Ascending Single-Dose Study of the Safety Profile, Tolerability, and Pharmacokinetics of Bosutinib Coadministered With Ketoconazole to Healthy Adult Subjects

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ABSTRACT

Background: Bosutinib (SKI-606) is an orally bioavailable, competitive tyrosine kinase inhibitor that selectively targets both Src and Abl tyrosine kinases. Bosutinib is metabolized primarily through the cytochrome P450 3A4 pathway. Inhibition of bosutinib metabolism by coadministration with the potent cytochrome P450 3A4 inhibitor ketoconazole could potentially increase plasma concentrations of bosutinib, allowing for the study of bosutinib tolerability at supratherapeutic concentrations in a healthy subject population.

Objective: This study assessed the safety profile, tolerability, and pharmacokinetics of different dose combinations of bosutinib coadministered with ketoconazole in healthy adults, and determined whether supratherapeutic concentrations of bosutinib can be achieved with ketoconazole.

Methods: This was a randomized, Phase I, double-blind, placebo-controlled, sequential-group study conducted in healthy adults. Single oral doses of bosutinib 100, 200, 300, 400, 500, and 600 mg or placebo were administered with ketoconazole and food on day 1; daily single oral doses of ketoconazole 400 mg were administered on days –1 and 1 through 4.

Results: Forty-eight subjects were enrolled. Their mean (SD) age was 32.0 (10.7) years (range, 18–50 years). The majority of the subjects (n = 44 [92%]) were white, 2 (4%) were black or African American, and 2 (4%) were of other races. Bosutinib was associated with acceptable tolerability at doses from 100 to 600 mg, with adverse events either mild (n = 30 [63%]) or moderate (n = 12 [25%]) in severity; no subject discontinued treatment due to adverse events, and no serious events were reported. Mean (SD) values for bosutinib 100 to 600 mg ranged from 58.4 (13.3) to 426 (100) ng/mL for C_{max} and 2980 (802) to 23,000 (4020) ng · h/mL for $AUC_{0-\infty}$; mean AUC_{0-24} and AUC_{0-last} ranged from 876 (234) to 7080 (1640) ng · h/mL and from 2740 (854) to 22,200 (3630) ng · h/mL, respectively. C_{max} and AUC were linear and dose proportional. Mean C_{max} at 600 mg was 2.1-fold higher than the steady-state C_{max} previously observed for patients with chronic myelogenous leukemia who received bosutinib 500 mg once daily with food.

Conclusions: Single doses of bosutinib up to 600 mg coadministered with multiple doses of ketoconazole were acceptably well tolerated in this small, selected group of healthy male volunteers. In addition, supratherapeutic exposure was achieved within this range for bosutinib when coadministered with ketoconazole. ClinicalTrials.gov identifier: NCT00777530. (*Clin Ther*. 2012;34:2011–2019)

Key words: bosutinib, ketoconazole, pharmacokinetics, tyrosine kinase inhibitor.

INTRODUCTION

The investigational drug bosutinib (SKI-606) is a substituted 4-anilino-3-quinoline carbonitrile and an orally bioavailable, competitive tyrosine kinase inhibitor that selectively targets both Src and Abl tyrosine kinases.[1–3] Src, 1 of at least 9 members of the Src-family of tyrosine kinases in vertebrates,[1] is upregulated in several types of human cancers, including breast, pancreatic, ovarian, lung, and prostate, where it is believed to play an important role in progression of these diseases.[4–7] The Bcr-Abl fusion, which is the oncogenic counterpart of the nonreceptor tyrosine kinase

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Abl, occurs as a molecular consequence of the reciprocal translocation between chromosomes 9 and 22 to generate the Philadelphia chromosome.[8] Chronic myelogenous leukemia (CML) is a clonal disorder characterized by the distinctive cytogenetic abnormality of the Philadelphia chromosome. Bosutinib has shown antitumor activity in a Philadelphia chromosome–positive CML xenograft model[1] and is currently under clinical development for the treatment of patients with CML.[9–13]

The cytochrome P450 (CYP) metabolic pathway,[14] in particular the CYP3A4 enzyme, is primarily responsible for the metabolism of bosutinib (unpublished preclinical data [Richat Abbas, Pfizer, Inc]). The antifungal agent ketoconazole is a potent CYP3A4 inhibitor used for evaluating potential drug–drug interactions in vitro and in vivo.[15] A dose-escalation study in healthy subjects reported acceptable tolerability for bosutinib 100 to 600 mg administered with food, with bosutinib dose limited to 400 mg when administered without food due to multiple adverse events (AEs); the most common AEs in this study population were related to the gastrointestinal system, predominantly diarrhea.[16] In this same study, the observed mean C_{max} and $AUC_{0-\infty}$ for the maximum dose (600 mg) were 141 ng/mL and 2960 ng · h/mL, respectively. In a single-dose study of oral bosutinib 100 mg coadministered with or without ketoconazole 400 mg in healthy adult subjects, ketoconazole increased bosutinib exposures, C_{max} and AUC, by ~5-fold and 9-fold, respectively,[17] thus indicating that bosutinib is susceptible to drug–drug interactions with potent CYP3A4 inhibitors such as ketoconazole. Moreover, the tolerability profiles for both study groups (bosutinib with and without ketoconazole) were similar, suggesting that the gastrointestinal AEs associated with bosutinib were due to local effects rather than systemic ones. These observations suggest that supratherapeutic bosutinib concentrations of acceptable tolerability are achievable in healthy subjects.

Coadministration of ketoconazole allowed supratherapeutic concentrations to be achieved with neratinib, another small-molecule inhibitor that is metabolized by the CYP3A4 pathway.[18] These boosted exposures allowed for the conduct of subsequent clinical studies in healthy subjects to more completely evaluate the effects of the drug, such as those on cardiac repolarization. In the current study, the goal was to achieve supratherapeutic concentrations in a similar manner for bosutinib. The goal of the current study was to assess the safety profile, tolerability, and pharmacokinetics (PK) of ascending single oral doses of bosutinib coadministered with multiple doses of ketoconazole in healthy adults, and determine whether supratherapeutic concentrations of bosutinib can be achieved with ketoconazole.

SUBJECTS AND METHODS

Subjects

Healthy men and women aged 18 to 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 to 30.0 kg/m^2; body weight ≥50 kg; and nonsmokers 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 the following: a family history of QT prolongation, syncope, seizure, or unexplained cardiac-related death; a history of drug abuse within 1 year of study day 1; any surgical or medical conditions that might have interfered with the absorption, distribution, metabolism, or excretion of the drug; any significant cardiovascular, hepatic, or gastrointestinal disease; and an automated ECG-corrected QT (QTc) interval reading at screening >450 msec.

This study was conducted from April 2008 to August 2008 in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice and the ethical principles that have their origins in the Declaration of Helsinki.[19] The study protocol was approved by an institutional review board, and written informed consent was obtained from all subjects before any study-specific screening procedures or enrollment in this study.

Study Design and Dose Administration

This was a randomized, Phase I, double-blind, sponsor-unblinded, placebo-controlled, inpatient, sequential-group study conducted at a single study center in the Netherlands (Kendle International BV, Clinical Pharmacology Unit, the Netherlands). Day 1 of the treatment period was established as the day that subjects received the dose of bosutinib. Single oral doses of bosutinib 100, 200, 300, 400, 500, and 600 mg (supplied as 100-mg capsules) or placebo were administered concomitantly with ketoconazole on study day 1 at ~8:00 AM and no later than 5 minutes after the comple-