Sponsor

Novartis

Generic Drug Name

Nilotinib

Trial Indication

Chronic myeloid leukemia (CML)

Protocol Number

CAMN107A2128

Protocol Title

An open-label, two-period, fixed-sequence study to evaluate the effects of multiple doses of nilotinib on the pharmacokinetics of midazolam in CML (chronic myeloid leukemia) patients who are resistant and/or intolerant against at least one prior therapy with a BCR-ABL tyrosine kinase inhibitor.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

25-Jun-2010 to 09-Oct-2012 (last patient last treatment/core study)
25-Jun-2010 to 04-Dec-2013 (last patient last visit/extension study)

Study Design/Methodology

This was an open-label, two-period (with or without nilotinib) fixed sequence study to evaluate the effects of multiple doses of nilotinib on the PK of midazolam in patients who are resistant and/or intolerant against at least one prior therapy with a BCR-ABL tyrosine kinase inhibitor with each patient used as his/her own control. The study included two phases: core and extension. The core study evaluated the drug-drug interaction (DDI) between nilotinib and midazolam. Patients who participated in the core study or discontinued prematurely from the core study due to safety reasons, but still required the benefit of nilotinib therapy were enrolled into the extension phase of 12 months following completion of core phase.

A single dose of 2 mg midazolam was administered alone in Period 1 on Day 1. In Period 2 Day 2 through Day 13: Nilotinib, 400 mg was administered orally bid for 12 days (12 days

dosing was proposed to attain steady-state levels for both nilotinib concentration and CYP enzymes induction). On Day 13 - a single oral dose of 2 mg midazolam was administered together with the morning dose of nilotinib under fasting condition after an overnight fast of about 10 hours.

Centers

Five centers in two countries: Germany (4 sites), one site did not enroll patients, United Kingdom (1 site)

Publication

Zhang H, Sheng J, Jinnie K et al. Single and Repeated Doses of Nilotinib Inhibit the Pharmacokinetics (PK) of CYP3A4 Substrate Midazolam. *AAPS Meeting Abstracts* 2014: T3336

Objectives:

Primary objective: to evaluate, the effects of multiple doses of nilotinib on the pharmacokinetics (PK) and metabolism of midazolam in CML patients.

Secondary objective: to evaluate, the safety and tolerability of multiple doses of nilotinib when midazolam is co-administered orally in CML patients.

Test Products, Doses, and Mode of Administration

Day 1: midazolam 2 mg per oral

Day 2 through Day 13: Nilotinib 400 mg bid per oral

Day 13: midazolam: 2 mg per oral

Statistical Methods

PK parameters AUCinf, AUClast and Cmax were analyzed as the primary PK variables. PK parameters Tmax, T1/2, CL/F, Vz/F, Lambda_z and metabolic ratio (MR) of 1-hydroxymidazolam to midazolam were analyzed as the secondary PK variables.

A statistical analysis was performed to estimate the effect of multiple doses of nilotinib on the PK of midazolam. A linear mixed effects model was fitted to the log-transformed primary PK parameters (AUClast, AUCinf and Cmax) of midazolam and 1-hydroxymidazolam. Included, in this model was treatment as a fixed factor and patients as a random factor. From this model, the two-sided 90% confidence interval (CI) for the arithmetic mean difference (midazolam with nilotinib-midazolam alone) on the log scale was calculated and the back-transformed 90% CIs for the ratio of geometric means was provided.

Lack of DDI (which denotes the absence of an effect by nilotinib on midazolam) was assumed on the midazolam PK parameters, if the 90% CI on the geometric mean ratio for all three parameters were completely contained within 0.8-1.25.

Descriptive statistics (geometric mean and CV%, mean and CV%, median, SD, minimum and maximum) were provided for all PK parameters by treatment for midazolam and 1-hydroxymidazolam. For Tmax the median values and ranges were provided.

The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. ECG, vital signs, and any other safety data) were summarized as appropriate.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Female or male ≥ 18 years of age.
- Patients, with a cytopathologically confirmed diagnosis of Ph+ or Ph- CML in AP or CP who were resistant and/or intolerant against at least one prior therapy with a BCR-ABL tyrosine kinase inhibitor.
- Patients, who were nilotinib naïve at study entry, e.g. did not receive any nilotinib treatment prior to the study.
- World health organization (WHO) Performance Status of ≤ 2.
- Patients who had the following normal or corrected laboratory values for potassium, magnesium, phosphorus and calcium within normal limits.
- Adequate end organ function as defined by:
  - alkaline phosphatase ≤ 2.5 × Upper limit normal (ULN) unless considered tumor related
  - serum bilirubin <1.5 × ULN
  - aspartate transaminase (AST) and Alanine transaminase (ALT) <2.5 × ULN
  - serum creatinine <1.5 × ULN or 24-hour creatinine clearance ≥ 50 mL/min
  - serum amylase and lipase ≤ 1.5 × ULN
- Ability to understand and willingness to sign a written informed consent.

Exclusion criteria

- Known cytopathologically confirmed central nervous system (CNS) infiltration.
- Impaired cardiac function.
- Patients with severe and/or uncontrolled concurrent medical disease that could cause unacceptable safety risks or compromise compliance with the protocol e.g. impairment of gastrointestinal (GI) function, or GI disease that might significantly alter the absorption of the study drugs, uncontrolled diabetes, active or uncontrolled infection.
- History of significant congenital or acquired bleeding disorder unrelated to cancer.
- History of acute pancreatitis within one year of study entry or past medical history of chronic pancreatitis.
- Acute or chronic uncontrolled liver, or severe renal disease considered unrelated to disease.

- Patients actively receiving therapy with the prohibited co-medications (CYP3A4 inhibitors or inducers, or CYP2C inducers) which could not be either discontinued or switched to a different medication two weeks prior to starting study drug.
- Patients who were currently receiving treatment with any medications that have the potential to prolong the QT interval and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug.
- Use of grapefruit, pomegranate, star fruit and Seville oranges seven days prior to dosing, or during the study period.
- Treatment with immunotherapy or chemotherapy within three days (six weeks for nitrosourea or mitomycin-C) prior to Day 1 or who had not recovered from side effects of such therapy.
- Treatment with imatinib within one week prior to Day 1 or who had not recovered from side effects of such therapy.
- Treatment with other investigational agents within four weeks prior to Day 1.
- Treatment with wide field radiotherapy within four weeks or limited field radiation (≥ 25% bone marrow irradiation) for palliation within two weeks prior to Day 1 or who had not recovered from side effects of such therapy.
- Patients with hypersensitivity to midazolam or related compounds.
- Major surgery within four weeks prior to Day 1 of study or who had not recovered from prior surgery.
- Patients who were: (a) pregnant, (b) breast feeding, (c) of childbearing potential without a negative pregnancy test prior to baseline and (d) male or female of childbearing potential unwilling to use contraceptive precautions throughout the study.
- Patients unwilling or unable to comply with the protocol.

Participant Flow Table

Core phase

Patient disposition-Full Analysis Set

Disposition	All Patients (N=19) n (%)
Completed the core phase	19 (100)
Continuing for extension phase	19 (100)
Reasons for end of treatment for the core phase	
Treatment duration completed as per protocol	19 (100)
Reasons for study evaluation completion for the core phase	
Follow up phase completed as per protocol	19 (100)

In the extension phase

Patient disposition-additional reporting (FAS)

Disposition	All Patients (N=19) n (%)
Discontinued the extension study	4 (21.1)
Completed the extension study	15 (78.9)
Reasons for end of treatment for the extension phase	
Adverse Events	3 (15.8)
New cancer therapy	1 (5.3)
Treatment duration completed as per protocol	15 (78.9)

Baseline Characteristics

Demographics and other baseline characteristics-Full Analysis Set

Demographic variable	All Patients (N=19)
Age at screening (years)	
N	19
Mean	45.5
SD	16.7
Median	47.0
Min	18
Max	75
Sex-n (%)	
Male	11(57.9)
Female	8(42.1)
Race-n (%)	
Caucasian	18(94.7)
Other	1(5.3)
Ethnicity-n (%)	
Other	19(100.0)
Weight at Baseline (kg)	
N	19
Mean	83.9
SD	22.2
Median	81.3
Min	54.0
Max	147.0
Height at Baseline (cm)	
N	19

Demographic variable	All Patients (N=19)
Mean	175
SD	8.36
Median	175
Min	162
Max	193
BMI (kg/m^2)	
N	19
Mean	27.4
SD	6.96
Median	25.8
Min	19.4
Max	46.4

The baseline weight (kg) and baseline height (cm) were defined as the last non-missing assessment of weight and height before study medication.
BMI (kg/m^^{2}) = weight (kg)/ (height (m)) ^2. BMI is calculated using the baseline weight and baseline height.

Summary of PK results

Primary Outcome Results

Geometric mean ratio with (90% CI) of midazolam plasma primary PK parameters (midazolam PK set)

					Treatment Comparison		
						90% CI	
PK Parameter (unit)	**Treatment**	**n***	**Adjusted Geo-mean**	**Comparison**	**Geo-mean Ratio**	**Lower**	**Upper**
AUCinf (ng*h/mL)	A	17	31.0				
	B	16	81.5	B/A	2.63	2.08	3.31
AUClast (ng*h/mL)	A	17	29.7				
	B	16	76.2	B/A	2.56	2.03	3.24
Cmax (ng/mL)	A	17	11.2				
	B	16	22.1	B/A	1.98	1.66	2.38

Treatment A: Single dose of midazolam at 2 mg on Day 1.
Treatment B: Midazolam at 2 mg with nilotinib on Day 13 following nilotinib 400 mg bid from Day 2 to 12.
A linear mixed effects model of the log-transformed PK parameters was used. Included in the model were treatment as a fixed factor and patients a random factor. Results were back transformed to get adjusted geometric mean, geometric mean ratio and 90% CI.
n*=number of patients with evaluable PK data.

Summary of primary plasma PK parameters of midazolam by treatment (midazolam PK set)

Treatment	Statistics	AUCinf (ng*h/mL)	AUClast (ng*h/mL)	Cmax (ng/mL)
A	N	17	17	17
	Mean (SD)	37.0 (22.4)	35.3 (21.0)	12.4 (5.7)
	CV% mean	60.4	59.5	46.1
	Geo-mean	31.2	29.9	11.2
	CV% geo-mean	71.4	70.5	50.5
	Median	28.7	28.3	11.0
	[Min; Max]	[5.64; 103]	[5.5; 96.8]	[3; 30]
B	N	16	16	16
	Mean (SD)	88.8 (35.3)	82.8 (32.8)	24.1 (9.07)
	CV% mean	39.8	39.7	37.6
	Geo-mean	83.0	77.5	22.7
	CV% geo-mean	38.7	37.6	37.0
	Median	77.9	71.2	21.5
	[Min; Max]	[45.7; 168]	[45.4; 152]	[13; 46]

Treatment A: Single dose of midazolam at 2 mg on Day 1.

Treatment B: Midazolam at 2 mg with nilotinib on Day 13 following nilotinib 400 mg bid from Day 2 to Day 12.

N = number of patients with evaluable PK data

CV% = coefficient of variation (%) = SD/Mean*100

CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Secondary Outcome Results

Summary of secondary plasma PK parameters of midazolam by treatment (midazolam PK set)

Treatment	Statistics	Tmax (hr)	T1/2 (hr)	Lambda_z (1/hr)	CL_F (L/hr)	Vz_F (L)
A	N	17	17	17	17	17
	Mean (SD)	N/A	6.07(3.07)	0.145 (0.093)	80.8 (75.6)	587 (376)
	CV% mean	N/A	50.5	64.0	93.6	64.1
	Geo-mean	N/A	5.44	0.127	64.1	503
	CV% geo-mean	N/A	53.3	53.2	71.4	59.8
	Median	0.50	5.70	0.122	69.6	443
	[Min; Max]	[0.25; 1.6]	[1.49; 15.6]	[0.044; 0.464]	[19.5; 355]	[189; 1700]
B	N	16	16	16	16	16
	Mean (SD)	N/A	6.93 (1.98)	0.109 (0.034)	25.6 (8.98)	249 (93.1)
	CV% mean	N/A	28.6	31.1	35.0	37.4

Treatment	Statistics	Tmax (hr)	T1/2 (hr)	Lambda_z (1/hr)	CL_F (L/hr)	Vz_F (L)
	Geo-mean	N/A	6.65	0.104	24.1	231
	CV% geo-mean	N/A	30.6	30.6	38.7	43.4
	Median	0.53	7.19	0.097	25.7	249
	[Min; Max]	[0.25; 1.5]	[3.67; 10.6]	[0.065; 0.189]	[11.9; 43.8]	[87.5; 448]

Treatment A: Single dose of midazolam at 2 mg on Day 1.
Treatment B: Midazolam at 2 mg with nilotinib on Day 13 following nilotinib 400 mg bid from Day 2 to Day 12
N = number of patients with evaluable PK data.
CV% = coefficient of variation (%) = SD/Mean*100.
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Geometric mean ratio with (90% CI) of 1-hydroxymidazolam plasma primary PK parameters (midazolam PK set)

					Treatment Comparison		
						90% CI	
PK Parameter (unit)	Treatment	n*	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
AUCinf (ng*h/mL)	A	16**	7.31				
	B	16	8.94	B/A	1.22	1.06	1.41
AUClast (ng*h/mL)	A	17	6.71				
	B	16	8.14	B/A	1.21	1.06	1.39
Cmax (ng/mL)	A	17	2.9				
	B	16	2.6	B/A	0.89	0.70	1.12

Treatment A: Single dose of midazolam at 2 mg on Day 1.
Treatment B: Midazolam at 2 mg with nilotinib on Day 13 following nilotinib 400 mg bid from Day 2 to Day 12.
A linear mixed effects model of the log-transformed PK parameters was used. Included in the model were treatment as a fixed factor and patients a random factor. Results were back transformed to get adjusted geometric mean, geometric mean ratio and 90% CI.
n*= number of patients with evaluable PK data.
**One patient 0902-00003 was excluded due to AUC %extrapolated >20.

Summary of plasma PK parameters of 1-hydroxymidazolam by treatment (midazolam PK set)

Treatment	Statistics	AUCinf (ng*h/mL)	AUClast (ng*h/mL)	Cmax (ng/mL)
A	N	16	17	17
	Mean (SD)	16.0 (35.9)	13.9 (30.5)	3.5 (2.6)
	CV% mean	225	220	73
	Geo-mean	7.64	6.97	3.0
	CV% geo-mean	120	114	64
	Median	6.52	5.77	3.0

Treatment	Statistics	AUCinf (ng*h/mL)	AUClast (ng*h/mL)	Cmax (ng/mL)
	[Min; Max]	[1.93; 150]	[1.72; 132]	[1; 12]
B	N	16	16	16
	Mean (SD)	8.37 (3.77)	7.55 (3.21)	2.8 (1.3)
	CV% mean	45.0	42.5	49
	Geo-mean	7.61	6.92	2.5
	CV% geo-mean	47.7	45.9	52
	Median	7.62	6.70	2.5
	[Min; Max]	[3.53; 17.2]	[3.33; 13.9]	[1.0; 6.0]

Treatment A: Single dose of midazolam at 2 mg on Day 1.
Treatment B: Midazolam at 2 mg with nilotinib on Day 13 following nilotinib 400 mg bid from Day 2 to Day 12
N = number of patients with evaluable PK data.
CV% = coefficient of variation (%) = SD/Mean*100.
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Summary of Safety

Adverse events, regardless of study drug relationship, by primary system organ class and treatment- initial (core phase) reporting (Safety set)

Primary System Organ Class Preferred Term (PT)	Day 1 (N=19) n (%)	Day 2 to the end of core phase) (N=19) n (%)	28 days following core phase* (N=0) n (%)	All patients (N=19) n (%)
Any primary system organ class	3 (15.79)	19 (100.0)	0	19 (100.0)
Eye Disorders	0	1 (5.26)	0	1 (5.26)
Gastrointestinal disorders	0	5 (26.32)	0	5 (26.32)
General disorders and administration site conditions	0	3 (15.79)	0	3 (15.79)
Metabolism and nutrition disorders	1 (5.26)	4 (21.05)	0	5 (26.32)
Musculoskeletal and connective tissue disorders	0	9 (47.37)	0	9 (47.37)
Nervous system disorders	2 (10.53)	9 (47.37)	0	9 (47.37)
Psychiatric disorders	0	3 (15.79)	0	3 (15.79)
Renal and urinary disorders	0	1 (5.26)	0	1 (5.26)
Reproductive system and breast disorders	0	1 (5.26)	0	1 (5.26)
Skin and subcutaneous tissue disorders	0	10 (52.63)	0	10 (52.63)

*The next day after the last study drug dosing until the 28 days after the last study drug dosing in the core phase for patients who discontinued during core phase. No patient discontinued the core phase and all patients entered the extension phase.

Adverse events, regardless of study drug relationship, by preferred term and period - initial (core phase) reporting (Safety set)

	Day 1 (N=19) n (%)	Day 2 to the end of core phase (N=19) n (%)	28 days following core phase* (N=0) n (%)	All patients (N=19) n (%)
Any preferred term (PT)	3 (15.79)	19 (100.0)	0	19 (100.0)
Headache	2 (10.53)	8 (42.11)	0	8 (42.11)
Dry Skin	0	4 (21.05)	0	4 (21.05)
Pain in extremity	0	4 (21.05)	0	4 (21.05)
Pruritus	0	3 (15.79)	0	3 (15.79)
Fatigue	0	2 (10.53)	0	2 (10.53)
Hyperbilirubinaemia	0	2 (10.53)	0	2 (10.53)
Hyperuricaemia	0	2 (10.53)	0	2 (10.53)
Hypokalaemia	0	2 (10.53)	0	2 (10.53)
Myalgia	0	2 (10.53)	0	2 (10.53)
Nausea	0	2 (10.53)	0	2 (10.53)
Rash	0	2 (10.53)	0	2 (10.53)
Abdominal discomfort	0	1 (5.26)	0	1 (5.26)
Abdominal pain upper	0	1 (5.26)	0	1 (5.26)
Anorectal discomfort	0	1 (5.26)	0	1 (5.26)
Arthralgia	0	1 (5.26)	0	1 (5.26)
Blood phosphorus increased	0	1 (5.26)	0	1 (5.26)
Decreased appetite	0	1 (5.26)	0	1 (5.26)
Diabetes mellitus	0	1 (5.26)	0	1 (5.26)
Diarrhoea	0	1 (5.26)	0	1 (5.26)
Dizziness	0	1 (5.26)	0	1 (5.26)
Dysgeusia	0	1 (5.26)	0	1 (5.26)
Electrocardiogram QT prolonged	0	1 (5.26)	0	1 (5.26)
Erythema	0	1 (5.26)	0	1 (5.26)
Eye irritation	0	1 (5.26)	0	1 (5.26)
Hyperhidrosis	0	1 (5.26)	0	1 (5.26)
Hypocalcaemia	1 (5.26)	0	0	1 (5.26)
Insomnia	0	1 (5.26)	0	1 (5.26)
Muscle spasms	0	1 (5.26)	0	1 (5.26)
Neck pain	0	1 (5.26)	0	1 (5.26)
Nervousness	0	1 (5.26)	0	1 (5.26)
Night sweats	0	1 (5.26)	0	1 (5.26)
Nipple pain	0	1 (5.26)	0	1 (5.26)
Osteoarthritis	0	1 (5.26)	0	1 (5.26)
Papule	0	1 (5.26)	0	1 (5.26)

	Day 1 (N=19) n (%)	Day 2 to the end of core phase (N=19) n (%)	28 days following core phase* (N=0) n (%)	All patients (N=19) n (%)
Parosmia	0	1 (5.26)	0	1 (5.26)
Piloerection	0	1 (5.26)	0	1 (5.26)
Pollakiuria	0	1 (5.26)	0	1 (5.26)
Poor dental condition	0	1 (5.26)	0	1 (5.26)
Skin burning sensation	0	1 (5.26)	0	1 (5.26)
Sleep disorder	0	1 (5.26)	0	1 (5.26)
Somnolence	0	1 (5.26)	0	1 (5.26)
Spinal pain	0	1 (5.26)	0	1 (5.26)
Transaminases increased	0	1 (5.26)	0	1 (5.26)
Vision blurred	0	1 (5.26)	0	1 (5.26)

*The next day after the last study drug dosing until the 28 days, after the last study drug dosing in the core phase for patients who discontinued during core phase.
PTs are sorted by descending order of frequencies, as reported in the "All patients" column.
A patient with multiple occurrences of an AE in one period is counted only once in the AE category for that period.
The next day after the last study drug dosing until the 28 days after the last study drug dosing in the core phase.

AEs, regardless of study drug relationship, by primary system organ class, preferred term-additional (extension phase) reporting (Safety set)

Primary system organ class	All patients N=19 n (%)
Any primary system organ class	13 (68.4)
Cardiac disorders	3 (15.8)
Endocrine disorders	1 (5.3)
Eye disorders	1 (5.3)
Gastrointestinal disorders	2 (10.5)
General disorders and administration site conditions	4 (21.1)
Hepatobiliary disorders	1 (5.3)
Immune system disorders	1 (5.3)
Infections and infestations	4 (21.1)
Injury, poisoning and procedural complications	1 (5.3)
Investigations	3 (15.8)
Metabolism and nutrition disorders	3 (15.8)
Musculoskeletal and connective tissue disorders	2 (10.5)
Nervous system disorders	1 (5.3)
Psychiatric disorders	2 (10.5)

Primary system organ class	All patients
	N=19 n (%)
Respiratory, thoracic and mediastinal disorders	3 (15.8)
Skin and subcutaneous tissue disorders	3 (15.8)
Vascular disorders	3 (15.8)

Most Frequently Reported AEs Overall by Preferred Term n (≥ 10%) -additional (extension phase) reporting (Safety set)

Preferred term	All patients
	N=19
	n (%)
Any preferred term	13 (68.4)
General physical health deterioration	3 (15.8)
Acute myocardial infarction	2 (10.5)
Constipation	2 (10.5)
Impaired healing	2 (10.5)
Nasopharyngitis	2 (10.5)
Sleep disorder	2 (10.5)
Cough	2 (10.5)
Dry skin	2 (10.5)
Pruritus	2 (10.5)

Serious Adverse Events and Deaths

There were no deaths in the entire study including core and extension phase.

Core phase

One patient reported a grade 4 serious adverse event (worsening of diabetes) which lasted for 10 days. Three patients experienced adverse events (AEs) requiring dose adjustments or interruptions in Period 2. Two patients (10.53%) reported skin rash as an AE which was an AE of special interest. One patient had a skin exanthema and the other patient had a skin rash. Both the events were suspected to be drug related and of grade 1 severity.

Extension phase

Serious adverse events, regardless of study drug relationship, by primary system organ class, preferred term- additional (extension phase) reporting (Safety set)

Primary system organ class	All patients
Preferred term	**N=19**
	n (%)
Any primary system organ class	8 (42.1)

Primary system organ class	All patients
Preferred term	**N=19**
	n (%)
Cardiac disorders	2 (10.5)
Acute myocardial infarction	2 (10.5)
Gastrointestinal disorders	1 (5.3)
Hemorrhoids	1 (5.3)
General disorders and administration site conditions	1 (5.3)
Impaired healing	1 (5.3)
Injury, poisoning and procedural complications	1 (5.3)
Fractured ischium	1 (5.3)
Investigations	2 (10.5)
Blood bilirubin increased	1 (5.3)
Blood creatine phosphokinase increased	1 (5.3)
Transaminases increased	1 (5.3)
Musculoskeletal and connective tissue disorders	1 (5.3)
Osteonecrosis	1 (5.3)
Psychiatric disorders	1 (5.3)
Depression	1 (5.3)
Vascular disorders	2 (10.5)
Peripheral artery stenosis	1 (5.3)
Peripheral vascular disorder	1 (5.3)

Conclusion:

- In chronic myeloid leukemia patients, multiple doses of nilotinib (400 mg twice daily for 12 days) increased the mean systemic exposure of oral midazolam (a sensitive substrate of CYP3A4) 2.6-fold. The results from this drug-drug interaction study conclude that nilotinib is a moderate CYP3A4 inhibitor.
- Consequently, appropriate monitoring and dose adjustment may be necessary with drugs that are mainly metabolized by CYP3A4, especially with those which also have a narrow therapeutic index when combined with nilotinib.
- Consistent with the known safety profile of nilotinib, multiple dosing of nilotinib with midazolam during the core phase was well tolerated.
- All reported adverse events were similar to the well-described safety profile of nilotinib.
- The AE results of this extension study, with nilotinib 400 mg bid treatment during the extension phase (up to 12 months), were consistent with the known safety profile of nilotinib (AMN107). The reported AEs were similar to the well-described safety profile of nilotinib.

Date of Clinical Trial Report

09-Mar-2014 (Core phase)
3-Jul-2014 (Extension phase)

Date of Initial Inclusion on Novartis Clinical Trial Results website

4-Nov-2014

Date of Latest Update

Reason for Update