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

PROTOCOL NO.: 3160A6-2207-WW (B1871010)

PROTOCOL TITLE: A Phase 2, Randomized, Open-Label Study of Bosutinib Administered in Combination With Letrozole Versus Letrozole Alone as First Line Therapy in Post-Menopausal Women With Locally Advanced or Metastatic ER+/ PgR+/erbB2- Breast Cancer

Study Centers: A total of 33 centers took part in the study and randomized subjects; 3 in Belgium, 2 in Australia, 1 each in China, Hong Kong, Hungary, Poland, and Singapore, and 23 centers in the United States of America (USA).

Study Initiation Date and Final Completion Date: 30 July 2009 to 31 May 2010
The study was terminated prematurely.

Phase of Development: Phase 2

Study Objectives: The primary objective of the study was to compare the efficacy, in terms of progression-free survival (PFS) assessed by an independent radiology vendor, of bosutinib in combination with letrozole versus letrozole alone as first line treatment or as recurrence of adjuvant treatment for estrogen receptor (ER) + / progesterone receptor (PgR) + /erbB2- advanced or metastatic breast cancer (MBC) in postmenopausal women.

The secondary objectives of the study were:

- To evaluate the safety profile of bosutinib in combination with letrozole;
- To evaluate the pharmacokinetics (PK) of both bosutinib and letrozole in combination;
- To evaluate additional efficacy parameters such as overall response rate (ORR), overall survival (OS) at 3 years, duration of response, and PFS assessed by investigational sites;
- To examine the health-related quality of life (HRQoL) of bosutinib in combination with letrozole versus letrozole alone.

METHODS

Study Design: This was a Phase 2, multicenter, open-label, 2-arm study of bosutinib in combination with letrozole versus letrozole alone, randomized in a 1:1 ratio. The study was to be conducted in 2 parts.

Part 1 was a safety lead-in phase, intended to confirm the tolerability of the dose of bosutinib to be used in the combination arm during the randomized period of the study, initially selected as bosutinib 400 mg in combination with 2.5 mg letrozole daily. An initial cohort of 10 subjects was to be enrolled and evaluated for safety. Subjects received 400 mg bosutinib and 2.5 mg letrozole daily, and were monitored for adverse events (AEs) and dose limiting toxicities (DLTs). The total sample size for Part 1 was dependent on the observed DLT rate in subjects treated with the combination regimen. If no safety concerns arose, all following eligible subjects were to be enrolled into the randomized Part 2 of the study. If safety criteria, defined as calculated DLT rate, were not sufficient to begin Part 2, an additional 10 subjects were to be enrolled at the same or lower dose of bosutinib. Up to 60 subjects could be enrolled in Part 1.

The study's risk/benefit ratio was evaluated early in Part 1 of the study after a case of Hy's law was reported. This assessment subsequently led to early study termination due to an unfavorable risk/benefit ratio. There was no overall determination of the study's efficacy, specifically PFS, due to early termination of the study. The planned Part 2 of this study was not initiated. The study flowcharts for Part 1 and Part 2 are summarized in Table 1 and Table 2, respectively.

Table 1. Study Flowchart - Part 1

Part 1 Study Procedures		Treatment Period						
	Screening	Month 1[a]				Month 2 and Higher[a]	End of Treatment Visit	Long-term Follow-up
Study Week		1	2	3	4	5		
Visit Day	-28 to 1	1	8	15	22	1	2-6 Weeks After Last Dose or Before Beginning Another Anti-Cancer Regimen	
Visit Window (Days)		±2	±2	±2	±2	±4		
Informed consent[b]	X							
Inclusion and exclusion criteria	X							
Demography data/medical and cancer history/receptor status[c]	X							
Tumor tissue collection[d]	X							
Physical examination	X							
Brief physical examination[e]		X	X	X		X	X	
ECOG performance status	X							
Vital signs[f]	X[f]	X[f]		X		X	X	
ECG (12-lead)[g]	X	X		X[g]		X[g]	X	
Left ventricular ejection fraction (ECHO or MUGA)[h]	X	Per footnote [h] as clinically indicated					X	
Hematology[i]	X	X[i]		X[i]		X[i]	X	
Serum chemistry panel[j]	X	X[j]		X[j]		X[j]	X	
Coagulation tests[k]	X	X[k]				X[k]	X	
Urinalysis	X					X[l]	X	
Radiographic evaluations[m]								
Bosutinib administration Letrozole administration		Oral-daily						
Concomitant medications/non-pharmacologic treatments and adverse events[n]	Continually							
Telephone contact					X			X[o]

AE = adverse event; ANC = absolute neutrophil count; BUN = blood urea nitrogen; eCRF = electronic case report form; ECG = electrocardiogram; ECHO = echocardiogram; ER = estrogen receptor; FACT-B = Functional Assessment of Cancer Therapy for breast cancer; ICF = informed consent form; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MUGA = multiple gated acquisition; RBC = red blood cell; ULN = upper limit of normal.

a. One (1) month = 28 days.
b. Informed consent was obtained >28 days from Day 1; however, it had to be obtained prior to any protocol required assessments being performed. Radiographic assessments and LVEF testing were done before consenting, if performed as part of the subject's routine care/procedures, and if done within the screening window (if applicable) and per the protocol-defined method(s) for this procedure.
c. Information on ER, PgR, and erbB2 status was retrieved for subject's eligibility. If not available, local assessment was required.
d. Formalin fixed paraffin-embedded tumor samples (blocks or slides), representing primary tumor tissue before any systemic therapy, was collected at screening. If the primary tumor tissue was not available, an alternate paraffin-embedded tumor sample was accepted.
e. Brief physical examination was a symptom-directed examination evaluating any clinically significant abnormalities.
f. Vital signs included height and weight only at screening (or Week 1 Day 1). Vital signs do not need to be repeated on Week 1 Day 1 if performed within 7 days of Week 1 Day 1. Health outcomes assessments (FACT-B) were done before test article administration on days of clinic visit. Health outcomes assessments were done at screening or before dose administration at Week 1 Day 1, Month 3 Day 1, Month 6 Day 1, Month 12 Day 1, and at the end of treatment visit.

Table 1. Study Flowchart - Part 1

g. Standard 12-lead digital ECGs were used. Investigators assessed all ECG measurements for safety. A central vendor was used to collect digital ECG information. At screening, ECG measurements were performed in triplicate. During active treatment, ECG measurements were performed after dose administration, 4 hours ± 30 minutes after administration of test article. Additional ECG measurements were done as clinically indicated.

h. LVEF, by ECHO or MUGA scan, were performed as part of routine care within 28 days of first dose, the result were accepted for screening. The same method of measurement, ECHO or MUGA scan, was used during the study. ECHO and MUGA scan was performed every 6 months (during the treatment period only) and also if clinically indicated. LVEF does not need to be repeated within 8-weeks before the end of treatment visit.

i. Hematology included WBC count including 3- or 5-part differential, RBC, hemoglobin, ANC, and platelet count.

j. Serum chemistry panel included sodium, potassium, chloride, BUN or urea, creatinine, glucose, calcium, phosphorus, albumin, total protein, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, total bilirubin (direct bilirubin was required if total bilirubin is >1.5 x ULN), and amylase.

k. Coagulation tests included PT and PTT (and INR for subjects on warfarin). PT was recorded in seconds, or as a ratio (INR); PT in percentage was not acceptable. Subjects on warfarin or were monitored regularly (eg, weekly for the first month, thereafter according to investigator's judgment) and their anticoagulant dose adjusted as needed.

l. Urinalysis was performed on Day 1 every 2 month (eg, months 2, 4, etc).

m. Tumor assessments had to be performed every 8 weeks (± 4 days) (ie, end of Months 2, 4, 6 etc.). They had to be performed every 8 weeks ± 4 days regardless of any treatment delays and/or interruptions.

n. All AEs were continually recorded in the source documents, from the signing of the consent form until 28 days after the last dose of test article. Concomitant medication, concomitant nonpharmacologic treatment or therapies were recorded from 14 days before ICF until the end of treatment visit. Documentation of AE and concomitant medication data were collected on the eCRF at each visit.

o. Long term survival follow-up procedures.

For subjects who discontinued the treatment period because of disease progression:

- Survival information was collected approximately every 12-weeks from the first day of test article administration;
- Information regarding first new anticancer therapy received was collected.

For subjects who discontinued the treatment period for reasons other than disease progression:

- Tumor assessments were continued to be performed every 8 weeks (± 4 days) until documented disease progression or until start of a new cancer treatment;
- Survival information was collected approximately every 12-weeks from the first day of test article administration; Information regarding first new anticancer therapy received was collected.

Table 2. Study Flowchart - Part 2

Part 2 Study Procedures		Treatment Period				
	Screening	Month 1[a]		Month 2 and Higher[a]	End of Treatment Visit	Long-term Follow-up
Study Week		1	3	5		
Visit Day	-28 to 1	1	15	1	2-6 Weeks After Last Dose or Before Beginning Another Anti-Cancer Regimen	
Visit Window (Days)		±2	±2	±4		
Informed consent[b]	X					
Inclusion and exclusion criteria	X					
Demography data/medical and cancer history/receptor status[c]	X					
Tumor tissue collection[d]	X					
Physical examination	X					
Brief physical examination[e]		X	X	X	X	
Vital signs[f]	X[f]	X[f]	X	X	X	
Health outcome assessments[f]	X[f]	X[f]		X[f]	X[f]	
ECG (12-lead)[g]	X	X	X[g]	X[g]	X	
Left ventricular ejection fraction (ECHO or MUGA)[h]	X	Per footnote[h] as clinically indicated			X	
Hematology[i]	X	X[i]	X[i]	X[i]	X	
Serum chemistry panel[j]	X	X[j]	X[j]	X[j]	X	
Coagulation tests[k]	X	X[k]		X[k]	X	
Urinalysis	X			X[l]	X	
Radiographic evaluations[m]						
Plasma samples for pharmacokinetic analysis						
Bosutinib administration Letrozole administration		Oral-daily				
Concomitant medications/non-pharmacologic treatments and adverse events[n]	Continually					
Telephone contact and/or LFTU procedures[o]						X

AE = adverse event; ANC = absolute neutrophil count; BUN = blood urea nitrogen; eCRF = electronic case report form; ECG = electrocardiogram; ECHO = echocardiogram; ER = estrogen receptor; FACT-B = Functional Assessment of Cancer Therapy for breast cancer; ICF = informed consent form; INR = international normalized ratio; LFTU = liver function test unit; LVEF = left ventricular ejection fraction; MUGA = multiple gated acquisition; PK = pharmacokinetic; PgR = progesterone receptor; PT = prothrombin time; PTT = partial thromboplasin time; RBC = red blood cell; ULN = upper limit of normal.

a. One (1) month = 28 days.
b. Informed consent was obtained >28 days from Day 1; however, it had to be obtained prior to any protocol required assessments being performed. Radiographic assessments and LVEF testing were done before consenting, if performed as part of the subject's routine care/procedures, and if done within the screening window (if applicable) and per the protocol-defined method(s) for this procedure.
c. Information on ER, PgR, and erbB2 status was retrieved for subject's eligibility. If not available, local assessment was required.
d. Formalin fixed paraffin-embedded tumor samples (blocks or slides), representing primary tumor tissue before any systemic therapy, was collected at screening. If the primary tumor tissue was not available, an alternate paraffin-embedded tumor sample was accepted.

Table 2. Study Flowchart - Part 2

e. Brief physical examination was a symptom-directed examination evaluating any clinically significant abnormalities.
f. Vital signs included height and weight only at screening (or Week 1 Day 1). Vital signs do not need to be repeated on Week 1 Day 1 if performed within 7 days of Week 1 Day 1. Health outcomes assessments (FACT-B) were done before test article administration on days of clinic visit. Health outcomes assessments were done at screening or before dose administration at Week 1 Day 1, Month 3 Day 1, Month 6 Day 1, Month 12 Day 1, and at the end of treatment visit.
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h. LVEF, by ECHO or MUGA scan, were performed as part of routine care within 28 days of first dose, the result were accepted for screening. The same method of measurement, ECHO or MUGA scan, was used during the study. ECHO and MUGA scan was performed every 6 months (during the treatment period only) and also if clinically indicated. LVEF was not repeated within 8-weeks before the end of treatment visit.
i. Hematology included WBC count including 3- or 5-part differential, RBC, hemoglobin, ANC, and platelet count.
j. Serum chemistry panel included sodium, potassium, chloride, BUN or urea, creatinine, glucose, calcium, phosphorus, albumin, total protein, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, total bilirubin (direct bilirubin was required if total bilirubin is >1.5 x ULN), and amylase.
k. Coagulation tests included PT and PTT (and INR for subjects on warfarin). PT was recorded in seconds, or as a ratio (INR); PT in percentage was not acceptable. Subjects on warfarin or were monitored regularly (eg, weekly for the first month, thereafter according to Investigator's judgment) and their anticoagulant dose adjusted as needed.
l. Urinalysis was performed on Day 1 every 2 month (eg, months 2, 4, etc).
m. Tumor assessments had to be performed every 8 weeks (±4 days) (ie, end of Months 2, 4, 6 etc.). They had to be performed every 8 weeks ± 4 days regardless of any treatment delays and/or interruptions.
n. All AEs were continually recorded in the source documents, from the signing of the consent form until 28 days after the last dose of test article. Concomitant medication, concomitant nonpharmacologic treatment or therapies were recorded from 14 days before ICF until the end of treatment visit. Documentation of AE and concomitant medication data were collected on the eCRF at each visit.
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For subjects who discontinued the treatment period because of disease progression:

- Survival information was collected approximately every 12-weeks from the first day of test article administration;
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For subjects who discontinued the treatment period for reasons other than disease progression:

- Tumor assessments were continued to be performed every 8 weeks (± 4 days) until documented disease progression or until start of a new cancer treatment;
- Survival information was collected approximately every 12-weeks from the first day of test article administration; Information regarding first new anticancer therapy received was collected.

Number of Subjects (Planned and Analyzed): A total of 60 subjects were planned. Of 20 subjects screened, 16 subjects were randomized (6 in Poland, 4 in United States, 2 in Belgium, and 1 each in Hungary, Hong Kong, China, and Singapore), and 16 subjects were treated, all receiving bosutinib 400 mg + letrozole 2.5 mg.

Diagnosis and Main Criteria for Inclusion: Subjects included in the study were women aged 18 years or older (surgically sterile or postmenopausal) with confirmed pathologic diagnosis of locally advanced, metastatic, or locoregional recurrent breast cancer not amenable to curative treatment with surgery or radiotherapy. Subjects had to have documented ER + and/or PgR + and erbB2- tumor based on most recently analyzed biopsy. Subjects having at least 1 radiologically measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST), and those having Eastern Cooperative Oncology Group (ECOG) performance status 0-2 were also included in the study.

Study Treatment: Subjects received 400 mg of bosutinib (corresponding to 4 × 100 mg tablets) once daily, by mouth with food, preferably in the morning, and 2.5 mg letrozole tablets once daily, by mouth. Letrozole was to be taken preferably in the morning, 30 minutes to 1 hour after bosutinib intake. The duration of treatment in the study was estimated to be 14 months for an average subject, however treatment could be continued until unacceptable toxicity or disease progression.

Efficacy Endpoints:

Primary Endpoint: The primary efficacy endpoint was PFS, the time interval from the date of randomization until the first date on which recurrence or progression (including symptomatic deterioration for investigator analyses), or death due to any cause, was documented, censored at the last tumor evaluation.

Secondary Endpoint: Secondary endpoints included OS, ORR, the proportion of subjects who achieved complete response (CR) or partial response (PR) assessed by the investigator or independent radiology vendor per RECIST, and duration of response, measured from the time to which measurements criteria were met for CR or PR (whichever status was recorded first) until the first date on which recurrence or progressive disease (PD) was objectively documented, taking as a reference for PD the smallest measurements recorded since randomization.

Safety Evaluations: The primary safety analysis employed in Part 1 was the percentage of subjects experiencing a DLT. DLTs were assessed from the first dose of study drug through Day 28 for subjects enrolled in Part 1 (safety lead-in phase) of the study. The safety of bosutinib in combination with letrozole was evaluated using the following assessments: monitoring of AEs, withdrawal due to AEs, review of treatment-related AE incidence and severity, concomitant medications, laboratory evaluations, vital signs, standard 12-lead electrocardiograms (ECGs), physical examinations, and assessment of left ventricular ejection fraction (LVEF).

Statistical Methods: The population sets analyzed in the study included:

Intent to treat (ITT) Population: Efficacy analysis was conducted on the (ITT) population. This included all subjects who were to be randomized into Part 2 of the study. The analysis based on the ITT population was considered primary. All subjects were to be analyzed as randomized when ITT population was used.

Evaluable Population: Additionally, analysis of primary and selected secondary efficacy endpoints (OS and ORR) were repeated on the evaluable population to assess the robustness of the result from ITT analyses. All subjects were analyzed as treated when evaluable population was used.

Safety Population: The safety population included all subjects who received at least 1 dose of test article. All subjects were analyzed as treated.

Efficacy analysis was conducted on the intent-to-treat (ITT) population; this included all enrolled subjects. Additionally, analysis of efficacy endpoints was repeated on the evaluable population to assess the robustness of the result from ITT analyses. The evaluable population included all subjects who met all of the following criteria: enrolled and received at least 2-weeks of each of assigned study treatment(s); no protocol eligibility violations; no use of prohibited anticancer therapy concomitant before last dose of study treatments; no use of prohibited concomitant medications between first and last dose of study treatments; a baseline tumor assessment and at least 1 valid post-baseline tumor assessment by the independent assessor, unless death or early progression prior to the first post-baseline tumor assessment. The planned efficacy analysis using confidence intervals (CIs) and Kaplan-Meier estimates were not performed due to early study termination.

The safety population included all subjects who received at least 1 dose of study treatment. The primary safety analysis employed in Part 1 was a two-sided exact 80% CI of the percentage of subjects experiencing a DLT. DLTs were assessed from the first dose of study drug through Day 28 for subjects enrolled in Part 1 (safety lead-in phase) of the study. Part 1 was a safety lead-in phase, intended to confirm the tolerability of the dose of bosutinib to be used in the combination arm during the randomized period of the study, initially selected as bosutinib 400 mg in combination with 2.5 mg letrozole daily. An initial cohort of 10 subjects was to be enrolled and evaluated for safety. Subjects received 400 mg bosutinib and 2.5 mg letrozole daily, and were monitored for (AEs) and DLTs. No formal statistical analysis was planned for this portion of the study. Evaluation of the data consisted primarily of summary displays (ie, descriptive statistics and tabulations). AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. Laboratory values were flagged according to the potentially clinically important (PCI) criteria, based on the NCI CTCAE, version 3.0, with guidance from the sponsor medical monitor. Vital signs and ECGs were also flagged according to PCI.

RESULTS

Subject Disposition and Demography: A total of 16 subjects were enrolled and received bosutinib 400 mg with letrozole 2.5 mg. All 16 subjects discontinued participation in the

study: 14 (87.5%) subjects due to the termination of the study by the sponsor, 1 subject (6.3%) withdrew consent, and 1 subject (6.3%) was withdrawn because of a protocol violation related to the use of prohibited medication during study.

All 16 subjects were included in the ITT population and were evaluable for safety; Table 3. Fifteen (93.8%) subjects were evaluable for DLTs, and 12 subjects (75.0%) were evaluable for efficacy.

Table 3. Summary of Subject Population

Number of Subjects	Bosutinib 400 mg + Letrozole 2.5 mg
Screen failure	4
Randomization	16
Intent-to-treat (total randomized)	16
Evaluable for safety	16
Evaluable for efficacy	12
DLT evaluable	15

Randomization/randomized refers to the number of subjects assigned to treatment (there was no randomization; all subjects received the same treatment).
DLT = Dose limiting toxicity.

The Part 1 study population consisted of female subjects with a median age of 60 years (range 45-81 years), with the majority of subjects (68.8%) age <65 years (Table 4). Most subjects (81.3%) were white. All 16 subjects had a primary diagnosis of breast cancer, with 1 subject (6.3%) having Stage 3 C cancer and 15 subjects (93.8%) having Stage 4 cancer at screening.

Table 4. Demographic and Baseline Characteristics Summary (Safety Population)

	Bosutinib 400 mg + Letrozole 2.5 mg (N=16)
Age (years)	
N	16
Mean	59.6
Standard deviation	9.78
Age group (years), N (%)	
Age <65	11 (68.8)
Age≥65	5 (31.3)
Sex, N (%)	
Female	16 (100)
Race, N (%)	
Asian	3 (18.8)
Black or African American	0
White	13 (81.3)
Other	0
Height (cm)	
N	16
Mean	162.09
Standard deviation	6.777
Weight (Kg)	
N	16
Mean	76.16
Standard deviation	18.184
Study duration (Days)	
N	16
Mean	101.1
Standard deviation	60.40
Therapy duration (Days)	
N	16
Mean	77.1
Standard deviation	60.86

DLT = dose limiting toxicity; N = number of subjects.

All 16 subjects discontinued participation in the study, mainly due to the termination of the study by the sponsor (14 subjects, 87.5%) Table 5. One subject (6.3%) withdrew their consent to participate in the study, and 1 subject (6.3%) was withdrawn for a reason categorized as other (protocol violation related to the use of prohibited medication during study; CPP1).

Table 5. Summary of Subject Participation Conclusion (ITT Population)

Conclusion Status Reason, Number (%) of Subjects	Bosutinib 400 mg + Letrozole 2.5 mg (N=16)
Total, n (%)	16 (100)
Study completed	0
Discontinued	16 (100)
Other	1(6.3)
Study terminated by sponsor	14 (87.5)
Withdrawal by subject	1 (6.3)

ITT = intent-to-treat; N = number of subjects; n = number of evaluable subjects.

Efficacy Results:

A total of 12 of the 16 subjects were evaluable for efficacy. The reasons for non-evaluability were subjects with no valid post-baseline tumor assessment by the Investigator (3 subjects) and prohibited concomitant medications between first and last dose of study treatments (1 subject). Because of the small number of subjects evaluated for efficacy and the duration of the follow-up, it was not possible to conduct a robust efficacy analysis. The sponsor discontinued treatment for 12 subjects prior to PD: 2 were discontinued with no tumor assessment, 6 were discontinued with an 8-week assessment, 2 were discontinued with a 16-week assessment, and 2 were discontinued with ≥24-week tumor assessments.

Progression-Free Survival: Overall, 13 subjects (81.3%) had a post-baseline tumor assessment. Median PFS was not evaluable Table 6. Three subjects (18.8%) had PD and 13 subjects (81.3%) were censored, ie, did not have progression.

Table 6. Progression Free Survival – Investigator Assessment (ITT Population)

Progression-Free Survival	Bosutinib 400 mg + Letrozole 2.5 mg (N=16)
No. subjects with post-baseline tumor assessment (n, %)	13 (81.3)
Median PFS in weeks (80% CI)	NE
No. subjects with PD or who died (n, %)	3 (18.8)
No. subjects with PD (n, %)	3 (18.8)
No. censored subjects (n, %)	13 (81.3)

CI = confidence interval; ITT = intent-to-treat; N = number of subjects; n = Number of subjects contributing to the summary statistics; NE = not evaluable; PFS = progression free survival; PD = progressive disease.

Investigator assessment of PFS in the efficacy-evaluable population is presented in Table 7. In this analysis 12 subjects had a post-baseline tumor assessment, the lower 80% CI for median PFS was evaluable (8.7-weeks), and the proportion of subjects who had PD was 25.0%.

Table 7. Progression Free Survival – Investigator Assessment (Evaluable Population)

Progression-Free Survival	Bosutinib 400 mg + Letrozole 2.5 mg (N=12)
No. subjects with post-baseline tumor assessment (n, %)	12 (100.0)
Median PFS in weeks (80% CI)	NE (8.7, NE)
No. subjects with PD or who died (n, %)	3 (25.0)
No. subjects with PD (n, %)	3 (25.0)
No. censored subjects (n, %)	9 (75.0)

CI = confidence interval; N = number of subjects; n = Number of subjects contributing to the summary statistics; NE = not evaluable; PFS = progression free survival; PD = progressive disease.

Overall Response Rate: Overall, 1 subject (6.3%; 80% CI: 0.7%, 22.2%) had an objective response, a confirmed PR Table 8 in the ITT population, and no subjects had a confirmed CR. Nine (56.3%) subjects had a best overall response of stable disease, 8 subjects for ≤24 weeks and 1 subject for >24-weeks, and 3 subjects (18.8%) had a best overall response of PD.

Table 8. Best Overall Response – Investigator Assessment (ITT Population)

Number (%) of Subjects	Bosutinib 400 mg + Letrozole 2.5 mg (N=16)
Complete response	0 (0.0)
Partial response	1 (6.3)
Stable disease[a]	9 (56.3)
≤24 Weeks	8 (50.0)
>24 Weeks	1 (6.3)
Progressive disease	3 (18.8)
Indeterminate[b]	0 (0.0)
Unknown/no post-baseline tumor assessment	3 (18.8)

24-Weeks (-2-week window) was from randomization to last over time point response of stable disease.
ITT = intent-to-treat; N = number of subjects.
a. Must have met the stable disease criterion at least once after randomization at a minimum of 8 weeks (-4 day window).
b. Had assessment of stable disease or unconfirmed response prior to 8-weeks (-4 Day window) after randomization.

In the efficacy-evaluable population (12 subjects), best overall response is summarized in Table 9. This population also included the 1 subject with a confirmed PR (8.3% for this population). The proportion of subjects with a best response SD was 66.7%, with 25.0% of subjects having a best response of PD.

Table 9. Best Overall Response – Investigator Assessment (Evaluable Population)

Number (%) of Subjects	Bosutinib 400 mg + Letrozole 2.5 mg (N=12)
Complete response	0 (0.0)
Partial response	1 (8.3)
Stable disease[a]	8 (66.7)
≤24 Weeks	8 (66.7)
>24 Weeks	0 (0.0)
Progressive disease	3 (25.0)
Indeterminate[b]	0 (0.0)
Unknown/no post-baseline tumor assessment	0 (0.0)

24-Weeks (-2-week window) was from randomization to last over time point response of stable disease.
N = number of subjects.
a. Must have met the stable disease criterion at least once after randomization at a minimum of 8-weeks (-4 Day window).
b. Had assessment of stable disease or unconfirmed response prior to 8 weeks (-4 day window) after randomization.

Safety Results: The analysis of AEs was based on the safety population of 16 subjects who received at least 1 dose of study treatment. Table 10 summarizes the incidence of all TEAEs according to their MedDRA classification. The most common AEs were gastrointestinal disorders, with diarrhea reported for 13 subjects (81.3%). The only other system organ class where ≥50% of subjects had an AE reported was skin and subcutaneous tissue disorders (9 subjects, 56.3%; mainly rash, 6 subjects, 37.5%), and investigations (8 subjects, 50.0%; alanine aminotransferase increased for 6 subjects, 37.5%, and aspartate aminotransferase increased for 4 subjects, 25.0%).

Table 10. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events With ≥5% (Safety Population)

System Organ Class[a] Preferred Term	Bosutinib 400 mg + Letrozole 2.5 mg (N=16)	Total (N=16)
Any adverse event	16 (100)	16 (100)
Blood and lymphatic system disorders	2 (12.5)	2 (12.5)
Lymphopenia	2 (12.5)	2 (12.5)
Gastrointestinal disorders	16 (100)	16 (100)
Abdominal pain	1 (6.3)	1 (6.3)
Abdominal pain upper	2 (12.5)	2 (12.5)
Constipation	2 (12.5)	2 (12.5)
Diarrhoea	13 (81.3)	13 (81.3)
Dry mouth	1 (6.3)	1 (6.3)
Dyspepsia	2 (12.5)	2 (12.5)
Nausea	7 (43.8)	7 (43.8)
Vomiting	7 (43.8)	7 (43.8)
General disorders and administration site conditions	6 (37.5)	6 (37.5)
Chest discomfort	1 (6.3)	1 (6.3)
Chills	1 (6.3)	1 (6.3)
Fatigue	4 (25.0)	4 (25.0)
Malaise	1 (6.3)	1 (6.3)
Oedema peripheral	1 (6.3)	1 (6.3)
Pyrexia	1 (6.3)	1 (6.3)
Infections and infestations	2 (12.5)	2 (12.5)
Upper respiratory tract infection	1 (6.3)	1 (6.3)
Viral upper respiratory tract infection	1 (6.3)	1 (6.3)
Injury poisoning and procedural complications	1 (6.3)	1 (6.3)
Post procedural diarrhoea	1 (6.3)	1 (6.3)
Investigations	8 (50.0)	8 (50.0)
Alanine aminotransferase increased	6 (37.5)	6 (37.5)
Aspartate aminotransferase increased	4 (25.0)	4 (25.0)
Blood bilirubin increased	1 (6.3)	1 (6.3)
Blood creatinine	1 (6.3)	1 (6.3)
Eosinophil count increased	1 (6.3)	1 (6.3)
Metabolism and nutrition disorders	3 (18.8)	3 (18.8)
Decreased appetite	2 (12.5)	2 (12.5)
Dehydration	1 (6.3)	1 (6.3)
Hyperkalaemia	1 (6.3)	1 (6.3)
Hypocalcaemia	2 (12.5)	2 (12.5)
Hyponatraemia	2 (12.5)	2 (12.5)
Hypophosphataemia	1 (6.3)	1 (6.3)
Musculoskeletal and connective tissue disorders	5 (31.3)	5 (31.3)
Back pain	1 (6.3)	1 (6.3)
Bone pain	1 (6.3)	1 (6.3)
Musculoskeletal chest pain	2 (12.5)	2 (12.5)
Musculoskeletal pain	1 (6.3)	1 (6.3)
Myalgia	1 (6.3)	1 (6.3)

Table 10. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events With ≥5% (Safety Population)

System Organ Class[a] Preferred Term	Bosutinib 400 mg + Letrozole 2.5 mg (N=16)	Total (N=16)
Nervous system disorders	3 (18.8)	3 (18.8)
Headache	3 (18.8)	3 (18.8)
Psychiatric disorders	1 (6.3)	1 (6.3)
Anxiety	1 (6.3)	1 (6.3)
Renal and urinary disorders	3 (18.8)	3 (18.8)
Hydronephrosis	1 (6.3)	1 (6.3)
Proteinuria	2 (12.5)	2 (12.5)
Reproductive system and breast disorders	1 (6.3)	1 (6.3)
Vaginal haemorrhage	1 (6.3)	1 (6.3)
Respiratory, thoracic and mediastinal disorders	4 (25.0)	4 (25.0)
Dyspnoea	4 (25.0)	4 (25.0)
Skin and subcutaneous tissue disorders	9 (56.3)	9 (56.3)
Alopecia	3 (18.8)	3 (18.8)
Dry skin	1 (6.3)	1 (6.3)
Pruritus	1 (6.3)	1 (6.3)
Rash	6 (37.5)	6 (37.5)
Vascular disorders	6 (37.5)	6 (37.5)
Deep vein thrombosis	1 (6.3)	1 (6.3)
Hot flush	3 (18.8)	3 (18.8)
Hypertension	3 (18.8)	3 (18.8)

N = Number of subjects.

a. Body system totals are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Dose-Limiting Toxicities: In the DLT-evaluable population (15 subjects), 4 subjects (26.7%) experienced a DLT Table 11. An initial cohort of 12 subjects (all 12 DLT-evaluable) was enrolled, treated with bosutinib 400 mg + letrozole 2.5 mg, and monitored for AEs and DLTs. As 3 subjects (25.0%) experienced DLTs for this first cohort with lower bound of CI less than 18% and upper bound of CI greater than 34%, (80% CI: 9.6%-47.5%), it was planned to extend Part 1 to enroll an additional 10 subjects at the same dose (bosutinib 400 mg + letrozole 2.5 mg), although only 4 were actually enrolled (3 DLT evaluable), with 1 of these subjects experiencing a DLT.

Table 11. Dose Limiting Toxicities

Age/Sex	Preferred Term	Day	Duration	SAE	Grade	Related to Treatment	Outcome
67/F	Rash	9	24	No	3	Yes	Resolved
61/F	Diarrhea	7	5	Yes	3	Yes	Resolved
	Vomiting	7	5	Yes	3	Yes	Resolved
45/F	ALT increased	15	8	Yes	4	Yes	Resolved
	AST increased	15	12	No	3	Yes	Resolved
64/F	ALT increased	15	15	Yes	3	Yes	Resolved
	AST increased	15	15	Yes	3	Yes	Resolved

ALT = Alanine aminotransferase; AST=Aspartate aminotransferase; F=Female; SAE=Serious adverse event.

The observation of a confirmed Hy's Law case during the conduct of Part 1 (safety lead-in phase) of this study triggered an early assessment of overall risk/benefit.

Treatment-Related AEs: Treatment-related AEs, defined as at least possibly related to the combination of bosutinib and letrozole treatment, were experienced by 15 subjects (93.8%). A summary of all treatment-related AEs is presented in Table 12. The most common treatment-related AEs were in the System Organ Class of gastrointestinal disorders, experienced by 13 subjects (81.3%).The most common treatment-related AE was diarrhea, experienced by 11 subjects (68.8%). Other common treatment-related AEs, each experienced by >20% of subjects, were nausea (6 subjects, 37.5%), vomiting (5 subjects, 31.3%), ALT increased (5 subjects, 31.3%), AST increased (4 subjects, 25.0%), and fatigue (4 subjects, 25.0%).

Table 12. Number (%) of Subjects Reporting Treatment Related Treatment Emergent Adverse Events With ≥5% (Safety Population)

System Organ Class[a] Preferred Term	Bosutinib 400 mg + Letrozole 2.5 mg (N=16)
Any adverse event	15 (93.8)
Blood and lymphatic system disorders	2 (12.5)
Lymphopenia	2 (12.5)
Cardiac disorders	1 (6.3)
Myocardial ischemia	1 (6.3)
Gastrointestinal disorders	13 (81.3)
Abdominal pain	1 (6.3)
Abdominal pain upper	1 (6.3)
Diarrhea	11 (68.8)
Dry mouth	1 (6.3)
Nausea	6 (37.5)
Vomiting	5 (31.3)
General disorders and administration site conditions	5 (31.3)
Fatigue	4 (25.0)
Malaise	1 (6.3)
Pyrexia	1 (6.3)
Injury poisoning and procedural complications	1 (6.3)
Post procedural diarrhoea	1 (6.3)
Investigations	6 (37.5)
Alanine aminotransferase increased	5 (31.3)
Aspartate aminotransferase increased	4 (25.0)
Blood bilirubin increased	1 (6.3)
Eosinophil count increased	1 (6.3)
Metabolism and nutrition disorders	2 (12.5)
Decreased appetite	1 (6.3)
Hypokalemia	1 (6.3)
Musculoskeletal and connective tissue disorders	1 (6.3)
Musculoskeletal pain	1 (6.3)
Nervous system disorders	2 (12.5)
Headache	2 (12.5)
Renal and urinary disorders	2 (12.5)
Proteinuria	2 (12.5)
Respiratory, thoracic and mediastinal disorders	1 (6.3)
Dyspnoea	1 (6.3)
Skin and subcutaneous tissue disorders	5 (31.3)
Alopecia	2 (12.5)
Dry skin	1 (6.3)
Pruritis	1 (6.3)
Rash	3 (18.8)
Vascular disorders	1 (6.3)
Hot flush	1 (6.3)

N = Number of subjects.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report 2 or more different adverse events in the same body system.

Serious Adverse Events: SAEs were experienced by 5 subjects (31.3%), including 3 subjects (18.8%) who experienced treatment-related SAEs Table 13.

Table 13. Number (%) of Subjects Reporting All and Drug-Related Treatment Emergent Serious Adverse Events (Safety Population)

System Organ Class[a] Preferred Term	Bosutinib 400 mg + Letrozole 2.5 mg (N=16)	
	All Adverse Events	Related Adverse Events
Any adverse event	5 (31.3)	3 (18.8)
Cardiac disorders	1 (6.3)	1 (6.3)
Myocardial ischemia	1 (6.3)	1 (6.3)
Gastrointestinal disorders	1 (6.3)	1 (6.3)
Diarrhea	1 (6.3)	1 (6.3)
Vomiting	1 (6.3)	1 (6.3)
General disorders and administration site conditions	1 (6.3)	1 (6.3)
Pyrexia	1 (6.3)	1 (6.3)
Hepatobiliary disorders	1 (6.3)	0
Cholecystitis chronic	1 (6.3)	0
Cholelithiasis	1 (6.3)	0
Injury, poisoning and procedural complications	1 (6.3)	0
Accidental overdose	1 (6.3)	0
Investigations	2 (12.5)	2 (12.5)
Alanine aminotransferase increased	2 (12.5)	2 (12.5)
Aspartate aminotransferase increased	1 (6.3)	1 (6.3)
Metabolism and nutrition disorders	1 (6.3)	1 (6.3)
Hypokalemia	1 (6.3)	1 (6.3)
Skin and subcutaneous tissue disorders	1 (6.3)	0
Rash	1 (6.3)	0

N = Number of subjects.

a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report 2 or more different adverse events in the same body system.

A summary of treatment-emergent SAEs is provided in Table 14. The only SAE reported for more than 1 subject was ALT increased, reported as an SAE for 2 subjects.

Table 14. Number (%) of Subjects Reporting Treatment Emergent Serious Adverse Events (Safety Population)

System Organ Class[a] Preferred Term	Bosutinib 400 mg + Letrozole 2.5 mg (N=16)	Total (N=16)
Any adverse event	5 (31.3)	5 (31.3)
Cardiac disorders	1 (6.3)	1 (6.3)
Myocardial ischemia	1 (6.3)	1 (6.3)
Gastrointestinal disorders	1 (6.3)	1 (6.3)
Diarrhea	1 (6.3)	1 (6.3)
Vomiting	1 (6.3)	1 (6.3)
General disorders and administration site conditions	1 (6.3)	1 (6.3)
Pyrexia	1 (6.3)	1 (6.3)
Hepatobiliary disorders	1 (6.3)	1 (6.3)
Cholecystitis chronic	1 (6.3)	1 (6.3)
Cholelithiasis	1 (6.3)	1 (6.3)
Injury, poisoning and procedural complications	1 (6.3)	1 (6.3)
Accidental overdose	1 (6.3)	1 (6.3)
Investigations	2 (12.5)	2 (12.5)
Alanine aminotransferase increased	2 (12.5)	2 (12.5)
Aspartate aminotransferase increased	1 (6.3)	1 (6.3)
Metabolism and nutrition disorders	1 (6.3)	1 (6.3)
Hypokalemia	1 (6.3)	1 (6.3)
Skin and subcutaneous tissue disorders	1 (6.3)	1 (6.3)
Rash	1 (6.3)	1 (6.3)

N = Number of subjects.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report 2 or more different adverse events in the same body system.

Discontinuations due to AEs: TEAEs leading to treatment discontinuation occurred in 4 subjects (25.0%) Table 15.

Table 15. Number (%) of Subjects Reporting Adverse Events Causing Discontinuation of Study Medications (Safety Population)

System Organ Class[a] Preferred Term	Bosutinib 400 mg + Letrozole 2.5 mg (N=16)
Any Adverse Event	4 (25.0)
Gastrointestinal disorders	1 (6.3)
Diarrhea	1 (6.3)
Vomiting	1 (6.3)
Investigations	2 (12.5)
Alanine aminotransferase increased	2 (12.5)
Aspartate aminotransferase increased	2 (12.5)
Skin and subcutaneous tissue disorders	1 (6.3)
Rash	1 (6.3)

N = Number of subjects.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

The number of subjects who temporarily stopped dose administration because of AEs is summarized in Table 16.

Table 16. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events Leading to Temporary Stop in Test Article (Safety Population)

System Organ Class[a] Preferred Term	Bosutinib 400 mg + Letrozole 2.5 mg (N=16)
Any adverse event	4 (25.0)
Hepatobiliary disorders	1 (6.3)
Cholecystitis chronic	1 (6.3)
Cholelithiasis	1 (6.3)
Injury poisoning and procedural complications	1 (6.3)
Accidental overdose	1 (6.3)
Investigations	1 (6.3)
Alanine aminotransferase increased	1 (6.3)
Aspartate aminotransferase increased	1 (6.3)
Skin and subcutaneous tissue disorders	1 (6.3)
Rash	1 (6.3)

N = Number of subjects.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report 2 or more different adverse events in the same body system.

Deaths: There were no deaths reported in the study.

Laboratory Evaluations: The most common on-treatment potentially clinically important (PCI) abnormality was ALT >5 x ULN, reported for 4/15 subjects (26.7%). AST >5 x ULN and phosphorous <0.6 mmol/L were both reported for 3/15 subjects (20.0%). No subjects had vital signs of PCI. The only ECG abnormalities reported were non-sinus rhythms, reported in 3/16 subjects (18.8%) at Baseline, 4/15 subjects (26.7%) on-therapy, and 2/8 subjects (25.0%) at Follow-up. Maximum on-therapy LVEF was normal for 5 subjects (31.3%), Grade 1 for 1 subject (6.3%), and Grade 2 for 1 subject (6.3%), with data missing for the other 9 subjects.

CONCLUSIONS:

- The recommended Part 2 dose of bosutinib was provisionally determined to be 400 mg in combination with letrozole 2.5 mg, with 4 of 15 advanced breast cancer subjects encountering DLTs of ALT increased, AST increased, diarrhea, vomiting, and rash at this dose level.

- The safety profile of bosutinib 400 mg once daily plus letrozole 2.5 mg once daily was generally acceptable, with most common AEs of diarrhea, nausea, vomiting, ALT increased, AST increased, and fatigue, though 8 of the 16 subjects experienced liver events, the majority of which were serious and/or Grade 3 or 4 in severity, including a confirmed Hy's Law case.

- The study's risk/benefit was evaluated early in Part 1 after a case of Hy's law was reported. This assessment subsequently led to early study termination due to an unfavorable risk/benefit ratio. There was no overall determination of the study's efficacy, specifically PFS, due to early termination of the study.