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PHARMACOKINETICS AND DISPOSITION

Effect of aprepitant, a moderate CYP3A4 inhibitor, on bosutinib exposure in healthy subjects

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Abstract
Purpose Bosutinib is an oral, dual Src and Abl tyrosine kinase inhibitor (TKI) approved for the treatment of Philadelphia chromosome—positive chronic myeloid leukemia resistant or intolerant to prior TKI therapy. Bosutinib is primarily metabolized by cytochrome P450 (CYP) 3A4, suggesting drug interaction potential with other CYP3A4 modulators. This open-label, randomized, 2-sequence, 2-period crossover study assessed the effect of single-dose aprepitant, a moderate CYP3A4 inhibitor, on the single-dose pharmacokinetic profile of oral bosutinib 500 mg.
Methods Nineteen healthy, fed adults received bosutinib (100 mg × 5) alone or coadministered with aprepitant (125 mg × 1) in each treatment period (with a ≥14-day washout); serial blood samples were analyzed. Safety was evaluated.
Results Following coadministration of aprepitant with bosutinib, the area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf}) and maximum plasma concentration (C_{max}) were higher than in bosutinib alone (AUC_{inf}, 4719 and 2268 ng•h/mL; C_{max}, 146.0 and 94.94 ng/mL). For bosutinib with aprepitant versus bosutinib alone, mean terminal elimination half-life was similar (25.99 vs 27.79 h), time to C_{max} was longer (6.02 vs 4.15 h), and apparent oral clearance (CL/F) was decreased (105.9 vs 220.4 L/h). The ratio of adjusted geometric means of AUC_{inf} and C_{max} for bosutinib with aprepitant relative to bosutinib alone were 199 % (90 % confidence interval, 167–237 %) and 153 % (127–184 %), respectively. Both treatments were well tolerated.
Conclusion In healthy volunteers, administering a single dose of aprepitant increased the AUC and C_{max} following a single dose of bosutinib by 99 and 53 %, respectively. These results are consistent with a moderate CYP3A4 inhibitor effect of aprepitant on bosutinib (Trial Registration: ClinicalTrials.gov NCT02058277).

Keywords Aprepitant · Bosutinib · Cytochrome P450 3A4 · Drug-drug interactions · Pharmacokinetics · Tyrosine kinase inhibitor

Introduction

Bosutinib is an oral active, dual Src and Abl tyrosine kinase inhibitor (TKI) that has demonstrated efficacy in a single-arm phase I/II trial as a second-line treatment for patients with Philadelphia chromosome–positive (Ph+), chronic phase (CP), chronic myeloid leukemia (CML) resistant or intolerant to imatinib [1, 2], and as third-/fourth-line treatment in patients with CP CML or advanced leukemias after failure of imatinib and dasatinib and/or nilotinib therapy [3, 4]. The recommended dose of bosutinib is 500 mg once daily with food, with dose escalation to 600 mg daily considered for some patients with suboptimal response and no grade ≥3 toxicities [5].

The pharmacokinetic (PK) profile of bosutinib after oral administration has been well characterized. Following administration of bosutinib with food in healthy volunteers, the median time to maximum concentration (t_{max}) was 6 h; mean

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clearance (CL/F) was 197 L/h and the mean terminal phase elimination half-life ($t_{1/2}$) was 33.8 h [6]. In addition, administration of bosutinib with food results in a ~2-fold increase in exposure and in improved tolerability [6]. A pooled population PK analysis indicated that bosutinib PK is described by a linear 2-compartment model with first-order absorption and an absorption lag time [7]. A high degree of PK variability was also evident in this model (percent coefficient of variance ranged from 63 to 66 % for AUC; 58 to 62 % for C_{max}). This was, in part, attributed to the fact that bosutinib is primarily metabolized by cytochrome P450 (CYP) 3A4 [7, 8] and that CYP3A4 is differentially expressed across different patient subpopulations [9, 10].

Drug-drug interactions are particularly important in clinical practice because an association may potentially alter drug activity, efficacy, and/or possibly exacerbate or cause unexpected adverse events (AEs) [11]. The centrality of CYP3A4 in the metabolism of bosutinib raises the possibility that other drugs that interact with CYP3A4 may affect bosutinib PK. Such a drug-drug interaction could result in an overdosage of bosutinib and in subsequently higher rates of AEs. Coadministration of bosutinib with the strong CYP3A4 inhibitor, ketoconazole, has been shown to increase C_{max} and AUC 5.2-fold and 8.6-fold, respectively [12]; coadministration with the strong CYP3A4 inducer, rifampin, has been shown to decrease C_{max} and AUC by 7-fold and approximately 13-fold, respectively [13].

Aprepitant is a selective, high-affinity P/neurokinin 1 receptor antagonist used to prevent chemotherapy-induced nausea and vomiting that is also primarily metabolized by CYP3A4, and is a dose-dependent inhibitor and weak inducer of this isozyme [14–16]. Aprepitant undergoes extensive metabolism and its PK are non-linear across the clinical dose range [16]. Following a single oral dose of aprepitant 125 mg on day 1 and single doses of aprepitant 80 mg on days 2 and 3, $AUC_{0–24h}$ was ~19.6 and 21.2 μg/h/mL on days 1 and 3, respectively [16]. C_{max} values of 1.6 and 1.4 μ/mL were reached ~4 h postdose [16]. The apparent $t_{1/2}$ of aprepitant ranged from approximately 9 to 13 h and its mean absolute bioavailability was 60 to 65 % over the 80 to 125 mg dose range [16]. Therefore, the present open-label, randomized, crossover study evaluated the effect of a single oral dose of aprepitant, which acts predominantly as a moderate CYP3A4 inhibitor in this setting, on the PK and safety profile of bosutinib in healthy subjects.

Methods

Study design

In this phase I, single-site, open-label, randomized, single-dose, 1-cohort, 2-sequence, 2-period crossover study (ClinicalTrials.gov ID: NCT02058277), healthy volunteers were randomized to one of two treatment sequences: oral bosutinib (100 mg × 5) alone in period 1 followed by bosutinib (100 mg × 5) in combination with single-dose aprepitant (125 mg × 1) in period 2, or bosutinib (100 mg × 5) in combination with single-dose aprepitant (125 mg × 1) in period 1 followed by oral bosutinib (100 mg × 5) alone in period 2. Treatment periods were separated by a minimum 14-day washout period. After fasting overnight for ≥10 h, subjects received study medication ≤5 min after completion of a standard breakfast that was consumed within 20 min on day 1 of each treatment period. No food was allowed ≤4 h postdose. Water could be consumed without restriction, except 1 h before and 1 h after dosing.

The protocol was approved by an independent ethics committee and was conducted in compliance with the ethical principles from the Declaration of Helsinki and with all International Conference on Harmonisation Good Clinical Practice guidelines. All subjects signed an informed consent document prior to enrollment.

Subjects

Eligible subjects were healthy men or women (aged 18–55 years) weighing >45 kg with a body mass index (BMI) of 17.5 to 30.5 kg/m^2. Exclusion criteria included the following: clinically relevant abnormalities identified by medical history and full physical examination performed at screening; any laboratory abnormality that could increase the risk associated with study participation or could interfere with the interpretation of study results; any condition potentially affecting drug absorption; blood pressure ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic); QTc duration ≥450 msec; positive urine illicit drug screen; consumption of alcoholic beverages or use of tobacco or nicotine-containing products ≤24 h before first dose; investigational drug therapy ≤30 days (or 5 half-lives) before first dose; use of prescription or nonprescription drugs or dietary supplements ≤7 days before first dose; history of sensitivity to heparin or heparin-induced thrombocytopenia.

Sampling and analysis methods

Blood samples (3 mL) were collected in potassium ethylenediamine tetraacetic acid (K_3-EDTA)-treated tubes to determine bosutinib PK on 2 h predose and at 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, 72, and 96 h postdose. Blood samples were immediately stored on ice pending centrifugation at approximately 1700×*g* for about 10 min at 4 °C. The resultant K_3-EDTA plasma samples were stored in screw capped polypropylene tubes at approximately –80 °C within 1 h of collection and were analyzed for bosutinib concentrations by inVentiv Health Clinical Lab, Inc. (East Princeton, NJ) using a validated high performance liquid chromatography-tandem mass spectrometry method. Calibration standard responses

were linear over the range of 1 to 200 ng/mL using a (L/concentration^2) linear least squares regression. The lower limit of quantification for bosutinib was 1 ng/mL (further details are provided in Supplementary Materials). The PK of aprepitant was not determined.

Assessments

Bosutinib PK parameters were calculated for each subject and treatment from a standard noncompartmental analysis of plasma concentration-time data using internally validated electronic noncompartmental analysis software (further details are provided in the online-only Supplementary Material).

Safety and tolerability was assessed from clinically significant signs and symptoms, laboratory tests (hematology, chemistry, urinalysis, and others), physical examinations, vital signs, and 12-lead electrocardiograms. Adverse events (AEs) were monitored during the study period and serious AEs (SAEs) of any causality were monitored from the time of informed consent to 28 days after study drug administration. Drug-induced liver injury was assessed based on elevations of aspartate or alanine transaminase levels concurrent with elevations in total bilirubin.

Statistical analyses

A sample size of approximately 14 subjects was required to provide 90 % confidence intervals (CI) for treatment-differences in $\log_e$ AUC_{inf} and C_{max} of ±0.1752 and ±0.1535, respectively, with 80 % coverage probability. This calculation was based on corresponding estimates of within subject standard deviations (SD) of 0.2266 and 0.2779, respectively [8].

All PK parameters were summarized descriptively by treatment. Estimates of the adjusted mean differences between bosutinib plus aprepitant (test) and bosutinib alone (reference) in AUC_{inf} (or AUC_{last}) and C_{max} for all subjects with corresponding 90 % CIs were obtained using a mixed effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. The adjusted mean differences and 90 % CIs for the differences were exponentiated to provide point estimates of the ratio of adjusted geometric means (test/reference) and 90 % CIs for the ratios.

Results

Subjects

A total of 20 subjects were randomized. Most of the subjects were male (12/20), white (14/20) with a mean age of 35.4 years (range 19 to 55 years), and mean weight and BMI of 76.5 kg (range 56.3 to 96.8 kg) and 25.9 kg/m^2 (range 20.6 to 30.4 kg/m^2; Table 1), respectively. Among the 20 subjects randomized, 1 subject from each treatment group discontinued the study (both withdrew consent between the treatment phase and washout period due to family emergencies). All 20 randomized subjects were analyzed for PK and safety; although 4 subjects receiving bosutinib alone were excluded from the PK analysis due to vomiting within a time period corresponding to 2 × median t_{max} and within 6 h after drug administration.

Pharmacokinetics

Higher median plasma bosutinib concentration-time profiles were observed following administration of bosutinib plus aprepitant than with bosutinib alone (Fig. 1). Mean values of C_{max} and AUC_{inf} were ~1.5- and 2.1-fold higher, respectively, following bosutinib plus aprepitant administration than with bosutinib alone (Table 2). Among other PK parameters assessed for bosutinib in combination with aprepitant alone and bosutinib alone, respectively, $t_{1/2}$ was similar, t_{max} was ~1.5-fold longer, and CL/F was ~2.1-fold lower.

Statistical comparisons of bosutinib PK parameters are summarized in Table 3. The adjusted geometric means of AUC_{inf} and C_{max} were ~2.0-fold and ~1.5-fold higher, respectively, following bosutinib with aprepitant relative to bosutinib alone. Moderate to high intersubject variabilities in bosutinib geometric mean AUC_{inf} and C_{max} was observed with percent coefficient of variation ranging from 31 to 51 % and 55 to 59 %, respectively Fig. 2.

Safety assessment

A total of 25 treatment-emergent AEs (TEAEs) were reported by 13 (68 %) subjects receiving bosutinib alone and a total of 22 TEAEs were reported by 12 (63 %) subjects receiving bosutinib plus aprepitant. Twenty-three of the 25 TEAEs reported by subjects receiving bosutinib only and all 22 TEAEs received by bosutinib plus aprepitant were considered treatment related by the investigator. All TEAEs were of mild or moderate severity. There were no SAEs, deaths, discontinuations, dose reductions, or dose delays due to AEs in the study.

The most frequent TEAEs were gastrointestinal events (Table 4); primarily diarrhea, which was reported by 10 subjects receiving bosutinib only (mild severity, n = 2; moderate severity, n = 8) and 11 subjects receiving bosutinib plus aprepitant (mild severity, n = 1; moderate severity, n = 10). Nausea was reported by 7 subjects receiving bosutinib alone (mild severity, n = 1; moderate severity, n = 6) and 5 subjects receiving bosutinib plus aprepitant (mild severity, n = 2; moderate severity, n = 3). Vomiting was reported by 4 subjects receiving bosutinib only and by no subjects receiving

Table 1 Demographics and baseline characteristics

Characteristic	Male (n = 12)	Female (n = 8)	Total (n = 20)
Mean (SD) age, y	37.0 (13.1)	32.9 (10.0)	35.4 (11.8)
Range	19–55	21–49	19–55
Race, *n*			
White	8	6	14
Black	4	1	5
Other	0	1	1
Mean (SD) weight, kg	78.4 (9.7)	73.6 (12.3)	76.5 (10.8)
Range	61.4–93.1	56.3–96.8	56.3–96.8
Mean (SD) body mass index, kg/m^{2a}	25.8 (3.3)	26.1 (2.7)	25.9 (3.0)
Range	20.6–29.9	20.7–30.4	20.6–30.4
Mean (SD) height (cm)	174.4 (3.9)	167.4 (6.6)	171.6 (6.1)
Range	167.6–180.3	158.7–178.5	158.7–180.3

SD standard deviation

[a] Body mass index was defined as weight/(height in meters)^2

bosutinib plus aprepitant. Two headache TEAEs among subjects receiving bosutinib alone were considered not treatment related by the investigator.

Discussion

The results of this study show that coadministration of bosutinib with aprepitant resulted in an increase in AUC_{inf} and C_{max} by approximately 100 and 50 %, respectively. In keeping with this increase in exposure, there was an approximately 50 % decrease in apparent CL/F and apparent volume of distribution (V_z/F) of bosutinib. There were no apparent differences in $t_{1/2}$, but t_{max} was more prolonged in the presence of aprepitant than with bosutinib alone (6.02 and 4.15 h, respectively). Values of PK parameters observed here were similar to those reported previously for bosutinib 500 mg in healthy subjects [13]. Together, these results are consistent with a moderate CYP3A4 inhibitor effect of aprepitant on bosutinib metabolism. The similar decrease in CL/F and V_z/F in the presence of aprepitant indicates that aprepitant changed the bioavailability of bosutinib through the reduction of first-pass metabolism, but did not change the clearance and volume of distribution of bosutinib.

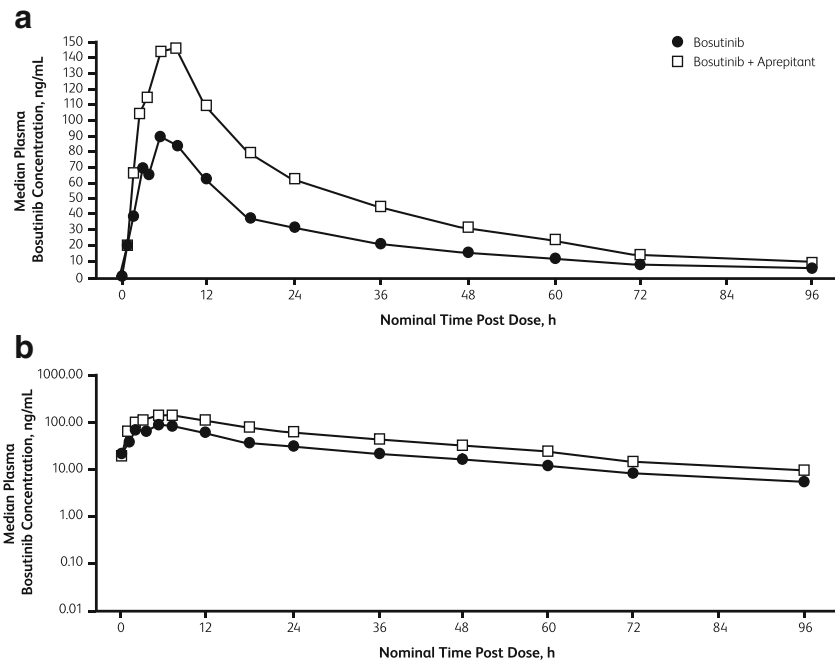

Fig. 1 Median plasma bosutinib concentration versus time profiles following single oral doses. A linear plot (**a**) and a semi-logarithmic plot (**b**) are shown in the panels. The PK data derived from 4 subjects receiving bosutinib treatment alone were excluded from this analysis because these subjects vomited within 6 h (2 × t_{max}) postdose

Table 2 Summary of plasma bosutinib pharmacokinetic parameter values following single oral doses

Parameter[a]	Bosutinib alone[b]	Bosutinib + aprepitant
N, *n*	15, 12	19, 17
AUC_{inf}, ng•h/mL	2268 (51)	4719 (31)
AUC_{last}, ng•h/mL	2193 (48)	4097 (47)
C_{max}, ng/mL	94.93 (55)	146.00 (59)
t_{max}, h	4.15 (2.00–8.17)	6.02 (1.90–11.9)
$t_{½}$, h	27.79 ± 5.22	25.99 ± 3.84
CL/F, L/h	220.4 (51)	105.9 (31)
V_z/F, L	8695 (62)	3935 (34)

AUC_{inf} area under the plasma concentration-time profile from time 0 extrapolated to infinite time, *AUC_{last}* area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), *C_{max}* maximum observed concentration, *CL/F* apparent oral clearance, *CV* coefficient of variation, *N* number of subjects in the treatment group contributing to the mean, *n* number of subjects where $t_{½}$, AUC_{inf}, CL/F and Vz/F were determined, *SD* standard deviation, *$t_{½}$* terminal elimination half-life, *t_{max}* time to reach peak or maximum concentration following drug administration, *V_z/F* apparent volume of distribution

[a] Geometric mean (geometric %CV) for all except: median (range) for t_{max}; arithmetic mean (±SD) for $t_{½}$

[b] The PK data of 4 subjects receiving bosutinib treatment alone were excluded as these subjects vomited within 6 h ($2 \times t_{max}$) postdose

When used for the prevention of chemotherapy-induced nausea or vomiting, the recommended dose of aprepitant is 125 mg on day 1 and 80 mg on days 2 and 3 of treatment [16]. However, since the $AUC_{0–24h}$ and C_{max} are similar after a single dose of 125 mg on day 1 and 80 mg once daily on days 2 and 3 (all 3 daily doses comprise the approved dose) [16], the highest dose and exposures of aprepitant were used in this study to maximize the inhibitory effect of aprepitant. Bosutinib can be administered to healthy volunteers only as a single dose because of potential safety concerns. Thus, bosutinib exposures in this study were lower than steady-state levels, likely resulting in a stronger or similar CYP3A4 inhibition by aprepitant, and a more conservative assessment of CYP3A4 inhibition than studies in which bosutinib exposure is at steady-state.

A physiologically-based pharmacokinetic (PBPK) model of bosutinib was developed in a previous study based on in vitro absorption, distribution, metabolism, and excretion (ADME) data to assess potential effects of moderate CYP3A4 inhibitors on systemic exposures of bosutinib following multiple oral dose administration [17]. Bosutinib exposures predicted by the PBPK model were in reasonable agreement with increases and decreases in bosutinib exposure resulting from coadministration with ketoconazole or rifampin, respectively, observed in phase 1 clinical trials [12, 13]. Simulation results also predicted that bosutinib exposures increased significantly upon coadministration of moderate CYP3A4 inhibitors, such as fluconazole and erythromycin. A similar approach has been used to assess potential drug-drug interactions involving a variety of CYP3A4 inhibitors and drug substrates [18]. Examples include the effects of 4-{(R)-(3-Aminophenyl)[4-(4-fluorobenzyl)-piperazin-1-yl]methyl}-*N*,*N*-diethylbenzamide (AZD2327), lanicemine (AZD6765), and telithromycin on midazolam exposure [19–21]; fluconazole on ruxolitinib exposure [22]; and ketoconazole and rifampin on alisporivir exposure [23]. However, with clinical interaction data for both strong and moderate CYP3A4 inhibitors and a strong CYP3A4 inducer, the PBPK model of bosutinib would be more robust and refined in a future analysis in which the present aprepitant-bosutinib PK interaction data were added. This could provide a powerful tool for quantitatively predicting bosutinib exposures resulting from PK interactions with other CYP3A4 inhibitors or inducers.

Overall, coadministration of bosutinib with aprepitant was safe and well tolerated in these healthy subjects; the incidence of TEAEs in subjects receiving bosutinib plus aprepitant was similar to that in subjects receiving bosutinib alone (68 and 63 %, respectively). Mild to moderately severe gastrointestinal TEAEs were the most commonly reported events in both treatment groups (68 and

Table 3 Statistical summary of bosutinib pharmacokinetic parameters

Parameter	Bosutinib alone[a] (reference)	Bosutinib + aprepitant (test)	Ratio (test/reference) of adjusted means (90 % CI)[b]
AUC_{inf}, ng•h/mL	2253	4488	199.2 (167.1–237.4)
AUC_{last}, ng•h/mL	2217	4128	186.2 (162.4–213.5)
C_{max}, ng/mL	96.1	146.9	152.9 (126.8–184.3)

AUC_{inf} area under the plasma concentration-time profile from time 0 extrapolated to infinite time, *AUC_{last}* area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), *CI* confidence interval, *C_{max}* maximum observed concentration

[a] The PK data of 4 subjects receiving bosutinib treatment alone were excluded as these subjects vomited within 6 h ($2 \times t_{max}$) postdose

[b] The ratios and 90 % CIs are expressed as percentages

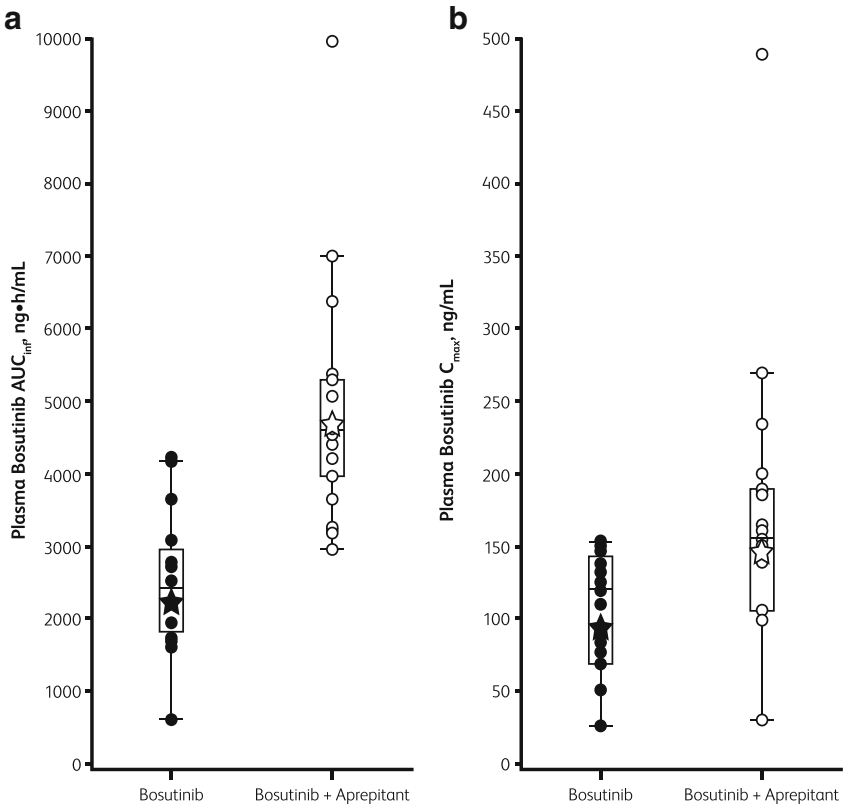

Fig. 2 Individual and geometric mean plasma bosutinib AUC_{inf} (**a**) and C_{max} (**b**). *Star* represents the geometric mean and *circles* represent individual values. Box plot provides median and 25/75 % quartiles with whiskers to the last point within 1.5× interquartile range. The PK data derived from 4 subjects receiving bosutinib treatment alone were excluded from this analysis because these subjects vomited within 6 h ($2 \times t_{max}$) postdose. AUC_{inf} area under the plasma concentration-time profile from zero time extrapolated to infinite time, C_{max} maximum observed concentration

63 %), with diarrhea being most frequent (53 and 58 %), which is consistent with bosutinib toxicity profiles reported previously in studies recruiting healthy volunteers [6, 12, 13, 24–26] or patients with Ph + CML receiving bosutinib [1, 3, 4, 27–29]. It is also notable that no vomiting events were reported among subjects receiving bosutinib plus aprepitant, compared with 4 subjects receiving bosutinib alone. Although this single-dose study was not designed to assess the antiemetic efficacy of aprepitant and the small sample sizes limit interpretation of these data, the data are consistent with the mode of action of aprepitant.

In conclusion, in healthy volunteers, administration of a single dose of aprepitant increased the AUC and C_{max} following a single dose of bosutinib by 99 and 53 %, respectively.

Table 4 Incidence of TEAEs[a]

TEAEs, all causality (treatment-related)	Bosutinib (n = 19)	Bosutinib + aprepitant (n = 19)
Gastrointestinal disorders	13 (13)	12 (12)
Abdominal pain	0	1 (1)
Diarrhea	10 (10)	11 (11)
Nausea	7 (7)	5 (5)
Vomiting	4 (4)	0
General disorders and administration site conditions	1 (1)	2 (2)
Fatigue	1 (1)	2 (2)
Nervous system disorders	3 (1)	3 (3)
Dizziness	0	1 (1)
Headache	3 (1)	2 (2)

TEAEs treatment-emergent adverse events

[a] TEAEs were monitored during the study period (Medical Dictionary for Regulatory Activities Version 17.0 coding dictionary was applied)

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The protocol was approved by an independent ethics committee and was conducted in compliance with the ethical principles from the Declaration of Helsinki and with all International Conference on Harmonisation Good Clinical Practice Guidelines. Informed consent was obtained from all individual participants included in the study.

Contributions of authors PH conceived and designed the study; PH provided the study material or patients; DSP, PH, KM analyzed and interpreted the data; PH and KM wrote the manuscript; and all authors approved the final manuscript.

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