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**PROPRIETARY DRUG NAME®/GENERIC DRUG NAME:** Bosulif® / Bosutinib

**PROTOCOL NO.**: 3160A2-201-WW (B1871014)

**PROTOCOL TITLE**: Phase 2 Study of Bosutinib (SKI-606) in Subjects With Advanced or Metastatic Breast Cancer

**Study Centers**: A total of 15 centers took part in the study and randomized subjects; 4 in the United States (US), 3 in Ukraine, 2 each in France and Poland, and 1 each in Australia, Hong Kong, Malta and the Russian Federation.

**Study Initiation and Final Completion Dates:** 26 May 2006 to 03 February 2009

**Phase of Development**: Phase 2

**Study Objectives:**

Primary Objective: To determine the rate of progression-free survival (PFS) at 16 weeks.

Secondary Objectives: To determine:

- The safety profile of 400 mg/day in this subject population.
- The objective response rate (ORR; complete response [CR] + partial response [PR]) within 1 year.
- The survival rate at 2 years (beginning from the subject's first dose of bosutinib).
- The population pharmacokinetics (PK) of bosutinib in this subject population.

**METHODS**

**Study Design:** This study was an open-label, 2-stage, multicenter, multicountry Phase 2 study of bosutinib in subjects with either relapsed or refractory advanced breast cancer or metastatic breast cancer. Subjects participated in the study until disease progression or unacceptable toxicity, with schedule of visits lasting approximately 160 weeks (4 weeks for Screening, 48 weeks on treatment, 2 weeks for final visit, and 102 weeks for long-term follow-up) and received 400 mg of bosutinib as a once-daily dose. The schedule of activities is presented in Table 1.

## Table 1. Schedule of Activities

| **Study Procedures** | **Screening**[a] | **Week Visit** | | | | | | | **Final**[b] |
|---|---|---|---|---|---|---|---|---|---|
| **Study Week** | | **1** | **2** | **4** | **8** | **12** | **16** | **q8wk** | **14 Days After Last Dose ±4 Days** |
| **Study Day (±2 Days)** | **Day 28-0** | **1** | **8** | **22** | **57** | **85** | **113** | **Q56d** | |
| Test article administration | | Continuous daily dosing | | | | | | | |
| Informed consent[c] | X | | | | | | | | |
| Inclusion/exclusion | X | | | | | | | | |
| Medical history & disease history[d] | X | | | | | | | | |
| KPS | X | X | | X | X | X | X | X | X |
| Previous cancer treatments | X | | | | | | | | |
| Tumor block request[e] | X | | | | | | | | |
| Pregnancy test[f] | X | X[g] | As clinically indicated | | | | | | X |
| Urinalysis | X | As clinically indicated | | | | | | | X |
| CBC & differential[h] | X | X[g] | X | X | X | X | X | X | X |
| Complete physical examination | X | | | | | | X | | X |
| Vital signs & focused PE[i] | | X[g] | | X | X | X | | X | |
| Tumor assessment with imaging[j] | X | | | X | X | | X | X | X[k] |
| Chemistry[l] | X | X[g] | X | X | X | X | X | X | X |
| LFTs[m] | X | | | X | X | X | X | X | X |
| Iron studies[n] | X | As clinically indicated | | | | | | | X |
| Coagulation profile (PT/PTT & INR)[o] | X | X[g] | X | X | X | X | X | X | X |
| Digital ECG[p] | X | X | X | X | X | X | X | X | X |
| MUGA or echocardiogram[q] | X | Once during Month 6 and as clinically indicated | | | | | | | |
| Ophthalmologic examination[r] | X | As clinically indicated | | | | | | | X |
| Adverse events | X | X | X | X | X | X | X | X | X[s] |
| Prior and concomitant treatments | X | X | X | X | X | X | X | X | |
| SAEs | X | Continuously throughout study | | | | | | | X[s] |
| Pain intensity[t] | X | | | X | | X | | X | |
| Health outcome assessment | X | | | X | X | X | X | X | X |

## Table 1. Schedule of Activities

CBC = complete blood count; ECG = electrocardiogram; INR = International normalized ratio; KPS = Karnofsky Performance Status; MUGA = multiple gate acquisition scan (heart); LFTs = liver function tests; PE = pulmonary embolism; PT = prothrombin time; PTT = partial thromboplastin time; q8wk = every 8 weeks; Q56d = every 56 days; SAEs = serious adverse events.

a. Screening visit within 28 days before first dose (Week 1).
b. Within 14±4 days from discontinuation of bosutinib. Subjects with evidence of stable disease or better remained on study past Week 48. Assessments were performed every 8 weeks as per protocol.
c. Signed and dated institutional review board (IRB) or independent ethics committee (IEC)-approved informed consent was obtained before any protocol-specific Screening procedures were performed.
d. Human epidermal growth factor receptor 2 (HER2)/ estrogen receptor (ER)/ partial response (PR) receptor status was collected via pathology report at the time of initial diagnosis as well as the most current receptor status (if available). In the case of HER2 status, pathology records had to indicate 3+ by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) +.
e. Most recent adequate tumor sample (fresh or previously collected) was requested on all subjects to document tumor receptor status (HER2/ER/PR status). This was sent to a central laboratory for analysis. In addition to determining receptor status, if a subject signed the optional consent, block was sent to a central laboratory for additional ribonucleic acid (RNA) and epidermal growth factor receptor (EGFR) analyses. If tissue block was not attainable, and there was no previous pathologic diagnosis, the subject's status remained "unknown," the subject was allowed to enroll. Every effort was made to collect a tumor block on all subjects.
f. Serum pregnancy test for all female subjects of childbearing potential at Screening, within a week of first dose, final visit, and whenever clinically indicated.
g. No need to repeat these tests if done within 7 days of first dose. However, they had to be repeated if not done within 7 days of first day of test article administration.
h. Hematology to include complete blood count (CBC) including a 3 or 5-part differential, platelet count, and absolute neutrophil count (ANC).
i. Vital signs included blood pressure (sitting or supine), heart rate, temperature (oral, axillary, or tympanic), and respiratory rate. Weight and body surface area (BSA) were not to be performed at each visit; however subjects were monitored throughout the study for significant weight loss.
j. Screening tumor assessments took place ≤28 days prior to dose Day 1.
k. Performed at the final visit only if no tumor assessment had been performed within the last 30 days, or to document progression detected clinically.
l. Blood chemistries included sodium, potassium, chloride, bicarbonate or carbon dioxide, calcium, phosphorus, magnesium, glucose, serum creatinine, and blood urea nitrogen (BUN or urea).
m. Liver function tests included albumin, total protein, aspartate transaminase, alanine transaminase, lactate dehydrogenase, alkaline phosphatase, total bilirubin (direct bilirubin was required if total bilirubin >1.5 × upper limit of normal [ULN]), amylase and lipase.
n. Fe, total iron-binding capacity (TIBC), Ferritin and percentage saturation were done if locally available at Screening and were repeated with any documented, unexplained, anemia and done at final visit.
o. Testing was done within 28 days of beginning treatment with bosutinib if the subject had not taken warfarin within the past 30 days. Testing was done within 3 days prior to bosutinib dosing if the subject had taken warfarin for the past 30 days.
p. Digital ECG recorders were used. Digital ECGs were performed 4-6 hours post bosutinib administration on day of clinic visit. Baseline ECG was done in triplicate.
q. If MUGA or echocardiogram was performed as part of routine care within 60 days of first dose, this result was accepted for Screening purposes. MUGA or ECHO was performed during Month 6 (Weeks 22-26).
r. If an ophthalmologic examination was performed as part of routine care within 60 days of first dose, this result was accepted for Screening purposes. Otherwise, an ophthalmologic examination was performed within 28 days prior to the first dose. A copy of the examination was maintained in the subjects' source documents.
s. Followed until resolution of drug related adverse event (AE)/serious adverse event (SAE). All AEs/SAEs were collected until 30 days after last dose of test article.
t. Pain assessment was completed twice each time pain was assessed. Once specifically for bone pain and the second time for "general" pain.

The PK/pharmacodynamics flow chart is presented in Table 2.

**Table 2. Pharmacokinetics/Pharmacodynamics Flow Chart**

| Week | 1 | | | 4 | | 8 | 12 | 16 | 24 | q8wk[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| Sampling time (hour) | 0[b] | 0 | 2 | 7 | 20-24[c] | 0[d] | 0[d] | 0[d] | 0[d] | 0[d] |
| PK plasma collection[e] | X | X | X | X | X | X | X | X | X | |
| Blood for bone biomarkers[f] | X | X | | | | | X | | X | X |
| Urine for bone biomarkers[f] | X | X | | | | | X | | X | X |

PK = pharmacokinetic; q8wk = every 8 weeks.

a. Subjects with evidence of stable disease or better could have stayed on study past Week 48. Assessments were to be performed every 8 weeks.
b. Prior to the first dose.
c. The latest possible draw was obtained after 20 hours post-dose, but before the next daily dose.
d. Prior to respective day's dose.
e. 5 mL of whole blood plasma was drawn into a tube containing potassium ethylenediaminetetraacetic acid (EDTA).
f. First sample for blood and urine for bone biomarkers was collected within 7 days prior to first dose.

Details of radiographic evaluations are provided in Table 3.

## Table 3. Radiographic Evaluation

| | Screening (Within 4 Weeks Prior to Week 1 Day 1) | Treatment Period[a] | 16 Week Evaluation[b] | Treatment Completion and Confirmation of PD |
|---|---|---|---|---|
| CT[c] or MRI of chest | Required | Required | Required | Required |
| CT[c] or MRI of abdomen, including entire liver | Required | Required for sites of disease documented at Screening, unless PD confirmed otherwise | Required | Required for sites of disease documented at Screening, unless PD confirmed with other imaging |
| Brain MRI (CT could be done if MRI was not available) | Required | Not required | Required in cases where central nervous system (CNS) disease documented at Screening, unless PD otherwise radiographically confirmed | Required for sites of disease documented at Screening, unless PD confirmed with other imaging |
| CT or MRI of any other sites of disease, as clinically indicated | Required | Required for sites of disease documented at Screening, unless PD confirmed otherwise | Required for sites of disease documented at Screening, unless PD otherwise radiographically confirmed | Required for sites of disease documented at Screening, unless PD otherwise radiographically confirmed |
| Bone Scan | Required | Required if clinically indicated | Required | Required for sites of disease documented at Screening, unless PD confirmed with other imaging |
| CT or MRI of bone scan positive regions | Required only if bone scan positive at Screening | Required for sites of disease documented at Screening, unless PD confirmed otherwise | Required for subjects with positive bone scan at Screening (ie. sites of bone involvement) | Required for sites of disease documented at Screening, unless PD confirmed with other imaging |

Tumor assessments was performed every 3 months for any subject who came off study for any reason other than PD (eg. adverse event), until the subject had documented PD, or subject began a new anticancer therapy.
CT = Computed tomography; MRI = magnetic resonance imaging; PD = progressive disease.

a. Tumor assessments occurred at Weeks 4, 8, and 16 in order to increase integrity of progression-free survival (PFS) endpoint. They occurred every 8 weeks thereafter.
b. Week 16 evaluation was not postponed due to treatment interruption.
c. Contrast was used unless contraindicated.

**Number of Subjects (Planned and Analyzed):** It was planned to enroll approximately 60 subjects. The study screened a total of 101 subjects: (14 in the US, 20 in Ukraine, 27 in France, 8 in Poland, 5 in Australia, 17 in Hong Kong, 6 in Malta and 4 in the Russian Federation). A total of 75 subjects were randomized but only 73 subjects received treatment as 2 subjects were randomly assigned in error (1 subject was found to have active brain metastases and 1 subject refused to participate for personal reasons [death of husband]). All 73 subjects who received treatment were analyzed.

**Diagnosis and Main Criteria for Inclusion:** Female subjects aged ≥18 years with Stage IIIB, IIIC or IV breast cancer not curable with available therapy, must have progressed after 1 but not more than 3 prior chemotherapy regimens, with life expectancy of at least 16 weeks and ability to swallow whole capsules were included in the study.

**Study Treatment:** Bosutinib capsules were supplied by the Sponsor as 100 mg capsules. Subjects took a dose of 400 mg bosutinib (4 x 100 mg capsules) orally once daily for 48 weeks preferably with water and food to improve tolerance and absorption.

**Efficacy and Safety Endpoints:**

Primary Efficacy Endpoint: PFS rate at 16 weeks, where progression was assessed by the investigator. The endpoint was defined as the proportion of subjects who survived progression-free to 16 weeks out of all subjects who progressed or died before 16 weeks or survived progression-free to 16 weeks.

Secondary and Exploratory Endpoints:

- ORR: ORR is the proportion of subjects attaining a CR or PR (lasting at least 4 weeks) within 1 year (48 weeks).
- Overall survival (OS) rate at 2 years was defined based on time-to-event methods. OS is the interval from the date of randomization until the date of death, censored at the last date the subject was known to be alive. A subject with no follow-up data after baseline was censored at the last baseline visit (effectively removing the subject from the analysis).
- Rate of clinical benefit (CR, PR, or stable disease [SD] lasting longer than 24 weeks).
- Safety profile (including incidence, severity and duration of adverse events [AEs; considered primary safety analysis], changes in laboratory tests including electrocardiogram [ECG], concomitant medications, and changes in Karnofsky Performance Status [KPS], physical examinations, and ophthalmologic examinations).

**Safety Evaluations:** The safety of bosutinib was evaluated through monitoring of AEs, including AEs leading to dose delay, reduction, or withdrawals; concomitant medications; physical and ophthalmologic examinations; standard 12-lead ECGs; vital signs; laboratory determinations; and changes in KPS. These were assessed at the timepoints indicated in Table 1.

**Statistical Methods:** Modified response evaluation criteria in solid tumors guidelines were used for assessment of response and progression. Efficacy analyses were based on 2 populations: the intent-to-treat (ITT) population (primary analysis), defined as all subjects randomized and having received at least 1 dose of bosutinib, and the efficacy evaluable (EE) population, defined as subjects who completed at least 14 days of treatment, had a Screening tumor assessment, and at least 1 tumor assessment after receiving test article. A subject who received at least 14 days of treatment and provided a Screening tumor assessment, who subsequently had clinical progression without a postbaseline scan or who died before the first postbaseline scan was collected, was also considered evaluable for efficacy. Eligibility violations and use of prohibited anticancer therapies excluded subjects from the EE population.

The design is a modification of the 2-stage Simon design. The null hypothesis was that the PFS rate at 16 weeks was no greater than the uninteresting rate of 20%. The alternative hypothesis was that the PFS rate at 16 weeks was no less than 40%. The overall probability of accepting the drug for further study under the null hypothesis was 0.05. The overall probability of rejecting the drug under the alternative hypothesis was 0.15.

ORR at 48 weeks in the primary cohort was calculated as a proportion and provided with an exact 95% confidence interval (CI).

OS rate at 2 years in the primary cohort was estimated via the Kaplan-Meier method, together with a 95% CI. If estimable, median OS was provided, together with a 95% CI and descriptive statistics for follow-up time.

Clinical Benefit rate in the primary and exploratory (ie, tumor type) cohorts was calculated as a proportion and provided with an exact 95% CI and descriptive statistics for follow-up time.

The probability of surviving without a bone fracture event was estimated via the Kaplan-Meier method. If estimable, the median time to bone fracture event was provided.

## RESULTS

**Subject Disposition and Demography:** A total of 101 subjects were screened. Overall, 75 subjects were randomly assigned to treatment, of whom 73 received at least 1 dose of bosutinib 400 mg. Two (2) subjects were randomly assigned in error and never received bosutinib: active brain metastases were discovered in 1 subject (exclusion criterion) and another subject refused to participate for personal reasons (her husband died the day she was scheduled to take the first dose of test article, and she opted out of study). A total of 21 subjects completed the 2-year long-term follow-up. Forty-six (46) subjects died; 2 during active study treatment and 44 during the long-term follow-up period. A summary of the subject population is provided in Table 4 and subject disposition at the conclusion of the study (completion of 2-year follow-up) is presented in Table 5.

**Table 4. Summary of Subject Population**

| | Number of Subjects in the Population Total Screening=101 |
|---|---|
| Screening failure | 26 |
| Randomization | 75 |
| Intent-to-treat | 73 |
| Safety | 73 |
| Evaluable for efficacy | 64 |

**Table 5. Subject Disposition at Conclusion of Study: Intent-to-Treat Population**

| Number of Subjects (%) | Total N=73 |
|---|---|
| Study completed | 21 (28.8) |
| Reason for discontinuation | |
| Subject request | 4 (5.5) |
| Death | 46 (63.0) |
| Discontinuation of study by Sponsor | 0 |
| Lost to follow-up | 2 (2.7) |

N = number of subjects analyzed.

Primary reasons for withdrawal from the study are presented in Table 6.

**Table 6. Primary Reasons for Subject Discontinuation From the Study**

| Conclusion Status<br>Reason[a] | Bosutinib 400 mg N=73 n (%) |
|---|---|
| Discontinued | 73 (100) |
| Adverse event[b] | 9 (12.3) |
| Death | 2 (2.7) |
| Discontinuation of study by Sponsor | 0 |
| Disease progression | 55 (75.3) |
| Failed to return | 1 (1.4) |
| Investigator request | 2 (2.7) |
| Protocol violation | 0 |
| Other | 0 |
| Subject request | 3 (4.1) |
| Symptomatic deterioration | 1 (1.4) |

N = number of subject analyzed; n = number of subject with specified criteria.

a. Total discontinued was the sum of individual reasons because they were mutually exclusive by subject.

b. Only subjects, for whom adverse event was the primary cause, were included, ie, not if it was a secondary cause.

Demographic and Baseline characteristics are summarized in Table 7.

**Table 7. Demographic and Baseline Characteristics of the Safety Population**

| Characteristic | Bosutinib 400 mg N=73 |
|---|---|
| Age (years) | |
| N* | 73 |
| Mean | 54.27 |
| Standard Deviation | 9.81 |
| Minimum | 33.00 |
| Maximum | 71.00 |
| Median | 54.00 |
| Age category, n (%) | |
| Age <65 | 58 (79) |
| Age ≥65 | 15 (21) |
| Sex, n (%) | |
| Female | 73 (100) |
| Race, n (%) | |
| Asian | 12 (16) |
| Hispanic | 1 (1) |
| Other | 1 (1) |
| White | 59 (81) |
| Weight (kg) | |
| N* | 71 |
| Mean | 68.27 |
| Standard deviation | 14.56 |
| Minimum | 39.00 |
| Maximum | 108.00 |
| Median | 66.50 |
| Missing | 2 |
| Height (cm) | |
| N* | 72 |
| Mean | 160.21 |
| Standard deviation | 6.54 |
| Minimum | 147.00 |
| Maximum | 176.00 |
| Median | 160.00 |
| Missing | 1 |
| Baseline Karnofsky Performance Status | |
| N* | 73 |
| Mean | 88.36 |
| Standard deviation | 9.43 |
| Minimum | 70.00 |
| Maximum | 100.00 |
| Median | 90.00 |
| Karnofsky scale category, n (%) | |
| 70 | 8 (11) |
| 80 | 15 (21) |
| 90 | 31 (42) |
| 100 | 19 (26) |

N* = number of subject with particular characteristic; N = number of subject analyzed; n = number of subject with specified criteria.

At Baseline, all subjects except 1 had metastatic breast cancer (Stage IV). One subject had Stage IIIC breast cancer. The median time between initial diagnosis of breast cancer and the first dose of bosutinib was 4.5 years (range <1 year to 29.5 years). Before entering this study, the median time from the first diagnosis of advanced or metastatic disease was 2 years (3 months to 17.5 years).

**Efficacy Results:**

Primary Efficacy Results:

ITT Population: The overall PFS rate at Week 16 was 39.6%. This rate was slightly higher in 2 subpopulations: hormone receptor positive and HER2 positive (Table 8).

**Table 8. Summary of Progression-Free Survival Rate at 16 Weeks in the Intent-to-Treat Population**

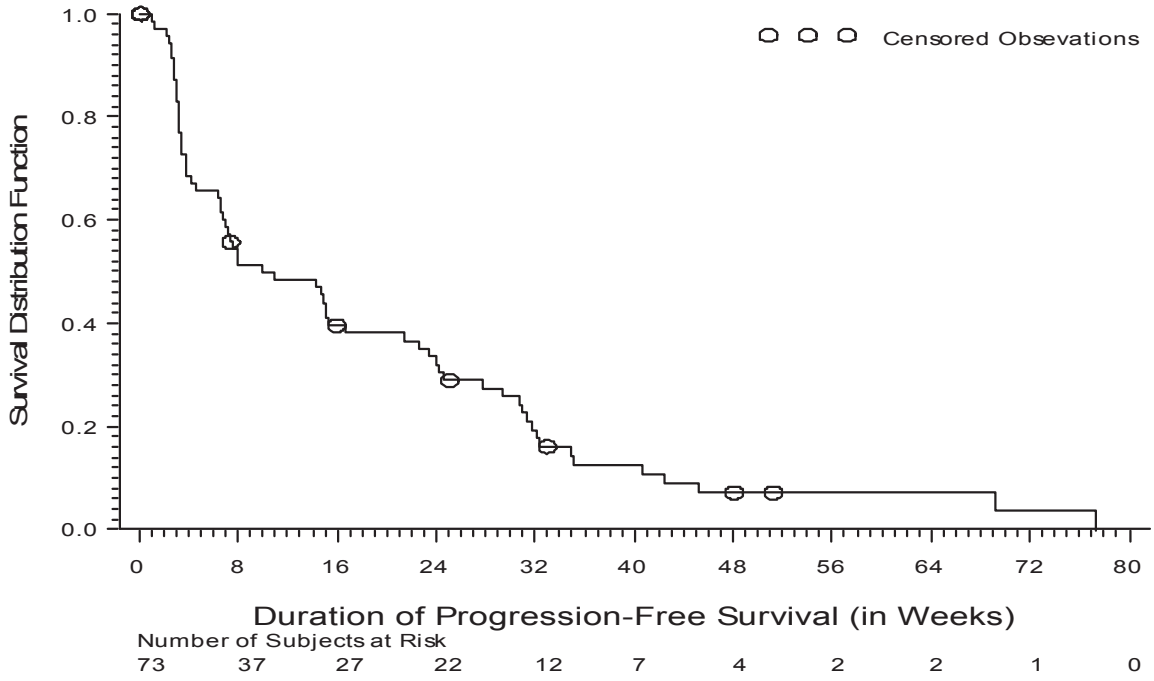
| | | | 80% CI | | 95% CI | |
|---|---|---|---|---|---|---|
| **Number of Subjects**[a] | | **Rate (%)** | **LB** | **UB** | **LB** | **UB** |
| All subjects | 73 | 39.6 | 32.0 | 47.0 | 28.1 | 50.8 |
| Hormone receptor positive | 49 | 43.1 | 33.7 | 52.0 | 28.8 | 56.5 |
| Hormone receptor positive and HER2- | 32 | 29.8 | 19.7 | 40.5 | 15.0 | 46.1 |
| HER2+ | 12 | 41.7 | 23.6 | 58.8 | 15.2 | 66.5 |
| Hormone receptor negative and HER2- | 13 | 25.0 | 11.1 | 41.8 | 6.0 | 50.5 |
| Unclassified | 6 | 60.0 | 27.9 | 81.5 | 12.6 | 88.2 |

CI = confidence interval; HER2 = human epidermal growth factor receptor 2; LB = lower bound; UB = upper bound.

a. The cohorts of clinical interest were not mutually exclusive. The total for all cohorts exceeded the total number of enrolled subjects.

PFS rates for the ITT population are illustrated in Figure 1.

**Figure 1. Kaplan-Meier Plot of Progression-Free Survival in the Intent-to-Treat Population**




The median PFS was 9.9 weeks (95% CI: 6.7 weeks, 16.7 weeks).

EE Population: PFS rates for the EE population and subpopulations based on tumor receptor status are presented at Week 16 in Table 9. The results are consistent with those in the ITT population. The median PFS was 14.7 weeks (95% CI: 7.1 weeks, 23.4 weeks).

**Table 9. Summary of Progression-Free Survival Rate at 16 Weeks in the Efficacy Evaluable Population**

| | | | 80% CI | | 95% CI | |
|---|---|---|---|---|---|---|
| **Number of Subjects[a]** | | **Rate (%)** | **LB** | **UB** | **LB** | **UB** |
| All subjects | 64 | 43.3 | 35.2 | 51.1 | 31.0 | 55.0 |
| Hormone receptor positive | 44 | 47.0 | 37.0 | 56.3 | 31.7 | 60.9 |
| Hormone receptor positive and HER2- | 29 | 32.9 | 21.9 | 44.3 | 16.6 | 50.1 |
| HER2+ | 12 | 41.7 | 23.6 | 58.8 | 15.2 | 66.5 |
| Hormone receptor negative and HER2- | 11 | 27.3 | 12.1 | 45.0 | 6.5 | 53.9 |
| Unclassified | 4 | 75.0 | 35.3 | 92.4 | 12.8 | 96.1 |

CI = Confidence Interval; HER2 = human epidermal growth factor receptor 2; LB = lower bound; UB = upper bound.

a. The cohorts of clinical interest were not mutually exclusive. The total for all cohorts exceeded the total number of enrolled subjects.

Secondary Efficacy Results:

Objective Response Rate:

Based on Investigator assessment of the response, the best overall responses to treatment in the ITT population are summarized in Table 10.

**Table 10. Summary of Best Overall Response in the Intent-to-Treat Population**

| Best Overall Response | HR+ (n=49) | HER2+ (n=12) | HR- and HER2- (n=13) | HR+ and HER2- (n=32) | Unclassified (n=6) | Total (n=73) |
|---|---|---|---|---|---|---|
| Complete response (CR) | 0 | 0 | 0 | 0 | 0 | 0 |
| Partial response (PR) | 4 (8.2) | 0 | 0 | 3 (9.4) | 0 | 4 (5.5) |
| Stable disease[a] (SD) | 17 (34.7) | 5 (41.7) | 3 (23.1) | 7 (21.9) | 3 (50.0) | 24 (32.9) |
| Stable disease ≤24 Weeks | 5 (10.2) | 2 (16.7) | 2 (15.4) | 2 (6.3) | 0 | 8 (11.0) |
| Stable disease >24 Weeks | 12 (24.5) | 3 (25.0) | 1 (7.7) | 5 (15.6) | 3 (50.0) | 16 (21.9) |
| Progressive disease (PD) | 22 (44.9) | 6 (50.0) | 9 (69.2) | 17 (53.1) | 2 (33.3) | 36 (49.3) |
| Indeterminate[b] | 6 (12.2) | 1 (8.3) | 1 (7.7) | 5 (15.6) | 1 (16.7) | 9 (12.3) |
| No post-baseline tumor assessment | 6 (12.2) | 1 (8.3) | 1 (7.7) | 4 (12.5) | 1 (16.7) | 9 (12.3) |

The cohorts of clinical interest were not mutually exclusive. The total for all cohorts exceeded the total number of enrolled subjects.
HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; SD = stable disease.
a. Must have met the SD criteria at least once after start of treatment at a minimum of 8 weeks (a window of -2 days). Twenty-four (24) weeks is from start of treatment (a window of -2 weeks).
b. Had assessment of SD or unconfirmed response prior to 8 weeks (a window of -2 days) after the start of treatment.

Four (4) subjects reported PR and 24 subjects had SD (16 had SD duration >24 weeks). The 4 responders in this trial were all confirmed hormone receptor-positive tumor types (estrogen receptor positive [ER+] and/or progesterone receptor positive [PgR+]). The subjects with hormone receptor-positive tumor types were evaluated separately for ORR: in the ITT subpopulation, ORR was 8.2%, and in the EE subpopulation, ORR was 9.1%. Among the 4 responders, 3 subjects were hormone receptor positive and HER2 negative, for an ORR of 9.4% in the ITT population and 10.3% in the EE population, whereas the fourth subject's HER2 status was unknown.

The best overall responses to treatment in the EE population are summarized in Table 11.

**Table 11. Summary of Best Overall Response in the Efficacy Evaluable Population**

| Best Overall Response | HR+ (n=44) | HER2+ (n=12) | HR- and HER2- (n=11) | HR+ and HER2- (n=29) | Unclassified (n=4) | Total (n=64) |
|---|---|---|---|---|---|---|
| Complete response (CR) | 0 | 0 | 0 | 0 | 0 | 0 |
| Partial response (PR) | 4 (9.1) | 0 | 0 | 3 (10.3) | 0 | 4 (6.3) |
| Stable disease[a] (SD) | 17 (38.6) | 5 (41.7) | 3 (27.3) | 7 (24.1) | 3 (75.0) | 24 (37.5) |
| Stable disease ≤24 Weeks | 5 (11.4) | 2 (16.7) | 2 (18.2) | 2 (6.9) | 0 | 8 (12.5) |
| Stable disease >24 Weeks | 12 (27.3) | 3 (25.0) | 1 (9.1) | 5 (17.2) | 3 (75.0) | 16 (25.0) |
| Progressive disease (PD) | 21 (47.7) | 6 (50.0) | 8 (72.7) | 17 (58.6) | 1 (25.0) | 33 (51.6) |
| Indeterminate[b] | 2 (4.5) | 1 (8.3) | 0 | 2 (6.9) | 0 | 3 (4.7) |
| No post-baseline tumor assessment | 1 (2.3) | 1 (8.3) | 0 | 1 (3.4) | 0 | 2 (3.1) |

The cohorts of clinical interest were not mutually exclusive. The total for all cohorts exceeded the total number of enrolled subjects.
HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; SD = stable disease.
a. Must have met the SD criteria at least once after start of treatment at a minimum of 8 weeks (a window of -2 days). Twenty-four (24) weeks was from the start of treatment (a window of -2 weeks).
b. Had assessment of SD or unconfirmed response prior to 8 weeks (a window of -2 days) after the start of treatment.

ORRs for the ITT population are summarized in Table 12.

**Table 12. Summary of Complete or Partial Response Rate at 48 Weeks in the Intent-to-Treat Population**

| | | | 80% Exact CI | | 95% Exact CI | |
|---|---|---|---|---|---|---|
| Number of Subjects[a] | | Rate (%) | LB | UB | LB | UB |
| All subjects | 73 | 5.5 | 2.4 | 10.7 | 1.5 | 13.4 |
| Hormone receptor positive | 49 | 8.2 | 3.6 | 15.7 | 2.3 | 19.6 |
| Hormone receptor positive and HER2- | 32 | 9.4 | 3.5 | 19.7 | 2.0 | 25.0 |
| HER2+ | 12 | 0 | 0 | 17.5 | 0 | 26.5 |
| Hormone receptor negative and HER2- | 13 | 0 | 0 | 16.2 | 0 | 24.7 |
| Unclassified | 6 | 0 | 0 | 31.9 | 0 | 45.9 |

The interesting rate was ≥40%, the uninteresting rate was ≤20%.
CI = confidence interval; HER2 = human epidermal growth factor receptor 2; LB = lower bound; UB = upper bound.
a. The cohorts of clinical interest were not mutually exclusive. The total for all cohorts exceeded the total number of enrolled subjects.

ORRs for the EE population are summarized in Table 13

**Table 13. Summary of Complete or Partial Response Rate at 48 Weeks in the Efficacy Evaluable Population**

| | | | 80% Exact CI | | 95% Exact CI | |
|---|---|---|---|---|---|---|
| **Number of Subjects**[a] | | **Rate (%)** | **LB** | **UB** | **LB** | **UB** |
| All subjects | 64 | 6.3 | 2.8 | 12.1 | 1.7 | 15.2 |
| Hormone receptor positive | 44 | 9.1 | 4.0 | 17.4 | 2.5 | 21.7 |
| Hormone receptor positive and HER2- | 29 | 10.3 | 3.9 | 21.6 | 2.2 | 27.4 |
| HER2+ | 12 | 0 | 0 | 17.5 | 0 | 26.5 |
| Hormone receptor negative and HER2- | 11 | 0 | 0 | 18.9 | 0 | 28.5 |
| Unclassified | 4 | 0 | 0 | 43.8 | 0 | 60.2 |

The interesting rate was ≥40%, the uninteresting rate was ≤20%.
CI = confidence interval; HER2 = human epidermal growth factor receptor 2; LB = lower bound; UB = upper bound
a. The cohorts of clinical interest were not mutually exclusive. The total for all cohorts exceeded the total number of enrolled subjects.

Survival:

Survival rates at 2 years for the ITT population are summarized in Table 14.

**Table 14. Summary of Overall Survival Rate at 2 Years in the Intent-to-Treat Population**

| | | | 80% CI | | 95% CI | |
|---|---|---|---|---|---|---|
| **Number of Subjects**[a] | | **Rate (%)** | **LB** | **UB** | **LB** | **UB** |
| All subjects | 73 | 26.4 | 18.4 | 35.0 | 14.7 | 39.7 |
| Hormone receptor positive | 49 | 27.2 | 17.7 | 37.5 | 13.4 | 43.0 |
| Hormone receptor positive and HER2- | 32 | 26.7 | 16.5 | 38.1 | 11.9 | 44.1 |
| HER2+ | 12 | 45.0 | 24.9 | 63.2 | 15.5 | 71.0 |
| Hormone receptor negative and HER2- | 13 | 31.2 | 14.0 | 50.0 | 7.5 | 59.1 |
| Unclassified | 6 | 16.7 | 3.2 | 39.4 | 0.8 | 51.7 |

CI = confidence interval; HER2=human epidermal growth factor receptor 2; LB = lower bound; UB = upper bound.
a. The cohorts of clinical interest were not mutually exclusive. The total for all cohorts exceeded the total number of enrolled subjects.

Survival rates at 2 years for the EE population are summarized in Table 15.

**Table 15. Summary of Overall Survival Rate at 2 Years in the Evaluable Population**

| | | | 80% CI | | 95% CI | |
|---|---|---|---|---|---|---|
| **Number of Subjects**[a] | | **Rate (%)** | **LB** | **UB** | **LB** | **UB** |
| All subjects | 64 | 29.3 | 20.5 | 38.7 | 16.3 | 43.6 |
| Hormone receptor positive | 44 | 30.3 | 19.8 | 41.5 | 14.9 | 47.3 |
| Hormone receptor positive and HER2- | 29 | 29.5 | 18.2 | 41.7 | 13.2 | 48.0 |
| HER2+ | 12 | 45.0 | 24.9 | 63.2 | 15.5 | 71.0 |
| Hormone receptor negative and HER2- | 11 | 31.2 | 14.0 | 50.0 | 7.5 | 59.1 |
| Unclassified | 4 | 25.0 | 4.6 | 53.7 | 0.9 | 66.5 |

CI = confidence interval; HER2=human epidermal growth factor receptor 2; LB = lower bound; UB = upper bound.

a. The cohorts of clinical interest were not mutually exclusive. The total for all cohorts exceeded the total number of enrolled subjects.

Clinical Benefit Rate: The clinical benefit rates for the ITT population are summarized in Table 16.

**Table 16. Summary of Clinical Benefit Rate in the Intent-to-Treat Population**

| | | | 80% Exact CI | | 95% Exact CI | |
|---|---|---|---|---|---|---|
| **Number of Subjects**[a] | | **Rate (%)** | **LB** | **UB** | **LB** | **UB** |
| All subjects | 73 | 27.4 | 20.6 | 35.2 | 17.6 | 39.1 |
| Hormone receptor positive | 49 | 32.7 | 23.7 | 42.7 | 19.9 | 47.5 |
| Hormone receptor positive and HER2- | 32 | 25.0 | 15.1 | 37.4 | 11.5 | 43.4 |
| HER2+ | 12 | 25.0 | 9.6 | 47.5 | 5.5 | 57.2 |
| Hormone receptor negative and HER2- | 13 | 7.7 | 0.8 | 26.8 | 0.2 | 36.0 |
| Unclassified | 6 | 50.0 | 20.1 | 79.9 | 11.8 | 88.2 |

CI = confidence interval; HER2=human epidermal growth factor receptor 2; LB = lower bound; UB = upper bound.

a. The cohorts of clinical interest were not mutually exclusive. The total for all cohorts exceeded the total number of enrolled subjects.

The clinical benefit rates for the EE population are summarized in Table 17.

**Table 17. Summary of Clinical Benefit Rate in the Efficacy Evaluable Population**

| | | | 80% Exact CI | | 95% Exact CI | |
|---|---|---|---|---|---|---|
| **Number of Subjects**[a] | | **Rate (%)** | **LB** | **UB** | **LB** | **UB** |
| All subjects | 64 | 31.3 | 23.6 | 39.8 | 20.2 | 44.1 |
| Hormone receptor Positive | 44 | 36.4 | 26.6 | 47.1 | 22.4 | 52.2 |
| Hormone receptor positive and HER2- | 29 | 27.6 | 16.8 | 40.9 | 12.7 | 47.2 |
| HER2+ | 12 | 25.0 | 9.6 | 47.5 | 5.5 | 57.2 |
| Hormone receptor negative and HER2- | 11 | 9.1 | 1.0 | 31.0 | 0.2 | 41.3 |
| Unclassified | 4 | 75.0 | 32.0 | 97.4 | 19.4 | 99.4 |

**Table 17. Summary of Clinical Benefit Rate in the Efficacy Evaluable Population**

| | | 80% Exact CI | | 95% Exact CI | |
|---|---|---|---|---|---|
| **Number of Subjects**[a] | **Rate (%)** | **LB** | **UB** | **LB** | **UB** |

CI = confidence interval; HER2=human epidermal growth factor receptor 2; LB = lower bound; UB = upper bound.

a. The cohorts of clinical interest were not mutually exclusive. The total for all cohorts exceeded the total number of enrolled subjects.

**Safety Results:**

Adverse Events: Overall 71 (97%) subjects reported treatment emergent AEs (TEAEs). The most frequently reported TEAEs (all causalities and treatment-related reported by ≥5% of subjects) are summarized in Table 18.

**Table 18. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related) For Events Having a Frequency Rate ≥5%**

| System Organ Class<br>Preferred Term | All Adverse Events<br>N=73<br>n (%) | Related Adverse Events<br>N=73<br>n (%) |
|---|---|---|
| Any study event | 71 (97) | 61 (84) |
| Blood and lymphatic system disorders | 7 (10) | 0 |
| Anaemia | 4 (5) | 0 |
| Gastrointestinal disorders | 61 (84) | 58 (79) |
| Abdominal pain | 9 (12) | 7 (10) |
| Abdominal pain upper | 6 (8) | 5 (7) |
| Constipation | 6 (8) | 1 (1) |
| Diarrhoea | 48 (66) | 47 (64) |
| Dyspepsia | 7 (10) | 3 (4) |
| Nausea | 40 (55) | 37 (51) |
| Vomiting | 34 (47) | 31 (42) |
| General disorders and administration site conditions | 45 (62) | 27 (37) |
| Asthenia | 14 (19) | 10 (14) |
| Fatigue | 19 (26) | 12 (16) |
| Malaise | 4 (5) | 3 (4) |
| Oedema peripheral | 8 (11) | 1 (1) |
| Pyrexia | 7 (10) | 0 |
| Investigations | 23 (32) | 15 (21) |
| Alanine aminotransferase increased | 9 (12) | 8 (11) |
| Aspartate aminotransferase increased | 9 (12) | 7 (10) |
| Weight decreased | 8 (11) | 5 (7) |
| Metabolism and nutrition disorders | 20 (27) | 14 (19) |
| Anorexia | 14 (19) | 12 (16) |
| Musculoskeletal and connective tissue disorders | 28 (38) | 6 (8) |
| Arthralgia | 9 (12) | 0 |
| Back pain | 9 (12) | 1 (1) |
| Musculoskeletal pain | 4 (5) | 0 |
| Myalgia | 5 (7) | 4 (5) |
| Nervous system disorders | 16 (22) | 5 (7) |
| Headache | 10 (14) | 3 (4) |
| Respiratory, thoracic and mediastinal disorders | 16 (22) | 2 (3) |
| Cough | 8 (11) | 2 (3) |
| Dyspnoea | 8 (11) | 0 |
| Skin and subcutaneous tissue disorders | 22 (30) | 14 (19) |
| Rash | 10 (14) | 7 (10) |

AEs and SAEs are not separated out.
Classifications of adverse events were based on the Medical Dictionary for Regulatory Activities (MedDRA).
AEs = adverse events; N = number of subject analyzed; n = number of subject with specified criteria; SAEs = serious adverse events.

Serious AEs (SAEs): Twenty-four (24, 32.9%) subjects reported SAEs (all causalities) during this study as summarized in Table 19.

## Table 19. Number (%) of Subjects Reporting Serious Adverse Events in the Safety Population

| System Organ Class[a]<br>Preferred Term | Bosutinib 400 mg<br>N=73<br>n (%) |
|---|---|
| Any adverse event | 24 (32.9) |
| Gastrointestinal disorders | 4 (5.5) |
| Diarrhoea | 2 (2.7) |
| Ileus | 1 (1.4) |
| Vomiting | 1 (1.4) |
| General disorders and administration site conditions | 7 (9.6) |
| Chest discomfort | 1 (1.4) |
| Disease progression | 2 (2.7) |
| General physical health deterioration | 1 (1.4) |
| Oedema peripheral | 2 (2.7) |
| Performance status decreased | 1 (1.4) |
| Hepatobiliary disorders | 2 (2.7) |
| Cytolytic hepatitis | 1 (1.4) |
| Hepatic failure | 1 (1.4) |
| Infections and infestations | 2 (2.7) |
| Gastroenteritis | 1 (1.4) |
| Lower respiratory tract infection | 1 (1.4) |
| Investigations | 3 (4.1) |
| Alanine aminotransferase increased | 3 (4.1) |
| Aspartate aminotransferase increased | 2 (2.7) |
| Musculoskeletal and connective tissue disorders | 3 (4.1) |
| Arthralgia | 1 (1.4) |
| Back pain | 1 (1.4) |
| Musculoskeletal pain | 1 (1.4) |
| Pathological fracture | 1 (1.4) |
| Nervous system disorders | 1 (1.4) |
| Coma | 1 (1.4) |
| Psychiatric disorders | 1 (1.4) |
| Confusional state | 1 (1.4) |
| Restlessness | 1 (1.4) |
| Reproductive system and breast disorders | 2 (2.7) |
| Breast pain | 2 (2.7) |
| Respiratory, thoracic and mediastinal disorders | 3 (4.1) |
| Dyspnoea | 2 (2.7) |
| Hydrothorax | 1 (1.4) |

Classifications of adverse events were based on the Medical Dictionary for Regulatory Activities (MedDRA).
N = number of subject analyzed; n = number of subject with specified criteria.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels because a subject may report 2 or more different adverse events within the higher-level category.

Eight (8, 11.0%) subjects reported SAEs deemed to be related to bosutinib by the Investigator. These are summarized in Table 20.

**Table 20. Number (%) of Subjects Reporting Serious Adverse Events Related to Bosutinib in the Safety Population**

| System Organ Class[a]<br>Preferred Term | Bosutinib 400 mg<br>N=73<br>n (%) |
|---|---|
| Any adverse event | 8 (11.0) |
| Gastrointestinal disorders | 2 (2.7) |
| Diarrhoea | 2 (2.7) |
| General disorders and administration site conditions | 2 (2.7) |
| Chest discomfort | 1 (1.4) |
| Oedema peripheral | 1 (1.4) |
| Hepatobiliary disorders | 1 (1.4) |
| Cytolytic hepatitis | 1 (1.4) |
| Investigations | 3 (4.1) |
| Alanine aminotransferase increased | 3 (4.1) |
| Aspartate aminotransferase increased | 2 (2.7) |

Classifications of adverse events were based on the Medical Dictionary for Regulatory Activities (MedDRA).
N = number of subject analyzed; n = number of subject with specified criteria.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels because a subject may report 2 or more different adverse events within the higher-level category.

Discontinuations: Eleven (15.1%) subjects were withdrawn from study treatment because of AEs as summarized in Table 21. This summarizes the incidence of AEs that were primary or secondary cause for withdrawal from the study.

**Table 21. Number (%) of Subjects Reporting Adverse Events That Led to Withdrawal in the Safety Population**

| System Organ Class[a]<br>Preferred Term | Bosutinib 400 mg<br>N=73<br>n (%) |
|---|---|
| Any adverse event | 11 (15.1) |
| Gastrointestinal disorders | 3 (4.1) |
| Abdominal discomfort | 1 (1.4) |
| Abdominal pain | 1 (1.4) |
| Diarrhoea | 1 (1.4) |
| Oesophageal pain | 1 (1.4) |
| General disorders and administration site conditions | 6 (8.2) |
| Asthenia | 2 (2.7) |
| Chest discomfort | 1 (1.4) |
| Fatigue | 2 (2.7) |
| General physical health deterioration | 1 (1.4) |
| Investigations | 1 (1.4) |
| Alanine aminotransferase increased | 1 (1.4) |
| Metabolism and nutrition disorders | 1 (1.4) |
| Anorexia | 1 (1.4) |
| Musculoskeletal and connective tissue disorders | 2 (2.7) |
| Arthralgia | 1 (1.4) |
| Back pain | 1 (1.4) |
| Respiratory, thoracic and mediastinal disorders | 2 (2.7) |
| Cough | 1 (1.4) |
| Hydrothorax | 1 (1.4) |

Classifications of adverse events were based on the Medical Dictionary for Regulatory Activities (MedDRA).
N = number of subject analyzed; n = number of subject with specified criteria.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels because a subject may report 2 or more different adverse events within the higher-level category.

Three-quarters of the safety population (55, 75.3%) had no dose delays for safety reasons. Eighteen (24.7%) subjects reported AEs requiring between 1 and 3 dose delays as summarised in Table 22.

**Table 22. Summary of Dose Delay Due to Adverse Events in the Safety Population**

| Number of Dose Delays | Bosutinib 400 mg<br>N=73<br>n (%) |
|---|---|
| None | 55 (75.3) |
| 1 | 13 (17.8) |
| 2 | 4 (5.5) |
| 3 | 1 (1.4) |
| At least one dose delay | 18 (24.7) |

Dose delay was defined as a temporary halt of 3 days or more in prescribed test article administration.
N = number of subject analyzed; n = number of subject with specified criteria.

Deaths: Five (5; 7%) subjects died during the study (within 30 days after the last dose of bosutinib) as summarized in Table 23.

**Table 23. Subjects Who Died Within 30 Days After the Last Dose of Bosutinib**

| Serial Number | Age | Number of Days Since Last Dose | Cause of Death |
|---|---|---|---|
| 1 | 59 | 0 | Disease progression: liver failure |
| 2 | 65 | 1 | Disease progression: circulatory and respiratory failure |
| 3 | 56 | 7 | Disease progression |
| 4 | 56 | 23 | Disease progression: cardiac arrest |
| 5 | 54 | 6 | Disease progression |

At the end of the 2-year follow-up period, 47 (64%) subjects had died. Causes of death included AEs not related to bosutinib (1 subject committed suicide) and disease progression (in 46 subjects). A summary of deaths is provided in Table 24.

**Table 24. Summary of Deaths**

| Characteristic | Bosutinib 400 mg (N=73) n (%) |
|---|---|
| Number subjects who died | |
| No | 26 (36) |
| Yes | 47 (64) |
| Number subjects who died within 30 days of last dose | |
| No | 68 (93) |
| Yes | 5 (7) |
| Reason for death | |
| Adverse event unrelated to test article | 1 (1) |
| Disease progression | 46 (63) |
| Not applicable | 26 (36) |

N = number of subject analyzed; n = number of subject with specified criteria.

Laboratory Tests: The number of subjects who had at least 1 test result that met the criterion for potential clinical importance during the active treatment period is shown in Table 25.

**Table 25 Number (%) of Subjects With Potentially Clinically Important Changes in Clinical Laboratory Evaluations During the Active Treatment Period**

| Category<br>Test<br>Criterion | Bosutinib 400 mg |
|---|---|
| Total | 23/68 (33.8) |
| Blood chemistry | 22/68 (32.4) |
| Sodium mmol/L | 2/68 (2.9) |
| Value <130 mmol/L | 2/68 (2.9) |
| Magnesium mmol/L | 6/66 (9.1) |
| Value <0.4 mmol/L | 3/66 (4.5) |
| Value >1.23 mmol/L | 3/66 (4.5) |
| Total bilirubin µmol/L | 1/52 (1.9) |
| Value >3 * ULN | 1/52 (1.9) |
| ALT mU/mL | 12/52 (23.1) |
| Value >5 * ULN | 12/52 (23.1) |
| AST mU/mL | 10/52 (19.2) |
| Value >5 * ULN | 10/52 (19.2) |
| Lipase µKat/L | 1/44 (2.3) |
| Value >2 * ULN | 1/44 (2.3) |
| Hematology | 1/68 (1.5) |
| Neutrophils 10^9/L | 1/67 (1.5) |
| Value <1 * 10^9 /L | 1/67 (1.5) |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

ECGs: Subjects who had at least 1 measurement that exceeded the ECG criteria for potential clinical importance at some time during the study are presented in Table 26.

**Table 26 Number (%) of Subjects With Potentially Clinically Important Changes in Electrocardiograms**

| Test<br>Criterion | Bosutinib 400 mg |
|---|---|
| Total | 21/64 (32.8) |
| Heart rate beats/minute | 2/64 (3.1) |
| Increase ≥15 bpm and value ≥120 bpm | 2/64 (3.1) |
| QTcB Interval ms | 1/64 (1.6) |
| Change from Baseline >60 ms | 1/64 (1.6) |
| Rhythm | 12/64 (18.8) |
| Not sinus rhythm | 12/64 (18.8) |
| Overall evaluation | 12/64 (18.8) |
| Not normal | 12/64 (18.8) |

Bpm = beats per minute; QTcB = QT corrected using the Bazett formula.

Concomitant Medications: A total of 68 (93.2%) subjects received concomitant therapy during the on-therapy phase of the study. The therapeutic classes of medications received most frequently were antiemetics (21.9% plus 30.1% of propulsives), analgesics (41.1% of subjects took opioids, 32.9% took other analgesics/antipyretics), antidiarrhea agents (42.5%), antiulcer drugs (32.9%), laxatives (28.8%), and nonsteroidal anti-inflammatory drugs (27.4%).

Physical Examinations: No additional clinical findings or pathology, other than what were previously reported as AEs, resulted from these examinations.

**CONCLUSIONS:** Bosutinib (SKI-606) is a protein tyrosine kinase inhibitor and was being developed for the treatment of breast cancer. The purpose of this study was to evaluate the efficacy and safety of bosutinib monotherapy at the dose of 400 mg daily in subjects with advanced or metastatic breast cancer.

Seventy-three (73) subjects were enrolled and treated in this study and included in the safety analysis; 64 subjects were included in the efficacy analysis.

The efficacy results were as follows:

- Overall, the PFS rate at Week 16 (primary endpoint) was 39.6% in the ITT population and 43.3% in the EE population. The median PFS values were 9.9 and 14.7 weeks in the ITT and the EE populations, respectively.

- Four (4) subjects reported PR and 24 had SD: ORR was 5.5% in the ITT population versus 6.3% in the EE population.

- All 4 subjects with responses had tumors that were ER+ and/or PgR+ (3 of these subjects were also human epidermal growth factor receptor 2 [HER2] negative). In the hormone receptor-positive subset, the ORR was 8.2% in the ITT and 9.1% in the EE population.

- Seventeen (17) hormone receptor-positive subjects had SD, including 12 subjects with SD for more than 24 weeks.

The efficacy results showed modest activity with single-agent bosutinib as a second- or third-line treatment in subjects with metastatic breast cancer. A comparison of these results between subpopulations of subjects based on receptor tumor types showed a potential higher efficacy of bosutinib in women with hormone receptor-positive tumors.

The safety results were as follows:

- 71 (97.3%) subjects reported AEs and TEAEs.

- The bosutinib-related TEAEs reported by the highest percentage of subjects were diarrhea (47 subjects, 64%), nausea (37 subjects, 51%), vomiting (31 subjects, 42%), fatigue and anorexia (12 subjects each, 16%), asthenia (10 subjects, 14%), elevated alanine aminotransferase (ALT) levels (8 subjects, 11%), and elevated aspartate aminotransferase (AST) levels and rash (7 subjects each, 10%).

- Transient elevations in ALT or AST levels were noted in a significant proportion of subjects (only 1 subject discontinued from the study).

- 11 (15.1%) subjects were withdrawn from the study because of safety-related AEs, 8 (11%) subjects were withdrawn because of bosutinib-related events, the majority for diarrhea.

- 24 (32.9%) subjects reported SAEs during the course of this study, 8 (11%) subjects had bosutinib-related SAEs.

- 5 deaths occurred during the treatment phase or within 30 days after the last dose of bosutinib (all due to PD).

Bosutinib was safe and generally well tolerated at the oral dose of 400 mg daily in subjects with advanced or metastatic breast cancer.