumors had progressed on the control arm and had crossed over to the nilotinib arm.
- The study was stopped due to meeting the primary efficacy endpoint of PFS at the interim analysis.
- Patients who were still being treated at the close of the Core study on the control arm or nilotinib arm (whose tumors have not progressed at the time of the end of the Core study).
- Patients must have had documented, confirmed stable, partial or complete response as defined by the RECIST criteria at the time of entry into the Extension study with the exception of patients who had progressed on the control arm.

Exclusion criteria for Extension phase

- Use of other anticancer treatments or investigational drugs (with exception of the study drugs)
- Patients with a history of noncompliance with study drug treatment in the Core study protocol.

Participant Flow

Patient disposition by treatment (Core FAS)

Disposition Reason	AMN N=165 n (%)	Control Total N=83 n (%)	Total N=248 n (%)
Entered the randomized treatment	165	83	248
Discontinued the randomized treatment	165 (100.0)	83 (100.0)	248 (100.0)
Adverse Event(s)[1]	22 (13.3)	6 (7.2)	28 (11.3)
Administrative problems	1 (0.6)	1 (1.2)	2 (0.8)
Subject withdrew consent	5 (3.0)	2 (2.4)	7 (2.8)
Death [2]	10 (6.1)	4 (4.8)	14 (5.6)
New cancer therapy	1 (0.6)	0	1 (0.4)
Disease progression*	126 (76.4)	59 (71.1)	185 (74.6)
Protocol deviation	0	1 (1.2)	1 (0.4)
Crossed-over to nilotinib therapy during Extension	0	10 (12.0)	10 (4.0)
Crossed-over to nilotinib therapy	0	67 (80.7)	67 (27.0)
Following Core study completion	0	57 (68.7)	57 (23.0)
During Extension study	0	10 (12.0)	10 (4.0)

(1) AEs also include clinical progression/general health deterioration without documented PD by RECIST.
(2) Includes only those patients for whom death was reported as the primary reason for discontinuation of therapy.
* One patient that had disease progression as the reason for discontinuation at visit 777, the Core study end of treatment but subsequently crossed-over to nilotinib during Extension study is only counted in crossed-over during Extension category.

Patient disposition (Treatment Crossover Analysis Set)

Disposition Reason	AMN N=67 n (%)
Crossed-over to nilotinib therapy	67
Discontinued crossover treatment - nilotinib(3)	67 (100.0)
Adverse Event(s)(1)	12 (17.9)
Subject withdrew consent	2 (3.0)
Death(2)	7 (10.4)
Protocol deviation	1 (1.5)
Treatment duration completed as per protocol	1 (1.5)
Disease progression	44 (65.7)

(1) AEs also include clinical progression/general health deterioration without documented PD by RECIST.
(2) Includes only those patients for whom death was reported as the primary reason for discontinuation of therapy.
(3) These reasons are coming from End of Treatment visit 779 in the Extension study CRF page.

Baseline Characteristics

Demographic summary by treatment (ITT population)

Demographic variable	Nilotinib N=165	Control N=83	Total N=248
Age (years)			
N	165	83	248
Mean	57.4	58.6	57.8
SD	12.69	10.57	12.01
Median	58.0	59.0	58.0
Min	18.0	37.0	18.0
Max	83.0	82.0	83.0
Age category – n (%)			
< 35 years	7 (4.2)	0	7 (2.8)
= 35 -< 55 years	59 (35.8)	27 (32.5)	86 (34.7)
= 55 -< 65 years	52 (31.5)	30 (36.1)	82 (33.1)
= 65 years	47 (28.5)	26 (31.3)	73 (29.4)
Sex – n (%)			
Male	101 (61.2)	47 (56.6)	148 (59.7)
Female	64 (38.8)	36 (43.4)	100 (40.3)
Race – n (%)			
Caucasian	134 (81.2)	67 (80.7)	201 (81.0)
Black	2 (1.2)	4 (4.8)	6 (2.4)
Asian	21 (12.7)	11 (13.3)	32 (12.9)
Pacific islander	2 (1.2)	0	2 (0.8)
Other	6 (3.6)	1 (1.2)	7 (2.8)
Ethnicity – n (%)			
Hispanic/Latino	8 (4.8)	1 (1.2)	9 (3.6)
Chinese	6 (3.6)	3 (3.6)	9 (3.6)
Indian	1 (0.6)	0	1 (0.4)
Japanese	1 (0.6)	0	1 (0.4)
Mixed Ethnicity	2 (1.2)	0	2 (0.8)
Other	147 (89.1)	79 (95.2)	226 (91.1)
Weight (kg)			
N	165	82	247
Mean	72.4	68.8	71.2

SD	17.10	16.27	16.88
Median	70.0	67.8	69.0
Min	41.0	36.0	36.0
Max	127.0	117.0	127.0
WHO performance status – n (%)			
Grade 0	90 (54.5)	33 (39.8)	123 (49.6)
Grade 1	62 (37.6)	41 (49.4)	103 (41.5)
Grade 2	13 (7.9)	8 (9.6)	21 (8.5)
Missing	0	1 (1.2)	1 (0.4)

Demographic summary for crossover nilotinib therapy by original treatment (Treatment Crossover Analysis Set)

	Control			
Demographic variable	**BSC+I N=42 n (%)**	**BSC+S N=20 n (%)**	**BSC N=5 n (%)**	**Total N=67**
Age (years)				
n	42	20	5	67
mean.	57.6	59.7	61.8	58.5
s.d	10.6	10.6	10.0	10.5
median	58.5	58.0	66.0	59.0
min	37	39	46	37
max	73	82	72	82
Age category (n(%))				
≥ 35 - < 55 years	15 (35.7)	7 (35.0)	1 (20.0)	23 (34.3)
≥ 55 - < 65 years	15 (35.7)	8 (40.0)	1 (20.0)	24 (35.8)
≥ 65 years	12 (28.6)	5 (25.0)	3 (60.0)	20 (29.9%)
Sex (n(%))				
Male	23 (54.8)	13 (65.0)	2 (40.0)	38 (56.7)
Female	19 (45.2)	7 (35.0)	3 (60.0)	29 (43.3)
Race (n(%))				
Caucasian	31 (73.8)	18 (90.0)	5 (100)	54 (80.6)
Black	1 (2.4)	2 (10.0)	0	3 (4.5)
Asian	9 (21.4)	0	0	9 (13.4)
Other	1 (2.4)	0	0	1 (1.5)
Ethnicity (n)(%)				
Hispanic/Latino	1 (2.4)	0	0	1 (1.5)
Chinese	3 (7.1)	0	0	3 (4.5)
Other	38 (90.5)	20 (100)	5 (100)	63 (94.0)
Weight (kg)				
n	42	20	5	67

mean	67.8	68.9	60.3	67.5
s.d	15.0	15.6	12.9	15.0
median	67.9	64.9	56.0	65.4
min	38	48	47	38
max	101	103	74	103
WHO performance status (n(%))				
Grade 0	14 (33.3)	10 (50.0)	2 (40.0)	26 (38.8)
Grade 1	18 (42.9)	10 (50.0)	2 (40.0)	30 (44.8)
Grade 2	6 (14.3)	0	0	6 (9.0)
Grade >2	4 (9.5)	0	1 (20.0)	5 (7.5)

Age is calculated at the start of crossover nilotinib therapy.

Weight and WHO Performance status is the last available assessment prior to crossover nilotinib therapy.

Height comes from baseline measurement of the Core study.

Outcome measures

Primary Outcome Result(s)

Summary of progression-free survival based on central radiology review (ITT population)

	Nilotinib N=165	Control N=83	P-value
Number censored – n (%)	47 (28.5)	31 (37.3)	
Number of events – n (%)	118 (71.5)	52 (62.7)	
Tumor progression – n (%)	108 (65.5)	46 (55.4)	
Death due to any cause (without PD) – n (%)	10 (6.1)	6 (7.2)	
Time to events (days)			0.5555
Median (95% CI)	109.0 (61.0,113.0)	111.0 (60.0,116.0)	
Min -Max	1 -343	1 -284	
Hazard Ratio (Nilotinib vs. Control)		0.90	
95% CI		(0.65, 1.26)	

Abbreviation: PD = progressive disease.
P-value is from a 2-sided log-rank test.
* Kaplan-Meier estimates.
Min-Max is observed range, including censored data.
HR is estimated from Cox regression model, assuming proportional hazards between treatment arms.

Summary of progression free survival (PFS) based on local investigator's assessment (Treatment Crossover Analysis Set)

	AMN N=67
Number of censored observations	14 (20.9%)
Number of events	53 (79.1%)
Tumor progression	42 (62.7%)
Death due to any cause (without PD)	11 (16.4%)
PFS (days)	
Median (95% CI)	84 (56, 109)
Min – Max	1 - 1273
K-M estimates of survival rate (95% CI)	
At month 3	43.0 (30.0, 55.3)
At month 6	16.2 (7.8, 27.3)
At month 12	6.9 (1.9, 16.6)

- Median and its 95% CI are Kaplan-Meier estimates (Min-Max is observed range, including censored data)

Secondary Outcome Result(s)

Summary of overall survival (Core FAS)

	AMN N=165	Control N=83	P-value
Number of censored observations	23 (13.9%)	8 (9.6%)	
Number of deaths	142 (86.1%)	75 (90.4%)	
Overall survival (days)			0.3547
Median (95% CI)	361 (265, 425)	300 (246, 386)	
Min – Max	4 - 1444	14 - 1450	
Hazard Ratio (AMN vs. Control)		0.88	
95% CI		(0.66, 1.16)	
K-M estimates of survival rate (95% CI)			
At month 3	87.7 (81.6, 91.9)	79.3 (68.9, 86.6)	
At month 6	74.7 (67.2, 80.7)	70.8 (59.6, 79.4)	
At month 12	49.0 (41.0, 56.4)	43.9 (33.0, 54.3)	
At month 18	34.3 (27.1, 41.7)	29.3 (19.9, 39.3)	
At month 24	25.9 (19.4, 32.9)	19.1 (11.4, 28.3)	

- Includes both Core and Extension data as well as survival follow up data.
- p-value is from a 2-sided log-rank test.
- Median and its 95% CI are Kaplan-Meier estimates (Min-Max is observed range, including censored data).
- HR is estimated from Cox regression model, assuming proportional hazards between treatment arms.

Summary of overall survival after crossover (Treatment Crossover Analysis Set)

	AMN N=67
Number of censored observations	7 (10.4%)
Number of deaths	60 (89.6%)
Time to death (days)	
Median (95% CI)	231 (196, 327)
Min – Max	3 - 1326
K-M estimates of survival rate (95% CI)	
At month 3	75.8 (63.5, 84.4)
At month 6	66.7 (53.9, 76.6)
At month 12	33.3 (22.3, 44.7)

Median and its 95% CI are Kaplan-Meier estimates (Min-Max is observed range, including censored data)

Best overall response (confirmed) based on local investigator's assessments (Treatment Crossover Analysis Set)

	AMN N=67	
	n (%)	(95% CI)
Overall response (CR/PR)	1 (1.5)	(0.0, 8.0)

Complete response (CR)	0	
Partial response (PR)	1 (1.5)	
Stable disease (SD)	24 (35.8)	
Progressive disease (PD)	22 (32.8)	(21.8, 45.4)
Unknown (UNK)	20 (29.9)	
Clinical benefits		
CR/PR/SD	25 (37.3)	(25.8, 50.0)
CR/PR/SD last > 6 months	5 (7.5)	(2.5, 16.6)
CR/PR/SD last > 12 months	4 (6.0)	(1.7, 14.6)

CI is exact CI based on binomial distribution.

Bioanalytical results: Among the 151 patients included in the PK population, 13 (9%) patients had total gastrectomy, 15 (10%) had partial gastrectomy, and 52 (34%) had small intestine resection. Population PK analysis suggested nilotinib bioavailability was decreased by 48% and 22%, respectively, in patients with total gastrectomy and with partial gastrectomy. The number of patients with total gastrectomy coupled with the study results does not allow a definite PK/PD relationship of total gastrectomy to be determined. However, nilotinib bioavailability was not found to be significantly altered in patients with small intestine resection.

For the same 400 mg bid dosage regimen, the PK profiles of nilotinib observed in this group of GIST patients were similar to those observed previously in CML patients. A positive correlation between nilotinib serum concentrations and QTcF change from baseline was observed. On average, an increase of 100 ng/ml in nilotinib serum concentrations was shown to be associated with a 0.6 ms increase in QTcF. These findings are consistent with those observed in a previous study in CML patients.

Safety Results

Adverse Events by System Organ Class

Adverse events overall and frequently affected system organ classes during randomized treatment (Core Safety Analysis Set)

System affected	AMN N=165 n (%)	Control BSC+I N=54 n (%)	Control BSC+S N=23 n (%)	Control BSC N=6 n (%)	Control Total N=83 n (%)	Total N=248 n (%)
-Any system organ class	164 (99.4)	53 (98.1)	21 (91.3)	4 (66.7)	78 (94.0)	242 (97.6)
Gastrointestinal disorders	129 (78.2)	47 (87.0)	17 (3.9)	4 (66.7)	68 (81.9)	197 (79.4)
General disorders and administration site conditions	114 (69.1)	39 (72.2)	10 (43.5)	1 (16.7)	50 (60.2)	164 (66.1)
Investigations	80 (48.5)	23 (42.6)	4 (17.4)	1 (16.7)	28 (33.7)	108 (43.5)
Metabolism and nutrition disorders	79 (47.9)	23 (42.6)	3 (13.0)	1 (16.7)	27 (32.5)	106 (42.7)
Musculoskeletal and connective tissue disorders	72 (43.6)	15 (27.8)	8 (34.8)	2 (33.3)	25 (30.1)	97 (39.1)
Skin and subcutaneous tissue disorders	66 (40.0)	8 (14.8)	11 (47.8)	0	19 (22.9)	85 (34.3)
Blood and lymphatic system disorders	52 (31.5)	22 (40.7)	9 (39.1)	0	31 (37.3)	83 (33.5)
Respiratory, thoracic and mediastinal disorders	53 (32.1)	19 (35.2)	5 (21.7)	1 (16.7)	25 (30.1)	78 (31.5)
Nervous system disorders	61 (37.0)	9 (16.7)	7 (30.4)	0	16 (19.3)	77 (31.0)
Infections and infestations	46 (27.9)	12 (22.2)	5 (21.7)	0	17 (20.5)	63 (25.4)
Psychiatric disorders	30 (18.2)	7 (13.0)	1 (4.3)	0	8 (9.6)	38 (15.3)
Vascular disorders	26 (15.8)	4 (7.4)	3 (13.0)	0	7 (8.4)	33 (13.3)
Renal and urinary disorders	24 (14.5)	6 (11.1)	1 (4.3)	1 (16.7)	8 (9.6)	32 (12.9)
Hepatobiliary disorders	27 (16.4)	4 (7.4)	0	0	4 (4.8)	31 (12.5)
Eye disorders	13 (7.9)	14 (25.9)	2 (8.7)	0	16 (19.3)	29 (1.7)
Cardiac disorders	20 (12.1)	4 (7.4)	1 (4.3)	0	5 (6.0)	25 (10.1)
Neoplasms benign malignant and unspecified, (including cysts and polyps)	14 (8.5)	3 (5.6)	0	0	3 (3.6)	17 (6.9)
Ear and labyrinth disorders	7 (4.2)	3 (5.6)	1(4.3)	1 (16.7)	5 (6.0)	12 (4.8)
Reproductive system and breast disorders	11 (6.7)	0	1(4.3)	0	1 (1.2)	12 (4.8)
Injury, poisoning and procedural complications	9 (5.5)	2(3.7)	0	0	2 (2.4)	11 (4.4)
Endocrine disorders	3 (1.8)	0	0	0	0	3 (1.2)
Immune system disorders	2 (1.2)	0	0	0	0	2 (0.8)
Congenital, familial and genetic disorders	1 (0.6)	0	0	0	0	1(0.4)

Adverse events overall and frequently affected system organ classes on crossover nilotinib therapy (Treatment Crossover Analysis Set)

System affected	AMN N=67 n (%)
Any SOC	66 (98.5)
Gastrointestinal disorders	44 (65.7)
General disorders and administration site conditions	42 (62.7)
Metabolism and nutrition disorders	27 (40.3)
Investigations	25 (37.3)
Musculoskeletal and connective tissue disorders	20 (29.9)
Respiratory, thoracic and mediastinal disorders	18 (26.9)
Blood and lymphatic system disorders	17 (25.4)
Skin and subcutaneous tissue disorders	17 (25.4)
Infections and infestations	13 (19.4)
Nervous system disorders	11 (16.4)
Renal and urinary disorders	10 (14.9)
Psychiatric disorders	9 (13.4)
Hepatobiliary disorders	6 (9.0)
Reproductive system and breast disorders	6 (9.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (6.0)
Vascular disorders	4 (6.0)
Cardiac disorders	3 (4.5)
Eye disorders	3 (4.5)
Injury, poisoning and procedural complications	2 (3.0)
Congenital, familial and genetic disorders	1 (1.5)
Ear and labyrinth disorders	1 (1.5)
Endocrine disorders	1 (1.5)

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

Adverse events overall and most frequent events (≥10% in any group) by preferred term during randomized treatment (Core Safety Analysis Set)

Preferred term	AMN N=165 n (%)	Control BSC+I N=54 n (%)	Control BSC+S N=23 n (%)	Control BSC N=6 n (%)	Control Total N=83 n (%)	Total N=248 n (%)
-Any event	164 (99.4)	53 (98.1)	21 (91.3)	4 (66.7)	78 (94.0)	242 (97.6)
Abdominal pain	70 (42.4)	15 (27.8)	6 (26.1)	3 (50.0)	24(28.9)	94 (37.9)
Nausea	52 (31.5)	30 (55.6)	3 (13.0)	0	33 (39.8)	85 (34.3)
Decreased appetite	48 (29.1)	16 (29.6)	1 (4.3)	1 (16.7)	18 (21.7)	66 (26.6)
Fatigue	47 (28.5)	9 (16.7)	6 (26.1)	0	15 (18.1)	62 (25.0)
Vomiting	36 (21.8)	23 (42.6)	3 (13.0)	0	26 (31.3)	62 (25.0)
Anaemia	41 (24.8)	20 (37.0)	0	0	20 (24.1)	61 (24.6)

Oedema peripheral	30 (18.2)	23 (42.6)	3 (3.0)	0	26 (1.3)	56 (22.6)
Asthenia	46 (27.9)	4 (7.4)	2 (8.7)	1 (16.7)	7 (8.4)	53 (21.4)
Constipation	42 (25.5)	8 (14.8)	0	1 (16.7)	9 (10.8)	51 (20.6)
Diarrhoea	28 (17.0)	12 (22.2)	8 (34.8)	0	20 (24.1)	48 (19.4)
Headache	34 (20.6)	3 (5.6)	6 (26.1)	0	9 (10.8)	43 (17.3)
Pyrexia	33 (20.0)	7 (13.0)	2 (8.7)	0	9 (0.8)	42 (16.9)
Weight decreased	35 (21.2)	5 (9.3)	1 (4.3)	1 (16.7)	7 (8.4)	42 (16.9)
Dyspnoea	23 (13.9)	10 (18.5)	2 (8.7)	0	12 (14.5)	35 (14.1)
Back pain	27 (16.4)	4 (7.4)	1 (4.3)	1 (16.7)	6 (7.2)	33 (13.3)
Rash	26 (15.8)	4 (7.4)	3 (13.0)	0	7 (8.4)	33 (13.3)
Abdominal pain upper	21 (12.7)	5 (9.3)	1 (4.3)	0	6 (7.2)	27 (10.9)
Cough	19 (11.5)	5 (9.3)	1 (4.3)	0	6 (7.2)	25 (10.1)
Myalgia	20 (12.1)	3 (5.6)	1 (4.3)	0	4(4.8)	24 (9.7)
Abdominal distension	17 (0.3)	6 (11.1)	0	0	6 (2)	23 (9.3)
General physical health deterioration	18 (10.9)	4 (7.4)	0	0	4 (4.8)	22 (8.9)
Pruritus	19 (11.5)	2 (3.7)	0	0	2 (2.4)	21 (8.5)
Blood alkaline phosphatase increased	15 (9.1)	3 (5.6)	0	1 (16.7)	4 (4.8)	19 (7.7)
Dyspepsia	13 (7.9)	3 (5.6)	2 (8.7)	1 (16.7)	6 (7.2)	19 (7.7)
Stomatitis	13 (7.9)	1 (1.9)	3 (13.0)	0	4 (4.8)	17 (6.9)
Hypertension	8 (4.8)	2 (3.7)	3 (13.0)	0	5 (6.0)	13 (5.2)
Ascites	5 (3.0)	6 (11.1)	0	0	6 (7.2)	11 (4.4)
Eyelid oedema	3 (1.8)	7 (13.0)	0	0	7 (8.4)	10 (4.0)
Palmar-plantar erythrodysaesthesia syndrom	3 (1.8)	0	6 (26.1)	0	6 (7.2)	9 (3.6)
Intestinal obstruction	5 (3.0)	2 (3.7)	0	1 (16.7)	3 (3.6)	8 (3.2)
Neutropenia	1 (0.6)	1 (1.9)	6 (26.1)	0	7 (8.4)	8 (3.2)
Pulmonary embolism	6 (3.6)	0	1 (4.3)	1 (16.7)	2 (2.4)	8 (3.2)
Flank pain	4 (2.4)	2 (3.7)	0	1 (16.7)	3 (3.6)	7 (2.8)
Dysuria	2 (1.2)	0	0	1 (16.7)	1 (1.2)	3 (1.2)
Ear discomfort	2 (1.2)	0	0	1 (16.7)	1 (1.2)	3 (1.2)
Oesophageal ulcer	0	1 (1.9)	0	1 (16.7)	1 (1.2)	2 (0.8)
Reflux oesophagitis	0	0	0	1 (16.7)	1 (1.2)	1 (0.4)

Adverse events overall and most frequent events (≥5%) during crossover nilotinib therapy (Treatment Crossover Analysis Set)

Preferred term	AMN N=67 n (%)
Any event	66 (98.5)
Weight decreased	20 (29.9)
Abdominal pain	16 (23.9)

Decreased appetite	16 (23.9)
Anaemia	15 (22.4)
Vomiting	15 (22.4)
Oedema peripheral	14 (20.9)
Nausea	13 (19.4)
Dyspnoea	12 (17.9)
Fatigue	12 (17.9)
Constipation	11 (16.4)
General physical health deterioration	11 (16.4)
Asthenia	10 (14.9)
Pyrexia	9 (13.4)
Abdominal pain upper	8 (11.9)
Back pain	7 (10.4)
Abdominal distension	6 (9.0)
Diarrhoea	5 (7.5)
Pain in extremity	5 (7.5)
Pleural effusion	5 (7.5)
Abdominal pain lower	4 (6.0)
Cough	4 (6.0)
Dehydration	4 (6.0)
Headache	4 (6.0)
Hyperbilirubinaemia	4 (6.0)
Hypoalbuminaemia	4 (6.0)
Hypokalaemia	4 (6.0)
Myalgia	4 (6.0)
Pruritus	4 (6.0)
Rash	4 (6.0)

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant adverse events or related discontinuations during randomized treatment (Core Safety Analysis Set)

	AMN N=165 n (%)	Control BSC+I N= 54 n (%)	Control BSC+S N= 23 n (%)	Control BSC N= 6 n (%)	Control Total N= 83 n (%)	Total N=248 n (%)
All deaths within 28 days of last randomized dose	24 (14.5)	10 (18.5)	0	1 (16.7)	11 (13.3)	35 (14.1)
-Deaths recorded as reason for randomized treatment discontinuation	15 (9.1)	6 (11.1)	0	1 (16.7)	7 (8.4)	22 (8.9)
-Other deaths	9 (5.5)	4 (7.4)	0	0	4 (4.8)	13 (5.2)
SAEs	81 (49.1)	22 (40.7)	4 (17.4)	1 (16.7)	27 (32.5)	108 (43.5)
Study-drug-related SAEs	11 (6.7)	4 (7.4)	0	0	4 (4.8)	15 (6.0)
AEs associated with discontinuation	25 (15.2)	5 (9.3)	1 (4.3)	0	6 (7.2)	31 (12.5)

AEs requiring dose adjustment/ interruption	67 (40.6)	14 (25.9)	9 (39.1)	0	23 (27.7)	90 (36.3)
AEs requiring significant additional therapy*	140 (84.8)	47 (87.0)	16 (69.6)	3 (50.0)	66 (79.5)	206 (83.1)

* Significant additional therapy refers to taking concomitant medication or receiving non-drug therapy.
Death was reported (on the end of treatment CRF page) page within 28 days of last dose) as the reason for randomized treatment discontinuation

Deaths, other serious or clinically significant adverse events or related discontinuations during randomized treatment (Treatment Crossover Analysis Set)

	AMN n=165 n (%)
All deaths within 28 days of last dose	18 (26.9)
-Deaths recorded as reason for treatment discontinuation	7 (10.4)
-Other deaths	11 (16.4)
SAEs	32 (47.8)
Study-drug-related SAEs	2 (3.0)
AEs associated with discontinuation	13 (19.4)
AEs requiring dose adjustment/ interruption	22 (32.8)
AEs requiring significant additional therapy*	53 (79.1)

* Significant additional therapy refers to taking concomitant medication or receiving non-drug therapy.

Other Relevant Findings

None

Date of Clinical Trial Report

07 Dec 2011

Date Inclusion on Novartis Clinical Trial Results Database

25-Jun-2010

Date of Latest Update

4-Sep-2012 (1 page was posted on 5-Jun-2012)