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ORIGINAL ARTICLE

A phase I ascending single-dose study of the safety, tolerability, and pharmacokinetics of bosutinib (SKI-606) in healthy adult subjects

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Abstract
Purpose Bosutinib (SKI-606), a dual Src/Abl tyrosine kinase inhibitor, is in clinical development for the treatment of patients with chronic myelogenous leukemia (CML). To support clinical development, we conducted a dose-escalation and food-effect evaluation of safety, tolerability, and pharmacokinetics (PK) of bosutinib in healthy adults.
Methods This was a randomized, double-blind, placebo-controlled, single-ascending dose, sequential-group study of oral bosutinib. Subjects randomly received bosutinib 200, 400, 600, and 800 mg with food; 200 and 400 mg without food; or placebo. Plasma concentrations were determined by a liquid chromatography-tandem mass spectrometry assay. Non-compartmental PK analyses were performed, and power models assessed dose linearity.
Results Of 55 enrolled subjects, 33 (81%) subjects had adverse events (AEs) after receiving bosutinib. Common AEs included diarrhea (39%), nausea (29%), and headache (22%). Bosutinib 200–600 mg with food was safe and well tolerated. Bosutinib exposures (C_{max} and AUC) were linear and dose proportional from 200 to 800 mg with food. Absorption was relatively slow; median time to C_{max} was 6 h. Apparent volume of distribution (V_z/F) was 131–214 L/kg, mean apparent clearance (CL/F) was 2.25–3.81 L/h/kg, and mean terminal elimination half-life ($t_{1/2}$) was 32–39 h. Preliminary food effect assessment showed that exposure to bosutinib increased by ~2.52-fold ($P = 0.002$) for C_{max} and ~2.28-fold ($P = 0.002$) for AUC when 200 mg bosutinib was administered with food compared with administration under fasting conditions; administration of 400 mg bosutinib with food increased AUC by ~1.5-fold ($P = 0.037$). Approximately 1% of administered dose was excreted in urine.
Conclusions Bosutinib 200–600 mg with food was safe and well tolerated. Under fed conditions, bosutinib exposures were linear and dose proportional, and C_{max} increased by ~1.5-fold. The $t_{1/2}$ supported a once-daily dosing regimen.

Keywords Bosutinib (SKI-606) · Dual Src/Abl tyrosine kinase inhibitor · Safety · Pharmacokinetics

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Introduction

Tyrosine kinases are prime targets for the development and screening of antibody-based as well as small-molecule chemotherapeutic agents. In particular, Src, one of at least nine members of the Src family of tyrosine kinases in vertebrates [1], has attracted attention as a target for anti-cancer therapeutic intervention because it has been linked to pathways that are involved in tumor growth and progression. Src kinase activity decreases intercellular adhesion and increases resistance to anoikis in human colon tumor cell lines leading to enhanced cellular motility and invasiveness [2, 3]. Src is upregulated in several types of human cancers, including breast, pancreatic, ovarian, lung, and prostate cancers [4–6], where it is thought to play an important role in the development of the disease. In addition to Src, the Abl family of non-receptor tyrosine kinases [7] has also been implicated in tumor progression [8].

In vertebrates, the Abl family of tyrosine kinases includes two homologous proteins, c-Abl and Abl-related genes (Arg), which are encoded by the *Abl1* and *Abl2* genes, respectively [7]. The oncogenic counterpart of Abl, the Bcr-Abl fusion protein, is a molecular consequence of the reciprocal translocation between chromosomes 9 and 22 to generate the Philadelphia chromosome. Chronic myelogenous leukemia (CML) is a clonal disorder characterized by the distinctive cytogenetic abnormality of the Philadelphia chromosome [9].

Bosutinib (SKI-606), a substituted 4-anilino-3-quinoline carbonitrile, is an orally administered, competitive tyrosine kinase inhibitor that selectively targets both Src and Abl tyrosine kinases [10, 11]. The reported half-maximal inhibitory concentration (IC_{50}) for bosutinib against Src kinase ranges from 1.2 to 3.8 nM, and the IC_{50} for Abl is 1.4 nM [12], with minimal inhibitory activity demonstrated against platelet-derived tyrosine kinase growth factor receptor (PDGFR) and stem cell factor receptor (c-KIT, CD117). Bosutinib has been shown to suppress migration and invasion of human breast cancer cells [12] and to demonstrate clinical activity against breast cancer [13]. Moreover, bosutinib was found to have promising clinical activity in patients with CML via Abl inhibition [10, 14, 15]. Phase II and III clinical trials with bosutinib are therefore ongoing in patients with CML.

To support the clinical pharmacology assessment of bosutinib, we conducted an ascending single-dose study of the safety, tolerability, and pharmacokinetics (PK) of bosutinib, including a preliminary assessment of the effect of food on systemic bosutinib exposures, in healthy adult subjects.

Methods

Subjects

Healthy men and women aged 18–50 years were eligible to enroll in this study if they met the following inclusion criteria: non-childbearing potential; body mass index in the range of 18.0–30.0 kg/m^2; body weight $\geq$50 kg; non-smokers or smokers of <10 cigarettes per day who abstained from smoking during the inpatient stay. Sexually active men had to agree to the use of a medically acceptable form of contraception during the study and for 12 weeks after administration of the last dose. The major exclusion criteria included any significant cardiovascular, hepatic, renal, or hematologic diseases.

This study (ClinicalTrials.gov Identifier: NCT00406406) was conducted from November 2006 to August 2007, in accordance with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to their enrollment in the study. The study protocol and informed consent forms were reviewed and approved by an independent ethics committee.

Study design and dose administration

This was a randomized, double-blind, inpatient, placebo-controlled, ascending single-dose, sequential, parallel group study of oral bosutinib in healthy subjects and comprised the following two study groups (seven bosutinib dose cohorts in total): (1) a fasted group with three dose cohorts (bosutinib 200, 400, and 400 mg expanded dose); and (2) a fed group with four dose cohorts (bosutinib 200, 400, 600, and 800 mg). The fasted subjects were originally to receive bosutinib doses of 200, 400, 600, 800, 1,000, and 1,200 mg. However, 8 of 12 subjects who received bosutinib 400 mg experienced grade 2 adverse events (AEs), including postural dizziness ($n = 5$), diarrhea ($n = 2$), increased heart rate ($n = 2$), and orthostatic hypotension ($n = 1$). Therefore, bosutinib doses >400 mg were administered under fed conditions only. The fasted subjects fasted overnight for $\geq$10 h before administration of bosutinib or placebo. The fed subjects were given a standard US Food and Drug Administration (FDA)—recommended high-fat breakfast followed by administration of bosutinib or placebo. Each subject participated in only one dose cohort and received only a single dose of oral bosutinib or placebo. Bosutinib was administered at one dose level at a time, starting at the 200 mg fasted dose level. The decision to administer bosutinib at the next higher dose was based on the safety and tolerability assessments of the previous dose.

Sample collection and bioanalytical methods

Venous blood samples (5 mL each) for quantitation of bosutinib concentrations were collected into potassium EDTA-treated tubes on study day 1 within 2 h of dose administration (0 h) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, 72, and 96 h after dose administration. Samples were stored at −70°C until shipment to the analytical laboratory (Taylor Technology Inc., Princeton, NJ). Bosutinib was shown to be stable under the method of sample collection for $\geq$749 days when stored at −70°C. The analytical laboratory used a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay to measure the bosutinib concentrations in the plasma. The linear range of the assay for bosutinib was 1–500 ng/mL, and the lower limit of quantitation (LLQ) was 1 ng/mL using 0.1 mL of plasma sample.

Pharmacokinetic assessments

For both studies, the scheduled sample collection times were used in the PK analyses, and the plasma concentration data for bosutinib were analyzed for each subject using a noncompartmental method [16] with WinNonlin Enterprise application, version 4.1 (Pharsight Corporation, Mountain View, CA). The following PK parameters were determined: the peak plasma concentration (C_{max}), the time to C_{max} (t_{max}), the terminal elimination half-life ($t_{1/2}$), the area under the concentration–time curve (AUC), the apparent volume of distribution for the terminal disposition phase (V_z/F), the apparent clearance (CL/F), and the terminal-phase disposition rate constant (λ_z). C_{max} and t_{max} were determined directly from observed concentration data, and λ_z was estimated by a log-linear regression of the terminal monoexponential phase of the observed plasma concentration–time curves. The $t_{1/2}$ was calculated as $0.693/\lambda_z$. The CL/F and V_z/F were calculated as the ratio of dose to AUC and ratio of CL/F to λ_z, respectively.

Safety and tolerability assessments

Safety and tolerability evaluations were based on reported signs and symptoms, scheduled physical examinations, vital signs measurement, cardiac rhythm monitoring, digital 12-lead electrocardiograms, and clinical laboratory results. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Statistical analysis

Descriptive statistics, including the mean and percent coefficient of variation (CV%) were computed, and PK parameters (C_{max}, AUC, t_{max}, $t_{1/2}$, CL/F, and V_z/F) were compared among the fed cohorts using the following 1-factor analysis of variance (ANOVA) with dose as a fixed effect:

$$Y = \mu + \text{DOSE}$$

where Y is the PK parameter, μ is the grand mean, and DOSE is mg bosutinib administered. Analyses for all PK parameters were performed on a log scale, and the dose-dependent PK parameters (C_{max} and AUC) were dose-normalized and then log-transformed for the statistical analyses. The preliminary assessments of dose proportionality for C_{max} and AUC were conducted using power models for the fed cohorts, and a lack-of-fit test was conducted to assess the fit of the models [17]. A preliminary assessment of food effect on PK exposure parameters (C_{max} and AUC) for the bosutinib 200- and 400-mg doses separately were performed using a 1-way ANOVA model with a fixed effect for fed/fasted treatment.

Exploratory analysis: urinary excretion

Urine samples were analyzed for bosutinib concentrations from subjects who received the highest doses of bosutinib in each study group, i.e., the 400 mg cohort under fasting conditions and the 800 mg cohort with food. The samples were collected at predose and at timed intervals through 96 h following administration of bosutinib. The urine bosutinib concentrations were measured by using a non-validated LC/MS/MS assay with a linear range of 5–500 ng/mL and an LLQ of 5 mg/mL using 0.5 mL samples. The assay used a deuterium-labeled internal standard. Basically, 10 µL of extracted sample was chromatographed on an Aquasil C_{18} reverse column using a high-performance liquid chromatography gradient elution. MS/MS analysis was performed using electrospray ionization in positive ion mode, and bosutinib concentrations in the urine were determined by a weighted (1/concentration^2) least-squares linear regression method.

Results

Study population

Demographics for the 55 subjects (47 men and 8 women) who enrolled in this study are presented in Table 1. The subjects had a mean age (standard deviation [SD]) of 32.0 (10.7) years (range: 18–50 years), and the majority of the subjects ($n = 44$, 92%) were white, 2 (4%) were black or African American, and 2 (4%) were of other races. Eight subjects were assigned per cohort; in each cohort 6 subjects received bosutinib and two received placebo, except in the 800 mg cohort, where five subjects received bosutinib and two received placebo.

Pharmacokinetics

Plasma samples for PK analysis were available for 41 subjects. The PK parameters are presented in Table 2. Following administration of bosutinib 200 mg and 400 mg without food, t_{max} was attained in 3–6 h and C_{max} and AUC increased by 3.7-fold and 2.4-fold, respectively (400 mg compared with the 200 mg dose). Mean apparent CL/F and V_z/F were similar for both dose cohorts.

Following administration of bosutinib with food, t_{max} was attained in 6 h and C_{max} and AUC increased over the entire dose range of 200–800 mg. Mean CL/F and V_z/F were similar across the dose range, except at the highest dose due to the large variability. The individual and mean C_{max} and AUC versus dose for the fed cohorts are presented in Fig. 1, and the assessment of dose proportionality for C_{max} and AUC are presented in Table 3. The power model exponents

Table 1 Subject demographics at baseline

Characteristics	Dose cohorts, mg bosutinib								
	200 (fasted) $n = 6$	200 (fed) $n = 6$	400 (fasted) $n = 6$	400[a] (fasted) $n = 6$	400 (fed) $n = 6$	600 (fed) $n = 6$	800 (fed) $n = 5$	Placebo $n = 14$	Total $N = 55$
Mean age (SD), year	33.7 (10.9)	35.0 (11.4)	34.5 (13.9)	30.2 (11.3)	25.8 (11.2)	28.5 (9.4)	29.6 (13.5)	31.7 (9.4)	31.2 (10.7)
Sex, *n*									
Male	5	5	5	6	6	5	4	11	47
Female	1	1	1	0	0	1	1	3	8
Race, *n*									
Asian	1	0	0	0	0	0	0	1	2
Black or African American	0	0	0	1	0	1	0	1	3
White	5	6	4	5	6	5	5	12	48
Mean weight (SD), kg	79.1 (3.7)	76.0 (5.5)	78.5 (11.7)	82.6 (14.6)	80.1 (8.1)	76.1 (4.8)	73.7 (13.7)	78.6 (15.6)	78.2 (11.1)
Mean BMI (SD), kg/m^2	25.3 (1.4)	23.8 (1.1)	24.4 (3.0)	24.5 (3.2)	23.4 (2.6)	23.9 (2.5)	22.2 (1.4)	23.9 (2.6)	23.9 (2.4)

SD standard deviation, *BMI* body mass index

[a] Expanded 400 mg cohort

Table 2 Summary of pharmacokinetic parameters for bosutinib in healthy adult subjects

Parameter, mean (CV%)	Dose cohorts, mg bosutinib					
	200 (fasted) $n = 6$	200 (fed) $n = 6$	400[a] (fasted) $n = 12$	400 (fed) $n = 6$	600 (fed) $n = 6$	800 (fed) $n = 5$
C_{max}, ng/mL	16.9 (67)	42.5 (24)	62.1 (66)	88.0 (26)	141 (34)	216 (40)
t_{max}[b] (range), h	6.0 (3.0, 36.1)	6.0 (3.0, 8.0)	3.0 (2.1, 6.0)	6.0 (4.0, 6.0)	6.0 (6.0, 24.0)	6.0 (4.0, 8.0)
$t_{1/2}$, h	41.2 (8)	39.1 (33)	37.3 (27)	32.4 (26)	32.6 (21)	33.8 (24)
AUC, ng h/mL	474 (25)	1,082 (30)	1,150 (54)	1,768 (16)	2,960 (23)	4,003 (38)
CL/*F*, L/h/kg	5.60 (23)	2.25 (24)	5.87 (62)	2.90 (16)	2.80 (24)	3.81 (93)
V_z/F, L/kg	344 (29)	131 (46)	313 (77)	132 (17)	133 (38)	214 (121)

CV% percent coefficient of variation, C_{max} peak plasma concentration, t_{max} time to peak plasma concentration, $t_{1/2}$ terminal phase elimination half-life, *AUC* area under the concentration–time curve, *CL/F* apparent oral dose clearance, V_Z/F apparent volume of distribution

[a] 400 mg cohort ($n = 6$) + expanded 400 mg cohort ($n = 6$)

[b] t_{max} reported as the median, [range: minimum, maximum]

for C_{max} and AUC were 1.10 and 0.942, respectively, and the corresponding confidence intervals were 0.80–1.41 and 0.67–1.18, respectively. The lack-of-fit tests for the power functions were not statistically significant ($P > 0.05$). This analysis suggested that the relationships between C_{max} and dose and between AUC and dose under fed conditions were linear and dose proportional.

Effect of food on bosutinib PK

Following administration of bosutinib 200 mg with food, bosutinib exposures (C_{max} and AUC) increased by ~2-fold ($P = 0.002$ for both) compared with the fasted cohort (Table 2). For the 400 mg cohort, food increased C_{max} and AUC by ~1.4-fold and ~1.5-fold, respectively ($P = 0.172$ and 0.037, respectively). This preliminary analysis suggested that there was a significant food effect at the 200 mg dose level and at the 400 mg dose level (Fig. 2); food did not have an effect on C_{max} at the 400 mg dose, but there was a significant increase in AUC.

Safety and tolerability

All 55 (100%) subjects who enrolled in the study were included in the safety evaluations (Table 4). The incidence of AEs was reported for 41 (75%) subjects. The most common category of AEs was gastrointestinal (GI) disorder, and the frequency and severity of GI AEs appeared to

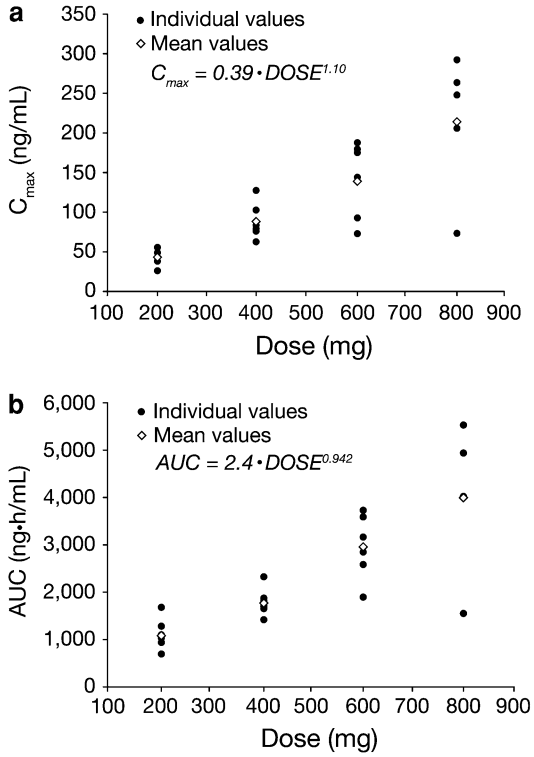

Fig. 1 Individual and mean bosutinib exposures versus dose following ascending single doses of oral bosutinib with food in healthy adult subjects. **a** C_{max} versus dose and **b** AUC versus dose. The power models used to assess dose linearity are included in each *plot*. C_{max} *peak* plasma concentration, *AUC* area under the concentration–time *curve*

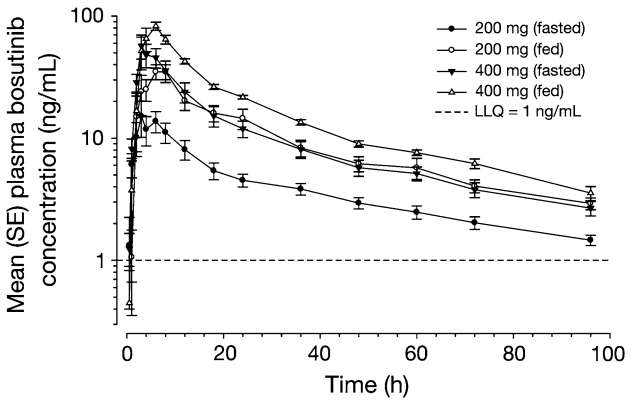

Fig. 2 Mean (SE) plasma bosutinib concentration versus time profiles following administration of oral bosutinib in healthy adult subjects under fasted and fed conditions. The LLQ is represented by the *broken line*. *SE* standard error, *LLQ* lower limit of quantification

be dose related. All AEs were mild (grade 1; 24 [44%] subjects) or moderate (grade 2; 17 [31%] subjects) in severity and were resolved by the end of the subject's participation in the study. No serious AEs that resulted in death, life-threatening conditions, hospitalization, or persistent or significant disability were reported during the study. The tolerability of bosutinib was improved at the 600 mg dose level with food; under fasting conditions bosutinib 400 mg was reasonably well tolerated (8 [67%] subjects with moderate AEs) whereas under fed conditions bosutinib 600 mg was well tolerated (1 [17%] subjects with moderate AEs). Diarrhea was reported by a majority of subjects who received bosutinib 400 mg in a fasted state (5 [83%] subjects); however, the incidence of this AE was decreased when bosutinib was administered with food (2 [33%] subjects and 1 [17%] subject at the 400 mg and 600 mg dose levels, respectively).

Exploratory analysis: urinary excretion

Urine samples from subjects who received the highest doses of bosutinib (400 mg fasted; 800 mg with food) were assayed for bosutinib concentrations. Preliminary data indicate that the excretion of bosutinib in the urine was very low and the percent of dose excreted in urine was ~1% (CV%: 60–71%).

Discussion

Bosutinib is a dual Src/Abl tyrosine kinase inhibitor in clinical development for the treatment of patients with CML. To support the clinical and pharmacological assessment of bosutinib, we evaluated the safety, tolerability, and PK profiles, including the preliminary effects of food on bosutinib exposures, in healthy adult subjects. PK analyses confirmed that bosutinib exposures (C_{max} and AUC) were linear and dose proportional following ascending single oral doses of bosutinib ranging from 200

Table 3 Power model fitting for preliminary dose-proportionality assessment of bosutinib in healthy adult subjects under fed conditions

PK parameter	Fitted power function	95% CIs of the exponents	Lack-of-fit *P* values
C_{max}	0.39·DOSE$^{1.10}$	0.80, 1.41	0.53
AUC	2.4·DOSE$^{0.942}$	0.67, 1.18	0.55

CIs confidence intervals, C_{max} peak plasma concentration, *AUC* area under the concentration–time curve

Table 4 Adverse events occurring in >10% of subjects

Adverse events, *n* (%)	Dose cohorts, mg bosutinib								
	200 (fasted) $n = 6$	200 (fed) $n = 6$	400 (fasted) $n = 6$	400[a] (fasted) $n = 6$	400 (fed) $n = 6$	600 (fed) $n = 6$	800 (fed) $n = 5$	Placebo $n = 14$	Total $N = 55$
Any adverse event	6 (100)	1 (17)	6 (100)	6 (100)	4 (67)	4 (67)	5 (83)	8 (57)	41 (75)
Specific adverse events									
Diarrhea	2 (33)	0	3 (50)	5 (83)	2 (33)	1 (17)	3 (60)	1 (7)	17 (31)
Nausea	1 (17)	0	2 (33)	2 (33)	1 (17)	2 (33)	4 (80)	1 (7)	13 (24)
Headache	3 (50)	1 (17)	1 (17)	1 (17)	0	1 (17)	2 (40)	2 (14)	11 (20)
Postural dizziness	0	0	4 (67)	4 (67)	0	1 (17)	0	1 (17)	10 (18)
Catheter site–related reaction	0	0	1 (17)	1 (17)	1 (17)	1 (17)	0	0	6 (11)
Fatigue	1 (17)	0	0	1 (17)	0	2 (33)	2 (40)	0	6 (11)

[a] 400 mg expanded cohort

to 800 mg with food. Bosutinib absorption was relatively slow with a median t_{max} of 6 h, and the $t_{1/2}$ ranged from 33 to 39 h, thus supporting a once-daily dosing regimen. The V_z/F for bosutinib was relatively large, with values ranging from 131 to 344 L/h/kg, thus indicating a high distribution of bosutinib to tissues.

Preliminary assessment of the effect of food on systemic bosutinib exposures at the 400 mg dose level revealed that a high-fat meal increased AUC by ~1.5-fold ($P = 0.037$) compared with AUC under fasted conditions; however, the observed ~1.4-fold increase in C_{max} with food was not statistically significant ($P = 0.172$). A significant food effect (AUC and C_{max}) was observed at the 200 mg dose level. Exploratory analysis revealed that bosutinib was excreted in the urine. However, the levels were relatively low and accounted for ~1% of the total administered dose.

Bosutinib doses up to 600 mg with food were generally safe and well tolerated in healthy subjects. However, under fasting conditions, bosutinib doses were limited to 400 mg because subjects experienced multiple AEs that stopped dose escalation. This in turn limited the assessment of the effect of food to doses ≤400 mg. The lower number of subjects reporting AEs for the 600 mg dose with food compared with the 400 mg dose under fasted conditions suggests that food increased the tolerability of bosutinib.

Study results suggest that food intake both increased bosutinib exposure and improved tolerability. Bosutinib has a pH-dependent solubility profile in vitro [unpublished data], and is a biopharmaceutics classification system (BCS) class II drug [18], characterized by high permeability and low solubility; the observed food effect resulting in increased bosutinib exposure could be explained by an increase in bosutinib solubility when taken with food. Increased exposure would lead to less bosutinib remaining to be absorbed in the gut, resulting in fewer GI AEs (e.g., diarrhea) and improved tolerability. In addition, increased exposure to bosutinib did not increase the incidence of AEs in another phase I study examining the effect of ketoconazole on the PK profile of bosutinib [19]. Bosutinib is primarily metabolized by cytochrome P450 (CYP) 3A4, and ketoconazole is a potent inhibitor of CYP3A4. Coadministration of ketoconazole increased bosutinib C_{max} 5.2-fold and AUC 8.6-fold. Despite this increase in bosutinib exposure, the incidence of AEs was comparable to administration of bosutinib alone [19]. Thus, AEs experienced on bosutinib are likely the result of local rather than systemic effects.

In conclusion, this study demonstrated that bosutinib doses from 200 to 600 mg with food were safe and well tolerated in healthy subjects, and systemic bosutinib exposures were linear and dose proportional following oral administration of single doses of bosutinib from 200 to 800 mg with food. The $t_{1/2}$ of bosutinib supported a once-daily dosing regimen.

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References

1. Thomas SM, Brugge JS (1997) Cellular functions regulated by Src family kinases. Annu Rev Cell Dev Biol 13:513–609
2. Avizienyte E, Frame MC (2005) Src and FAK signaling controls adhesions fate and the epithelial-to-mesenchymal transition. Curr Opin Cell Bio 17:542–547
3. Windham TC, Parikh NU, Siwak DR, Summy JM, McConkey DJ, Kraker AJ, Gallick GE (2002) Src activation regulates anoikis in human colon tumor cell lines. Oncogene 21:7797–7807
4. Frame MC (2002) Src in cancer: deregulation and consequences for cell behaviour. Biochim Biophys Acta 1602:114–130

5. Fizazi K (2007) The roles of Src in prostate cancer. Ann Oncol 18:1765–1773
6. Homsi J, Cubitt C, Daud A (2007) The Src signaling pathway: a potential target in melanoma and other malignancies. Expert Opin Ther Targets 11:91–100
7. Pendergast AM (2002) The Abl family kinases: mechanisms of regulation and signaling. Adv Cancer Res 85:51–100
8. Srinivasan D, Plattner R (2006) Activation of Abl tyrosine kinases promotes invasion of aggressive breast cancer cells. Cancer Res 66:5648–5655
9. Hantschel O, Superti-Furga G (2004) Regulation of the c-Abl and Bcr-Abl tyrosine kinases. Nat Rev Mol Cell Biol 5:33–34
10. Golas JM, Arndt K, Etienne C, Lucas J, Nardin D, Gibbons J, Frost P, Ye F, Boschelli DH (2003) SKI-606, a 4-anilino-3-quinolinecarbonitrile dual inhibitor of Src and Abl kinases, is a potent antiproliferative agent against chronic myelogenous leukemia cells in culture and causes regression of K562 xenografts in nude mice. Cancer Res 63:375–381
11. Puttini M, Coluccia AM, Boschelli F, Cleris L, Marchesi E, Donella-Deana A, Ahmed S, Redaelli S, Piazza R, Magistroni V, Andreoni F, Scapozza L, Formelli F, Gambacorti-Passerini C (2006) In vitro and in vivo activity of SKI-606, a novel Src-Abl inhibitor, against imatinib-resistant Bcr-Abl + neoplastic cells. Cancer Res 66:11314–11322
12. Vultur A, Buettner R, Kowolik C, Liang W, Smith D, Boschelli F, Jove R (2008) SKI-606 (bosutinib), a novel Src kinase inhibitor, suppresses migration and invasion of human breast cancer cells. Mol Cancer Ther 7:1185–1194
13. Campone M, Bondarenko I, Brincat S, Epstein RJ, Munster PN, Dubois E, Martin EC, Turnbull K, Zacharchuk C (2007) Preliminary results of a phase 2 study of bosutinib (SKI-606), a dual Src/Abl kinase inhibitor, in patients with advanced breast cancer. Breast Cancer Res Treat 106: abstract 6062
14. Gambacorti-Passerini C, Pogliani EM, Baccarani M, Martinelli G, Kantarjian HM, Chandy M, Khoury HJ, Kim D, Brummendorf TH, Arkin S, Cortes J (2008) Bosutinib (SKI-606) demonstrates clinical activity and is well tolerated in patients with AP and BP CML and Ph + ALL. Blood 112: abstract 1101
15. Cortes J, Kantarjian H, Brümmendorf T, Khoury HJ, Kim D, Turkina A, Volkert A, Wang J, Arkin S, Gambacorti-Passerini C (2010) Safety and efficacy of bosutinib (SKI-606) in patients (pts) with chronic phase (CP) chronic myelogenous leukemia (CML) following resistance or intolerance to imatinib (IM). J Clin Oncol 28(Suppl 15): abstract 6502
16. Evans WE, Schentag JJ, Jusko WJ (1992) Principles of therapeutic drug monitoring, 3rd edn. Applied Therapeutics, Inc., Vancouver, WA
17. Gough K, Hutchison M, Keene ON, Byrom B, Ellis S, Lacey LF, McKellar J (1995) Assessment of dose proportionality: report from the statisticians in the pharmaceutical industry/pharmacokinetics UK joint working party. Drug Inf J 29:1039–1048
18. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (2000) Guidance for industry. Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. August 2000. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246 pdf 2000 [cited 2011 May 11]; Available from: URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf
19. Abbas RA, Hug BA, Leister C, Burns J, Sonnichsen D (2011) Effect of ketoconazole on the pharmacokinetics of oral bosutinib in healthy subjects. J Clin Pharmacol. doi:10.1177/009127001 0387427