Sponsor

Novartis

Generic Drug Name

Nilotinib

Therapeutic Area of Trial

Chronic myelogenous leukemia

Approved Indication

Indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant or intolerant to prior therapy that included imatinib.

Study Number

CAMN107A2117

Title

A randomized, open label, two-arm, three-period crossover bioavailability study comparing two new nilotinib tablet formulations to an established nilotinib capsule formulation in healthy volunteers.

Phase of Development

Phase I

Study Start/End Dates

25 Jul 2006 to 19 Aug 2006

Study Design/Methodology

This was a randomized, open label, two-arm, three-period crossover bioavailability study to compare two new nilotinib tablet formulations (each formulation in both 200 mg and 400 mg strengths) to the current nilotinib 200 mg capsule formulation in healthy volunteers. A total of twenty-four subjects (12 subjects per arm) were to have been enrolled into the study. Each subject received a single dose of either 200 mg (arm 1) or 400 mg (arm 2) of nilotinib on three occasions, randomized differently during the three study periods:

Oral dosing with 200 mg (1 x 200 mg) of nilotinib using the current gelatin capsule in arm 1, or oral dosing with 400 mg (2 x 200 mg) of nilotinib using the current gelatin capsule in arm 2;

Oral dosing of 200 mg (Tablet variant A) of nilotinib in arm 1, or oral dosing of 400 mg (Tablet variant A) of nilotinib in arm 2; and

Oral dosing of 200 mg (Tablet variant B) of nilotinib in arm 1, or oral dosing of 400 mg (Tablet variant B) of nilotinib in arm 2.

Subjects were randomized to one of twelve treatment sequences.

- Arm 1: Single oral dose of nilotinib 200 mg capsule (reference formulation)
- Arm 1: Single oral dose of nilotinib 200 mg tablet (Variant A)
- Arm 1: Single oral dose of nilotinib 200 mg tablet (Variant B)
- Arm 2: Single oral dose of nilotinib 400 mg (2 X 200 mg capsules; reference formulation)
- Arm 2: Single oral dose of nilotinib 400 mg tablet (Variant A) and
- Arm 2: Single oral dose of nilotinib 400 mg tablet (Variant B)

Study subjects in each treatment sequence (n=2) remained in the same assigned sequence for all periods of the study. There were six treatment sequences per treatment arm, to test all potential combinations (sequential effect).

Treatment sequence

Total study subjects (N = 24)							
Study Arm 1 (N = 12)				Study Arm 2 (N = 12)			
Treatment Sequence (n=2/seq.)*	Period 1 (Day 1)	Period 2 (Day 9)	Period 3 (Day 17)	Treatment Sequence (n=2/seq)*	Period 1 (Day 1)	Period 2 (Day 9)	Period 3 (Day 17)
1	A	B	C	7	D	E	F
2	B	C	A	8	E	F	D
3	C	A	B	9	F	D	E
4	A	C	B	10	D	F	E
5	C	B	A	11	F	E	D
6	B	A	C	12	E	D	F
* = Description in Randomization List as Treatment Group Description : A,B,C,D,E,F							

The study consisted of 5 visits to the clinic; a screening evaluation visit, three treatment periods and a study completion visit. There was a washout interval of 7 days post-dose between each treatment period. Study completion evaluations (EOS) were performed 4 days after the last dose of study drug (on day 21).

Centers

1 center in 1 country: United States (1)

Publication

Ongoing

Objectives

Primary objective(s)

To compare the bioavailability of two new nilotinib tablet formulations (each variant in both 200 mg and 400 mg strengths) to the current nilotinib 200 mg capsule formulation in healthy volunteers.

Secondary objective(s)

To evaluate the safety and tolerability of single doses of nilotinib in healthy volunteers.

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

Single dose nilotinib 200 mg and 400 mg oral tablets (both variants A and B).

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

Single dose nilotinib 200 mg hard gelatin capsules for oral administration.

Criteria for Evaluation

Primary variables

Nilotinib serum concentrations were determined by a validated liquid chromatography tandem mass spectrometry assay with a lower limit of quantification at 2.5 ng/mL. Non-compartmental method was used to derive pharmacokinetic parameters from individual serum concentration-time data.

Secondary variables

Secondary variables were safety and tolerability assessments, which are described below.

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), the monitoring of hematology, blood chemistry and urinalysis, ECG recordings and the regular monitoring of vital signs and physical condition.

Pharmacology

Evaluation of nilotinib serum concentration on days 1, 9 & 17 at pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48 and 72 hours post-dose.

Statistical Methods

Formal statistical analysis was done for AUC0-t last, AUC0-inf, Cmax and Tmax of nilotinib by treatment arm (200 mg or 400 mg nilotinib). A linear mixed effects model has been fitted to the log-transformed PK parameters. Included in the model are treatment, period and sequence as fixed factors and subjects nested within sequence as a random factor. For the bioavailability analysis the tablet formulation variants are the tests and the capsule formulation is the reference. The two-sided 90% confidence intervals for the arithmetic mean of the difference (test – reference on the log-scale been calculated and the back-transformed 90% confidence intervals for the geometric mean of the ratio is provided.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Healthy adult male (18 - 55 yrs) or sterile or post menopausal female subjects:

   Male subjects as determined by absence of clinically significant deviation from normal in medical history, physical examination, vital signs, ECG and clinical laboratory determinations, and/or:

   Female subjects who were sterile or post-menopausal as defined by any of the following: subjects less than 55 years of age and amenorrheic for at least 24 months; subjects under 55 years of age and follicle-stimulating hormone (FSH) values within post-menopausal range (was to have been confirmed by a plasma 17ß-estradiol concentration of <20 pg/mL and a plasma FSH level of >40 IU/L); prior documented bilateral oophorectomy and not receiving hormonal replacement therapy and showed no clinically significant deviation from normal in medical history, physical examination, ECGs and clinical laboratory determinations

   Screening and baseline vital signs (after 3 minutes resting and measured in supine position) within the range of: Systolic blood pressure: 90 - 160 mm Hg, Diastolic blood pressure: 50 - 90 mm Hg, Pulse rate: 50 - 90 bpm

2. Body weight between =50 kg and <100 kg, with a body mass index (BMI) >18 but <33
3. Laboratory parameters values (blood electrolytes, including potassium, magnesium, and calcium) within the normal range

Exclusion criteria

1. Smokers (use of tobacco or nicotine products in the previous 30 days). Urine nicotine levels were measured during screening and baseline in all subjects. Smokers were defined as any subject who reported cigarette use during the preceding 3 months or had a urine nicotine greater or equal to 500 ng/mL
2. A past medical history of clinically significant ECG abnormalities or a family history of long QT-interval syndrome.
3. Abnormal ECG defined as:
   - PR >220 msec, QRS complex >110 msec, QTcF >430 msec
   - Any cardiac conduction abnormality
   - Any morphologic abnormality
   - Any ST/T wave abnormalities
   - Any atrial or ventricular arrhythmias
4. History of fainting spells.
5. History of myocardial infarction, angina pectoris, atherosclerosis or other clinically significant heart disease.
6. Other concurrent severe and/or uncontrolled medical conditions.

7. Administration of CYP3A4/5 enzyme inducing or inhibiting drugs within 4 weeks prior to study initiation.
8. Use of any prescription drug within 2 weeks or over-the-counter (OTC) medication within 72 hours prior to dosing. Ibuprofen was acceptable, but was to have been documented in the Concomitant medications/significant non-drug therapies case report form (CRF). No other exceptions were allowed
9. Consumption of grapefruit, grapefruit juice, star fruit, star fruit juice, or caffeinated beverages within 72 hours of dosing.
10. Participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulation.
11. History of immunodeficiency, including a positive human immunodeficiency virus (HIV) infection (ELISA and Western Blot) test result.
12. A positive hepatitis B surface antigen (HBsAg) or Hepatitis C test result.
13. Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing.
14. Significant illness within the two weeks prior to dosing.
15. History of recent or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary lung disease, treated or not treated).
16. History of clinically significant drug allergy; history of atopic allergy (asthma, urticaria, eczematous dermatitis).
17. Any surgical or medical condition which may have significantly altered the absorption, distribution, metabolism or excretion of any drug. Evidence of the following:
18. History or presence of chronic liver injury or liver or renal disease indicated by an abnormal liver function profile such as abnormal SGOT (AST), SGPT (ALT), GGT, alkaline phosphatase, or serum bilirubin or by an abnormal serum creatinine.
19. History of urinary obstruction or difficulty in voiding.
20. History of pancreatic injury or pancreatitis; indications of impaired pancreatic function/injury as indicated by abnormal lipase or amylase.
21. History of inflammatory bowel syndrome, gastritis, ulcers, gastrointestinal or rectal bleeding.
22. History of major gastrointestinal tract surgery such as gastrectomy, gastroenterestomy, or bowel resection.
23. Known ongoing alcohol and or/drug abuse within 12 months prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or baseline evaluations.

Number of Subjects

Thirty seven subjects were screened; eleven of these were screen failures. Screen failures were mainly due to unacceptable medical histories and existing medical conditions. A total of

twenty-six healthy subject volunteers (14 subjects in Arm 1 and 12 subjects Arm 2) were enrolled into the study and twenty two subjects completed the study.

Subject disposition by arm and treatment

Disposition/Reason	Arm 1 A N=14 n (%)	Arm 1 B N=12 n (%)	Arm 1 C N=11 n (%)	All Subjects in arm 1 N=14 n (%)	Arm 2 D N=12 n (%)	Arm 2 E N=12 n (%)	Arm 2 F N=11 n (%)	All Subjects in arm 2 N=12 n (%)
Enrolled	14 (100.0)	12 (100.0)	11 (100.0)	14 (100.0)	12 (100.0)	12 (100.0)	11 (100.0)	12 (100.0)
Completed	12 (85.7)	11 (91.7)	11 (100.0)	11 (78.6)	12 (100.0)	11 (91.7)	11 (100.0)	11 (91.7)
Discontinued	2(14.3)	1(8.3)		3(21.4)		1(8.3)		1(8.3)
Protocol violation	1(7.1)	1(8.3)		2(14.3)		1(8.3)		1(8.3)
Subject withdrew consent	1(7.1)			1(7.1)				

Treatment: A = nilotinib 200 mg tablet variant A, B = nilotinib 200 mg tablet variant B, C = nilotinib 200 mg capsule,

D = nilotinib 400 mg tablet variant A, E = nilotinib 400 mg tablet variant B, F = nilotinib 2x200 mg capsule.

Demographic and Background Characteristics

The majority of the subjects were black and apart from the fact that all subjects recruited into Arm 1 were males, there were no obvious differences in the demographic characteristics of the subjects in each of the treatment arms. No obvious differences were apparent between the medical histories of the subjects in each of the treatment arms which would be considered likely to influence the outcome of the investigation or the interpretation of the results.

Demographic summary by treatment group (safety population)

Demographic	All Subjects Arm 1	All Subjects Arm 2
Variable	N= 14	N= 12
Age (years) Mean ± SD Median Min - Max	 27.4 ± 8.59 24.5 18 - 44	 31.7 ± 7.41 31 21 - 46
Sex Male Female	14 (100.0%)	9 (75.0%) 3 (25.0%)
Race Caucasian Black	 4 (28.6%) 10 (71.4%)	 4 (33.3%) 8 (66.7%)

Weight (kg) Mean ± SD Median Min -Max	 78.6 ± 15.518 77.77 57.3 -99.5	 81.65 ± 16.471 85.45 50 - 98.2
Height (cm) Mean ± SD Median Min -Max	 179.2 ± 7.14 178 170 - 194	 176.1 ± 8.05 178 162 - 187

Primary Objective Result(s)

Pharmacokinetics results:

There is a large inter-subject variability in the disposition of nilotinib in 13 healthy subjects in the current study. However, variant 200 mg tablet formulations (A and B) appear to have less variability in AUC than the reference capsules. Dose proportionality was not found between 200 and 400 mg doses. The 200 mg Variant A or B formulation or 400 mg Variant A formulation were similar in Cmax and AUC to the reference capsules suggesting that using Variant A/B in 200 mg or Variant A in 400 mg tablets to establish bioequivalency (BE) in a subsequent study may be possible. However, it is not likely that 400 mg variant tablet B could be established as bioequivalent to the reference capsule based on this pilot study. A washout period of greater than 7 days is recommended for nilotinib 400 mg doses in future crossover design to avoid a possible carryover effect.

Summary PK variables in mean (SD) of nilotinib following an oral doses of 200 mg (ABC) or 400 mg (DEF) in fasted healthy volunteers

	200 mg			400 mg		
	A (variant A) N=12 or 13	B (variant B) N=10 or 11	C (1 x ref) N=11	D (variant A) N=9 or 12	E (variant B) N=9 or 12	F (2x ref) N=7 or 11
C_{max} (ng/mL)	439 (125)	388 (112)	430 (212)	491 (196)	740 (484)	568 (361)
¥T_{max} (hr)	4 (2-10)	4 (1-6)	4 (2-5)	4 (2-8)	4 (1-5)	4 (2-5)
AUC_{0-24} (ng*hr/mL)	5101	5099	5220	6331	6775	5935
	(1264)	(1609)	(2138)	(3113)	(2682)	(2653)
$AUC_{0-tlast}$ (ng*hr/mL)	6846	7394	3563	10097	10781	8866
	(2083)	(2689)	(4299)	(5937)	(4768)	(4374)
T_{last} (hr)	62.8	68.7	65.5	69.0	72	67.6
	(12.2)	(10.9)	(11.2)	(10.4)	(0)	(9.7)
$T_{1/2}$ (hr)	13.1	13.4	13.3	13	14.6	14.7
	(7.8)	(3.7)	(5.3)	(8.5)	(5.9)	(6.7)
AUC_{0-inf} (ng*hr/mL)	7492	8210	7589	8713	9910	8909
	(1940)	(2298)	(3840)	(3851)	(3759)	(5081)
CV% of AUC_{0-inf}	26%	28%	51%	44%	38%	57%

¥ Median (range)

Treatments: A = nilotinib 200 mg tablet variant A, B = nilotinib 200 mg tablet variant B, C = nilotinib

200 mg capsule,

D = nilotinib 400 mg tablet variant A, E = nilotinib 400 mg tablet variant B, and F = nilotinib 2 x 200

mg capsule.

- N = Number of subjects with reported PK parameters the lower subject number refers to $AUC_{0\text{-inf}}$.

Ratio of geometric mean with (90% confidence interval) for PK parameters comparing between formulations

PK variable	Comparison of interest	Adjusted Geo-mean*		Geo-mean ratio*	
Arm 1				Estimate	90% CI
Cmax (ng/mL)	A:C	428.2	388.4	1.10	0.93, 1.31
Cmax (ng/mL)	B:C	363.7	388.4	0.94	0.78, 1.12
AUC (0-24) (ng*h/mL)	A:C	4997.1	4647.1	1.08	0.89, 1.31
AUC (0-24) (ng*h/mL)	B:C	4590.2	4647.1	0.99	0.81, 1.21
AUC(0-inf) (ng*h/mL)	A:C	7274.0	6412.9	1.13	0.92, 1.40
AUC(0-inf) (ng*h/mL)	B:C	7041.1	6412.9	1.10	0.88, 1.37
Tmax (h)	A:C	4.0	4.0	0.00	0.00, 1.00
Tmax (h)	B:C	4.0	4.0	0.00	-1.00, 0.00
Arm 2					
Cmax (ng/mL)	D:F	455.8	453.8	1.00	0.81, 1.25
Cmax (ng/mL)	E:F	617.3	453.8	1.36	1.10, 1.69
AUC (0-24) (ng*h/mL)	D:F	5709.3	5206.1	1.10	0.92, 1.30
AUC (0-24) (ng*h/mL)	E:F	6292.4	5206.1	1.21	1.02, 1.44
AUC(0-inf) (ng*h/mL)	D:F	8487.1	7552.1	1.12	0.88, 1.44
AUC(0-inf) (ng*h/mL)	E:F	9166.7	7552.1	1.21	0.96, 1.54
Tmax (h)	D:F	4.0	4.0	0.00	-1.00, 0.00
Tmax (h)	E:F	4.0	4.0	0.00	-1.00, 0.00

Treatment: A = nilotinib 200 mg tablet variant A, B = nilotinib 200 mg tablet variant B, C = nilotinib 200

mg capsule, D = nilotinib 400 mg tablet variant A, E = nilotinib 400 mg tablet variant B, F = nilotinib 2 x

200 mg capsule.

*Back-transformed from log scale; geo-mean=geometric mean

^ Medians, difference median, difference Q1 and difference Q3 for T_{max}

Secondary Objective Result(s)

Secondary objective results are safety results which are given below.

Safety Results

The study drug was generally well tolerated, no clinically significant AEs were reported and no patient was prematurely withdrawn from the study because of AEs. The AEs lack of a dose proportionality between the PK parameters for the 200 mg and 400 mg doses observed in this study. The AEs reported were mild in intensity and generally resolved spontaneously during continued treatment.

Adverse Events by System Organ Class

The AEs seen in the study were as expected for a population of healthy volunteers in a study of this duration. They were transient and did not seem to be dose-related and gave no indication of target organ toxicity.

AEs by primary system organ class, preferred term and treatment arm (safety population)

	Arm 1 N= 14 n (%)	Arm 2 N= 12 n (%)	All N= 26 n (%)
Primary system organ class			
Preferred term			
Any system organ class	4 (28.6%)	3 (25.0%)	7 (26.9%)
Nervous system disorders	1 (7.1%)	2 (16.7%)	3 (11.5%)
Headache	1 (7.1%)	2 (16.7%)	3 (1.5%)
Gastrointestinal disorders	2 (14.3%)	0 (0.0%)	2 (7.7%)
Abdominal pain upper	1 (7.1%)	0 (0.0%)	1 (3.8%)
Nausea	1 (7.1%)	0 (0.0%)	1 (3.8%)
Investigations	1 (7.1%)	1 (8.3%)	2 (7.7%)
Blood magnesium decrease	1 (7.1%)	1 (8.3%)	2 (7.7%)
Respiratory disorders	0 (0.0%)	1 (8.3%)	1 (3.8%)
Sinus congestion	0 (0.0%)	1 (8.3%)	1 (3.8%)

ECG evaluations

Detailed analysis of the influence of the study drug on ECG intervals revealed no significant effects on QT, QTcF, QTcB, QRS, PR, RR or VR intervals. In overall, at the single doses tested in this study, no tendency for consistent QTc prolongation was observed and no serious ventricular arrhythmias were reported.

Most Frequently Reported AEs

The most frequently reported AEs were mild headaches, gastrointestinal disturbances and laboratory abnormalities. None of the AEs resulted in premature discontinuation of treatment

and most AEs resolved spontaneously during continued treatment.

Serious Adverse Events and Deaths

No deaths, SAEs or other significant AEs were reported during the course of the investigation.

Other Relevant Findings

The pharmacokinetics parameters have been described under Primary Objective Result(s).

Date of Clinical Trial Report

8 March 2007

Date Inclusion on Novartis Clinical Trial Results Database

XXXXXXX

Date of Latest Update

27 Feb 2008