PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: 3160A6-2208-WW (B1871011)

PROTOCOL TITLE: A Phase 1/2, Open-Label Study of Bosutinib Administered in Combination with Capecitabine in Subjects With Solid Tumor and ErbB2 Negative Locally Advanced or Metastatic Breast Cancer

Study Centers: A total of 7 centers took part in the study and randomized subjects; 2 in the United States, and 1 each in Hong Kong, Spain, Belgium, Australia and France.

Study Initiation Date and Final Completion Dates: 21 September 2009 to 31 March 2011. The study was terminated prematurely.

Phase of Development: Phase 1/2

Study Objectives: The study was planned in 2 parts. The primary and secondary objectives are presented accordingly below.

Primary Objectives:

Part 1: To assess the safety and tolerability, and to determine the maximum tolerated doses MTD(s) of bosutinib plus capecitabine in subjects with locally advanced or metastatic breast cancer (MBC) or pancreatic cancer or colorectal cancer or cholangiocarcinoma or glioblastoma (GBM).

Part 2: To determine the overall response rate (ORR) in females with estrogen receptor (ER) + and/or progesterone receptor (PgR) +, human epidermal growth factor receptor 2 (erbB2) - and ER-, PgR-, erbB2- locally advanced or MBC.

Secondary Objectives:

Part 1: To assess preliminary anti-tumor activity for bosutinib plus capecitabine.

Part 2: To confirm the MTD(s) identified in Part 1 by collecting further data on the safety and tolerability of bosutinib plus capecitabine, to evaluate the pharmacokinetic (PK) of bosutinib in combination with capecitabine, to evaluate additional efficacy parameters such as progression-free survival (PFS), duration of response and clinical benefit rate (CBR) (ORR+ stable disease [SD] ≥24 wks).

METHODS:

Study Design: This was a Phase 1/2, multicenter, open-label study of bosutinib in combination with capecitabine planned as 2 parts. Due to sponsor decision during Part 1, this study was terminated at the conclusion of Part 1, and no subjects were enrolled into Part 2 of the study. The study was not terminated due to safety reasons. The study design of Part 1 and Part 2 is summarized below.

Part 1: This study used an open-label, adaptive trial design. The goal of Part 1 was to determine the MTD and toxicity profile of the combination of bosutinib and capecitabine in subjects with solid tumors, including breast cancer. The study was designed to explore multiple oral doses of bosutinib in combination with capecitabine using an "Up and Down" design. Up to 9 dose combinations (3 dose levels of bosutinib [200 mg, 300 mg, and 400 mg] and 3 dose levels of capecitabine [625 mg, 750 mg, and 1000 mg]) were selected as possible dose levels in this design until a total of up to 24 evaluable subjects were treated. Further information on treatment administration is provided under the study treatment section.

Part 2: In Part 2, up to 62 females per arm were to be enrolled to study the efficacy, and confirm the safety and tolerability of the MTD combination(s) in 2 populations:

- Arm A: Females with ER+ and/or PgR+, erbB2- locally advanced or MBC;
- Arm B: Females with ER-/PgR-/erbB2- locally advanced or MBC.

This study was projected to last approximately 26 months: approximately 6 months for Part 1 and 20 months for Part 2, including 12 months estimated accrual and 8 months for subject participation (this included 4 weeks of screening, an estimated 24 weeks of treatment, and approximately 4 weeks for final follow-up visit).

A time-table of study procedures in Part 1 and Part 2 is shown in Table 1 and Table 2 respectively.

Table 1. Study Flowchart - Part 1

Part 1 Study Procedures			Treatment Period				
	Screening		Cycle 1[a]			Cycles 2 and Higher[a]	End of Treatment Visit
Study Week			1	2	3	4 and Higher	
Cycle Day	-28 to 1	-14 to 1	1	8	15	1	2-6 Weeks After Last IP Dose
Visit Window (Days)			±2	±2	±2	±3	
Informed consent[b]	X						
Inclusion and exclusion criteria	X						
Medical and cancer history/demography	X						
Physical examination	X						
Brief physical examination[c]			X	X	X	X	X
Vital signs[d]		X			X	X	X
ECOG performance status		X					X
β-hCG for women of childbearing potential[e]		X					X
Complete blood count with differential[f]		X		X		X	X
Blood chemistries[g]		X		X		X	X
Coagulation panel[h]		X				X[h]	X
Urinalysis[i]		X				X	X
ECG (12 lead)[j]		X	X[j]			X	X
Left ventricular ejection fraction (MUGA or ECHO)[k]	X		Per footnote[k] as clinically indicated				X
Tumor assessments[l]							
Bosutinib dosing			Oral daily				
Capacetabine dosing			Oral on days 1-14 of each 21 day cycle				
Concomitant medications/non-pharmacologic treatments and adverse events[m]	Continually						

AE = adverse event; β-hCG = Beta human chorionic gonadotropin; eCRF = electronic case report form; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; IP = investigational product; LVEF = left ventricular ejection fraction; MUGA = multiple gated acquisition; PT = prothrombin time; PTT = partial thromboplastin time.

a. One Cycle =21 days.

b. Informed consent was obtained >28 days from Cycle 1 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. Brief physical examination was a symptom-directed examination evaluating any clinically significant abnormalities.

d. Vital signs included height, weight, blood pressure, heart rate, respiratory rate, temperature (oral or tympanic). Height and weight were only recorded at screening.

e. The sample could be serum or urine.

f. Complete blood count included white blood cell count including 3 or 5-part differential, red blood cell count, hemoglobin, absolute neutrophil count, and platelet count. Key laboratory values were reviewed prior to each cycle and prior to dispensing IP to the subject. Additional laboratory tests were done if clinically indicated.

g. Blood chemistries included sodium, potassium, chloride, blood urea nitrogen or urea, creatinine, glucose, calcium, phosphorus, albumin, total protein, aspartate

Table 1. Study Flowchart - Part 1

aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, total bilirubin (direct bilirubin is required if total bilirubin was >1.5 x upper limit of normal [ULN]), and amylase. Key laboratory values were reviewed prior to each cycle and prior to dispensing IP to the subject. Additional laboratory tests were done if clinically indicated.

h. Coagulation panel included PT and PTT (and INR for subjects on warfarin). PT was either recorded in seconds, or as international normalized ratio; PT in % was not acceptable. Subjects on warfarin or equivalent were monitored regularly (eg, weekly for the first cycle, thereafter according to Investigator's judgment), and their anticoagulant dose adjusted as needed. In Cycle 2 and higher, coagulation panel was performed on Day 1 of every other cycle only (ie, Cycles 2, 4, 6 etc.). Additional laboratory tests were done if clinically indicated.

i. Urinalysis was performed on Day 1 of every other cycle (eg, Cycles 2, 4, 6 etc.). Additional laboratory tests were done if clinically indicated.

j. Standard 12-lead digital ECGs were used. Investigators had assessed all ECG measurements for safety. A central vendor was used to collect digital ECG information. A single ECG was performed at screening and 3 serial ECGs were performed before dosing on Cycle 1 Day 1. A single ECG was performed at any time on Day 1 of subsequent cycles. Additional ECGs were done as clinically indicated.

k. LVEF assessment by ECHO or MUGA was accepted for screening if performed as part of routine care within 28 days of Cycle 1 Day 1. The same method of measurement, ECHO or MUGA, was used during the study. ECHO and MUGA was performed every 6 Cycles and if clinically indicated. LVEF did not need to be repeated, if done within 8 weeks before the end of treatment visit.

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

m. All AEs were continually recorded in the source documents, from the signing of the consent form until 28 days after the last dose of IP. Concomitant medication, concomitant non-pharmacologic treatment/therapies were recorded from 14 days prior to signing of the consent form until the end of treatment visit. Documentation of AE and concomitant medication data were collected on the eCRF at each visit.

Table 2. Study Flowchart - Part 2

Part 1 Study Procedures			Treatment Period				
	Screening		Cycle 1[a]			Cycles 2 and Higher[a]	End of Treatment Visit
Study Week			1	2	3	4 and Higher	
Cycle Day	-28 to 1	-14 to 1	1	8	15	1	2-6 Weeks After Last IP Dose
Visit Window (Days)			±2	±2	±2	±3	
Informed consent[b]	X						
Inclusion and exclusion criteria	X						
Medical and cancer history/demography /erbB2/estrogen and progesterone receptor status[c]	X						
Tumor tissue collection[d]	X						
Physical examination	X						
Brief physical examination[e]			X	X	X	X	X
Vital signs[f]		X			X	X	X
ECOG performance status		X					X
β-hCG for women of childbearing potential[g]		X					X
Complete blood count with differential[h]		X		X		X	X
Blood chemistries[i]		X		X		X	X
Coagulation panel[j]		X				X[j]	X
Urinalysis[k]		X				X	X
ECG (12 lead)[l]		X	X[l]		X[l]	X	X
Left ventricular ejection fraction (MUGA or ECHO)[m]	X		Per footnote[m] as clinically indicated				X
Tumor assessments[n]							
Pharmacokinetic samples							
Bosutinib dosing			Oral daily				
Capacetabine dosing			Oral on days 1-14 of each 21 day cycle				
Concomitant medications/non-pharmacologic treatments and adverse events[o]	Continually						

AE = adverse event; β-hCG = Beta human chorionic gonadotropin; eCRF = electronic case report form; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; erbB2 = estrogen receptor beta 2; INR = international normalized ratio; IP = investigational product; LVEF = left ventricular ejection fraction; MUGA = multiple gated acquisition; PT = prothrombin time; PTT = partial thromboplastin time.

a. One Cycle=21 days.

b. Informed consent was obtained >28 days from Cycle 1 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 were retrieved. Local assessment was used for subject eligibility. If not available, local assessment was required.

d. FFPE tumor samples (preferably block or alternatively slides) representing primary tumor tissue before any systemic therapy were collected at Screening. If the primary tumor tissue was not available, an alternate paraffin-embedded tumor sample were 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, weight, blood pressure, heart rate, respiratory rate, temperature (oral or tympanic). Height and weight were only recorded at screening.
g. The sample could be serum or urine.
h. Complete blood count included white blood cell count including 3 or 5-part differential, red blood cell count, hemoglobin, absolute neutrophil count, and platelet count. Key laboratory values were reviewed prior to each cycle and prior to dispensing IP to the subject. Additional laboratory tests were done if clinically indicated.
i. Blood chemistries included sodium, potassium, chloride, blood urea nitrogen or urea, creatinine, glucose, calcium, phosphorus, albumin, total protein, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, total bilirubin (direct bilirubin is required if total bilirubin was >1.5 x upper limit of normal [ULN]), and amylase. Key laboratory values were reviewed prior to each cycle and prior to dispensing IP to the subject. Additional laboratory tests were done if clinically indicated.
j. Coagulation panel included PT and PTT (and INR for subjects on warfarin). PT was either recorded in seconds, or as international normalized ratio; PT in % was not acceptable. Subjects on warfarin or equivalent were monitored regularly (eg, weekly for the first cycle, thereafter according to Investigator's judgment), and their anticoagulant dose adjusted as needed. In Cycle 2 and higher, coagulation panel was performed on Day 1 of every other cycle only (ie, Cycles 2, 4, 6 etc.). Additional laboratory tests were done if clinically indicated.
k. Urinalysis was performed on Day 1 of every other cycle (eg, Cycles 2, 4, 6 etc.). Additional laboratory tests were done if clinically indicated.
l. Standard 12-lead digital ECGs were used. Investigators had assessed all ECG measurements for safety. A central vendor was used to collect digital ECG information. A single ECG was performed at screening and 3 serial ECGs were performed before dosing on Cycle 1 Day 1. A single ECG was performed at any time on Day 1 of subsequent cycles, except on Cycle 1 Day 14, 3 serial ECGs were performed 4 hrs±30 minutes after bosutinib administration. Additional ECGs were done as clinically indicated.
m. LVEF assessment by ECHO or MUGA was accepted for screening if performed as part of routine care within 28 days of Cycle 1 Day 1. The same method of measurement, ECHO or MUGA, was used during the study. ECHO and MUGA was performed every 6 Cycles and if clinically indicated. LVEF did not need to be repeated, if done within 8 weeks before the end of treatment visit.
n. Tumor assessments had to be performed every 6 weeks (±4 days) (ie, end of Cycles 2, 4, 6 etc.). They had to be performed every 6 weeks ± 4days regardless of any treatment delays and/or interruptions.
o. All AEs were continually recorded in the source documents, from the signing of the consent form until 28 days after the last dose of IP. Concomitant medication, concomitant non-pharmacologic treatment/therapies were recorded from 14 days prior to signing of the consent form until the end of treatment visit. Documentation of AE and concomitant medication data were collected on the eCRF at each visit.

Number of Subjects (Planned and Analyzed): It was estimated that a total of 28 subjects would need to be enrolled to achieve a total of 24 evaluable subjects (12 cohorts of 2 subjects each) in Part 1. A total of 41 subjects (11 in Hong Kong, 10 each in the USA and Spain, 4 in Australia, and 3 each in Belgium and France) were enrolled, out of which 32 subjects were randomized in Part 1. All 32 subjects received at least 1 dose of study treatment and were evaluable for safety. Of these 32 subjects, 30 were included in the efficacy evaluations.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, ≥18 years old, with a confirmed pathologic diagnosis of advanced breast cancer or pancreatic cancer or colorectal cancer or cholangiocarcinoma or GBM that was not curable with available therapies, but for which bosutinib plus capecitabine was a reasonable treatment option, with at least 1 radiologically measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v 1.0, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

Study Treatment: Subjects received bosutinib as 100 mg tablets. Each subject was instructed to take the appropriate number of tablets daily according to treatment dose. Capecitabine was supplied as 150 mg and 500 mg tablets. The capecitabine daily oral dose was for 14 days followed by 7 days off (Days 1 to 14 of a 21-day cycle). Capecitabine doses were rounded to the nearest higher or lower multiple of 150 mg and/or 500 mg, corresponding to the available tablets.

The study was designed to explore ascending and descending multiple oral doses of bosutinib in combination with capecitabine using an "Up and Down" design. The dose combinations of the design are shown in Figure 1. A cohort of 2 subjects was assigned to a specific dose combination at a time.

Figure 1 Potential Dose Combination of Bosutinib Plus Capecitabine

Capecitabine (mg/m²; BID)	Bosutinib (mg)			
1000				
750	X			
625		X		
	200	300	400	

BID = Twice daily

The first 2 cohorts open to enrollment were as follows:

- Cohort 1: Capecitabine 750 mg/m² twice daily (BID) on Days 1 to 14 and bosutinib 200 mg daily.
- Cohort 2: Capecitabine 625 mg/m² BID on Days 1 to 14 and bosutinib 300 mg daily.

Dosing was on a 21-day cycle. Subjects were closely monitored for 21 days for adverse events (AEs) and dose-limiting toxicities (DLTs). The dose combination of the subsequent cohorts was determined according to an "Up-and-Down" rule based on 3 factors:

- The number of DLTs in the first 21 days of treatment out of the current cohort of 2 subjects.
- The cumulative toxicity rate at that dose combination.
- The current level of bosutinib and capecitabine.

Subjects were enrolled at the next dose level when 2 evaluable subjects at the same dose level had been evaluated for 21 days of the first treatment cycle or experienced a DLT, whichever came first. If a subject withdrew from the study before completing the 21-day period without experiencing a DLT, another subject was enrolled to replace that subject at the current dose combination.

Efficacy Endpoints:

Primary Endpoint: The primary efficacy endpoint is ORR, which was defined as the proportion of subjects who achieve confirmed tumor response (complete response [CR] or partial response [PR]) assessed by the site Investigators during the study. All data in the database, regardless of the data cutoff date, were included in the analysis of ORR. At designated time points, the Investigator assessed the best overall response (BOR) based on the target lesions, non target lesions, and new lesions (if any). The BOR was the best response recorded from randomization until disease progression/recurrence (taking as reference for progressive disease [PD]) the smallest measurements recorded since randomization.

Secondary Endpoints: PFS was the secondary efficacy endpoint and was defined as the time from the first dose until the earlier date of progression or death from any cause assessed by the site Investigators. Subjects without an event before the specified data cutoff date were censored at the earlier of the date of last valid tumor assessment prior to initiation of new anticancer therapy and the data cutoff date. Subjects with 2 or more consecutive missed or unevaluable scheduled radiographic tumor assessments, or, more generally, subjects for whom there was an interval of at least 92 days (4 days +12 weeks +4 days) between consecutive valid assessments, were censored at the last valid assessment prior to this gap. A valid tumor assessment visit was defined as the tumor assessment visit with overall time point response of CR, PR, SD, or PD, but not 'Not Done' or 'Unknown'. Subjects without post-baseline a tumor assessment or death (before missing their second consecutive valid tumor assessment) before the data cutoff date were censored on the date of first dose.

Safety Evaluations: The following safety parameters were assessed: physical examinations, medical history, vital sign measurements (including height, weight, blood pressure and heart rate), 12-lead electrocardiograms (ECGs), left ventricular ejection fraction (LVEF) measurement via multiple gated acquisition (MUGA) or echocardiogram (ECHO), laboratory evaluations (including hematology, serum chemistry, coagulation test, urinalysis, and beta

human chorionic gonadotropin [β-HCG; for females of childbearing potential]). Laboratory test results, 12-lead ECGs, and treatment-related AE incidence and severity were reviewed.

AEs were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAEs) version 3.0. Serious adverse events (SAEs) were reported until 28 days following the last dose of investigational product(s) (IPs) and were followed until resolution to grade ≤1, return to baseline, or in the case of impairment, until the condition stabilized. Any SAEs beyond 28 days after the last dose of IPs that were considered to be related to IPs were reported.

A DLT was defined as any of the following occurring during the first 21-day cycle:

- any Grade 3 or 4 non hematologic AE (including nausea, vomiting, and diarrhea despite optimal medical therapy, and asthenia >3 days);
- any Grade 4 hematologic AE;
- delayed recovery from one of the above AEs causing delay of investigational product administration by more than 3 weeks.

Statistical Methods:

Analysis Populations: There were 3 populations analyzed for this study:

- The Per Protocol (PP) population was the primary analysis population used for efficacy endpoints. The PP population was a subset of the intent-to treat (ITT) population that consisted of subjects who received at least 14 doses of bosutinib and at least 10 doses of capecitabine within a 21-day period, had a baseline and at least 1 post-baseline tumor assessment, and who had no major protocol violations (eg, protocol deviations that could affect subject safety or the analysis of safety or efficacy outcomes).
- ITT population was defined as all subjects registered to the study who received at least 1 dose of IP (bosutinib or capecitabine). Efficacy endpoints were also summarized for the ITT population.
- The safety population where subjects receiving at least 1 dose of study treatment (bosutinib or capecitabine) were evaluable for safety.

Evaluation of tumor response in this study was based on the modified RECIST v1.0 criteria. Primary analyses of the efficacy endpoints were based on tumor response as assessed by the Investigator CR, PR, PD, or SD.

Clinical activity of the study treatment (bosutinib or capecitabine) was obtained by performing tumor assessments for all subjects at Screening, and then every 6 weeks ±4 days (starting from the initiation of therapy on Cycle 1 Day 1) throughout the course of the study regardless of treatment schedule. Computed tomography (CT) and magnetic resonance

imaging (MRI) were the recommended methods to measure target lesions selected for response assessment, but the same method of assessment had to be used throughout the course of the study. Additional evaluations of disease at Baseline were performed as clinically indicated. All subsequent measurements were compared with the baseline measurement, thus establishing an objective review.

To estimate the overall tumor burden at baseline, a maximum of 5 lesions per organ and 10 measurable lesions in total were identified as target lesion(s) and recorded and measured at Baseline. All sites of disease identified at Screening were followed for the duration of the study with the same method of assessment throughout the study. Target lesions were selected based on their size (those with longest diameter) and their suitability for accurate repeated measurements. All other lesions (or sites of disease) were identified as non target lesions and recorded at Baseline. Their presence or absence was noted throughout follow-up. Disease progression was defined as ≥20% increase in the sum of longest diameters (SLD) of target lesions over the minimum recorded SLD since randomization, or unequivocal increase in non target disease or development of new lesions.

Part 1 Primary Safety Analysis: The primary safety analysis employed in Part 1 was the number and percentage of subjects experiencing a DLT in each dosing group. No formal statistical analysis was planned for this portion of this study. Evaluation of the data consisted primarily of summary displays (ie, descriptive statistics and tabulations). In general, categorical variables were presented using counts and percentages, continuous variables were presented using the mean, standard deviation, median, minimum, maximum, and number of subjects. All analyses were performed on the untransformed data (ie, original scale). Listings of laboratory test results collected at Baseline and during the study were generated. Descriptive statistics summarizing the changes in those laboratory tests over time were presented. Baseline Value: The baseline value was considered the last measurement observed prior to the first dose of study treatment (bosutinib or capecitabine). If no value was recorded on that date, then the last available record prior to the date of first dose was considered baseline.

RESULTS

Subject Disposition and Demography: A total of 32 subjects were enrolled, randomized and received at least 1 dose of the study medication in Part 1 of the study. Thirty (93.8%) subjects were included in the PP population (2 subjects were excluded because they had taken prohibited concomitant medications during the treatment period) and 31 (96.9%) in the DLT evaluations (1 subject was excluded for not receiving enough doses of study medication). Analysis populations are summarized in Table 3.

Table 3. Summary of Subject Population, Intent-to-Treat Population

Population	BOSU 400 mg + CAPE 1000 mg (N=2)	BOSU 400 mg + CAPE 750 mg (N=2)	BOSU 400 mg + CAPE 625 mg (N=0)	BOSU 300 mg + CAPE 1000 mg (N=9)	BOSU 300 mg + CAPE 750 mg (N=4)	BOSU 300 mg + CAPE 625 mg (N=5)	BOSU 200 mg + CAPE 1000 mg (N=4)	BOSU 200 mg + CAPE 750 mg (N=4)	BOSU 200 mg + CAPE 625 mg (N=2)	Total (N=32)
Screen failure										
Randomization	2 (100)	2 (100)	-	9 (100)	4 (100)	5 (100)	4 (100)	4 (100)	2 (100)	32 (100)
Intent-to-treat (Total randomized)	2 (100)	2 (100)	-	9 (100)	4 (100)	5 (100)	4 (100)	4 (100)	2 (100)	32 (100)
Evaluable for safety	2 (100)	2 (100)	-	9 (100)	4 (100)	5 (100)	4 (100)	4 (100)	2 (100)	32 (100)
Evaluable for efficacy	1 (50.0)	2 (100)	-	9 (100)	4 (100)	5 (100)	4 (100)	4 (100)	1 (50.0)	30 (93.8)
DLT evaluable	2 (100)	2 (100)	-	9 (100)	4 (100)	4 (80.0)	4 (100)	4 (100)	2 (100)	31 (96.9)

BOSU = bosutinib; CAPE = capecitabine; DLT = dose limiting toxicity; N = total number of subjects.

All subjects have discontinued from Part 1 of the study. The 32 subjects ranged in age from 42 to 82 years, with a median age of 62.0 years. The majority of subjects were younger than 65 years of age (68.8%). Subjects were primarily white (75.0%). There were more females than males in the study (56.3% vs 43.8%, respectively). Subject disposition and discontinuations from treatment during Part 1 are summarized by dose group in Table 4 and Table 5 provides a summary of demographic characteristics.

Table 4. Summary of Conclusion of Study and Reasons for Discontinuation, Intent-to-Treat Population

Conclusion Status Reason	BOSU 400 mg + CAPE 1000 mg (N=2)	BOSU 400 mg + CAPE 750 mg (N=2)	BOSU 400 mg + CAPE 625 mg (N=0)	BOSU 300 mg + CAPE 1000 mg (N=9)	BOSU 300 mg + CAPE 750 mg (N=4)	BOSU 300 mg + CAPE 625 mg (N=5)	BOSU 200 mg + CAPE 1000 mg (N=4)	BOSU 200 mg + CAPE 750 mg (N=4)	BOSU 200 mg + CAPE 625 mg (N=2)	Total (N=32)
Total	2 (100)	2 (100)	0	9 (100)	4 (100)	5 (100)	4 (100)	4 (100)	2 (100)	32 (100)
Completed										
Study completed	0	0	0	0	0	0	0	0	0	0
Discontinued	2 (100)	2 (100)	0	9 (100)	4 (100)	5 (100)	4 (100)	4 (100)	2 (100)	32 (100)
Adverse event	0	0	0	1 (11.1)	0	1 (20.0)	2 (50.0)	0	0	4 (12.5)
Death	0	0	0	1 (11.1)	0	0	0	0	0	1 (3.1)
Disease progression	2 (100)	2 (100)	0	6 (66.7)	4 (100)	4 (80.0)	2 (50.0)	4 (100)	2 (100)	26 (81.3)
Withdrawal by subject	0	0	0	1 (11.1)	0	0	0	0	0	1 (3.1)

BOSU = bosutinib; CAPE = capecitabine; N = total number of subjects.

Table 5. Summary of Demographic and Baseline Characteristics, Intent-to-Treat Population

Characteristics	BOSU 400 mg + CAPE 1000 mg (N=2)	BOSU 400 mg + CAPE 750 mg (N=2)	BOSU 400 mg + CAPE 625 mg (N=0)	BOSU 300 mg + CAPE 1000 mg (N=9)	BOSU 300 mg + CAPE 750 mg (N=4)	BOSU 300 mg + CAPE 625 mg (N=5)	BOSU 200 mg + CAPE 1000 mg (N=4)	BOSU 200 mg + CAPE 750 mg (N=4)	BOSU 200 mg + CAPE 625 mg (N=2)	Total (N=32)
Age (years)			-							
Mean	61.5	51.5	-	63.8	56.0	63.0	67.3	56.8	53.0	60.7
SD	4.95	6.36	-	5.49	8.45	8.43	10.05	16.32	4.24	9.24
Age group, N (%)										
<65	1 (50.0)	2 (100)	0	5 (55.6)	4 (100)	3 (60.0)	2 (50.0)	3 (75.0)	2 (100)	22 (68.8)
≥65	1 (50.0)	0	0	4 (44.4)	0	2 (40.0)	2 (50.0)	1 (25.0)	0	10 (31.3)
Sex, N (%)										
Male	1 (50.0)	1 (50.0)	0	5 (55.6)	1 (25.0)	1 (20.0)	2 (50.0)	3 (75.0)	0	14 (43.8)
Female	1 (50.0)	1 (50.0)	0	4 (44.4)	3 (75.0)	4 (80.0)	2 (50.0)	1 (25.0)	2 (100)	18 (56.3)
Race, N (%)										
Asian	1 (50.0)	1 (50.0)	0	0	2 (50.0)	1 (20.0)	0	1 (25.0)	1 (50.0)	7 (21.9)
American	0	0	0	1 (11.1)	0	0	0	0	0	1 (3.1)
White	1 (50.0)	1 (50.0)	0	8 (88.9)	2 (50.0)	4 (80.0)	4 (100)	3 (75.0)	1 (50.0)	24 (75.0)
Height (cm)										
Mean	171.25	167.50	-	167.87	165.48	168.20	164.28	169.70	156.00	166.85
SD	27.224	17.678	-	10.158	12.076	7.596	11.777	2.376	12.728	10.629
Weight (kg)										
Mean	96.99	66.72	-	78.51	67.04	63.10	78.95	72.25	51.25	72.65
SD	63.625	17.275	-	15.875	7.648	21.619	10.129	13.845	3.465	20.100
Study duration (Days)										
Mean	343.5	70.5	-	101.0	184.8	59.6	74.3	56.0	151.5	112.4
SD	108.19	34.65	-	69.02	102.95	28.40	36.04	33.50	135.06	94.96
Therapy duration (Days)										
Mean	333.5	64.0	-	87.8	170.0	45.0	49.5	50.0	129.5	98.5
SD	118.09	26.87	-	62.13	103.72	23.84	23.81	22.96	115.26	93.00

BOSU = bosutinib; CAPE = capecitabine; N = total number of subjects; SD = standard deviation.

Efficacy Results: On the basis of the Investigator assessment, the BOR for the PP population was PR (2 subjects [6.7%] - both subjects were in the bosutinib 300 mg + capecitabine 750 mg/m^2 BID dose group). There were 12 subjects (40.0%) with a BOR of SD [10 subjects had SD for ≤24 weeks and 2 subjects had SD for >24 weeks], and 15 subjects (50.0%) with a BOR of PD. There was 1 subject with a BOR of indeterminate because this subject did not have a post Baseline assessment. No subject had reported a BOR of CR (Table 6). Similar results were observed in the ITT population.

Table 6. Best Overall Response (Investigator Assessment), Per-Protocol (Evaluable) Population

Best Response	BOSU 400 mg + CAPE 1000 mg (N=0)	BOSU 400 mg + CAPE 750 mg (N=1)	BOSU 400 mg + CAPE 625 mg (N=0)	BOSU 300 mg + CAPE 1000 mg (N=2)	BOSU 300 mg + CAPE 750 mg (N=9)	BOSU 300 mg + CAPE 625 mg (N=4)	BOSU 200 mg + CAPE 1000 mg (N=5)	BOSU 200 mg + CAPE 750 mg (N=4)	BOSU 200 mg + CAPE 625 mg (N=4)	Total (N=30)
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.7)
Stable disease[a]	1 (100.0)	1 (50.0)	0 (0.0)	6 (66.7)	1 (25.0)	0 (0.0)	2 (50.0)	1 (25.0)	0 (0.0)	12 (40.0)
≤24 weeks	0 (0.0)	1 (50.0)	0 (0.0)	5 (55.6)	1 (25.0)	0 (0.0)	2 (50.0)	1 (25.0)	0 (0.0)	10 (33.3)
>24 weeks	1 (100.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.7)
Progressive disease	0 (0.0)	1 (50.0)	0 (0.0)	2 (22.2)	1 (25.0)	5 (100)	2 (50.0)	3 (75.0)	1 (100.0)	15 (50.0)
Indeterminate[b]	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)

24-weeks (-2-weeks window) is from start of treatment to last over time point response of stable disease.
BOSU = bosutinib; CAPE = capecitabine; N = total number of subjects.
a. Must have met the stable disease criteria at least once after randomization at a minimum of 6-weeks (-3 day window).
b. Had assessment of stable disease or unconfirmed response prior to 6 weeks (-3 day window) after randomization.

Safety Results: Of the 32 subjects enrolled and treated in the study, 31 (96.9%) subjects were evaluable for DLTs (1 subject was excluded from the DLT evaluation because this subject had not received ≥14 doses of bosutinib or ≥10 doses of capecitabine). All 32 enrolled subjects received at least 1 dose of study treatment (eg, at least 1 dose of bosutinib or 1 dose of capecitabine) and were included in the safety evaluation.

Dose-Limiting Toxicities: Overall, 2 (6.5%) subjects experienced DLTs. One subject in the bosutinib 400 mg + capecitabine 750 mg/m^2 BID cohort experienced Grade 3 neuralgia on Day 5 which was considered to be treatment-related. One subject in the bosutinib 400 mg + capecitabine 1000 mg/m^2 BID cohort experienced Grade 3 increased alanine aminotransferase (ALT) on Day 7, Grade 3 pruritus on Day 10, and Grade 3 rash on Day 10, which were considered to be treatment-related. Based on the 2 DLTs occurring in this study the MTD was determined to be bosutinib 300 mg daily + capecitabine 1000 mg/m^2 BID. All subjects recovered from these events after temporarily stopping treatment. None of these events were considered by the Investigators to be SAEs.

Adverse Events: Overall, at least 1 treatment-emergent AE (TEAE) was experienced by all 32 (100%) subjects treated with the combination study treatment Table 7. A total of 29 (90.6%) subjects experienced at least 1 treatment-related TEAE and 10 (31.3%) subjects experienced at least 1 SAE.

The most frequently reported TEAEs (all causalities) were diarrhea (71.9%), nausea (43.8%), fatigue (37.5%), palmar-plantar erythrodysesthesia syndrome (31.3%), vomiting (28.1%), decreased appetite (21.9%) and dyspnea (18.8%). The most frequently reported treatment-related TEAEs (Table 8) were diarrhea (65.6%), nausea (40.6%), palmar-plantar erythrodysesthesia syndrome (31.3%), fatigue (28.1%), and vomiting (25.0%).

Table 7. Number (%) of Subjects Reporting Treatment-Emergent Non-Serious Adverse Events (All Causalities) With Percentage ≥5, Safety Population

System Organ Class Preferred Term[a]	BOSU 400 mg + CAPE 1000 mg (N=2)	BOSU 400 mg + CAPE 750 mg (N=2)	BOSU 400 mg + CAPE 625 mg (N=0)	BOSU 300 mg + CAPE 1000 mg (N=9)	BOSU 300 mg + CAPE 750 mg (N=4)	BOSU 300 mg + CAPE 625 mg (N=5)	BOSU 200 mg + CAPE 1000 mg (N=4)	BOSU 200 mg + CAPE 750 mg (N=4)	BOSU 200 mg + CAPE 625 mg (N=2)	Total (N=32)
Any adverse event	2 (100)	2 (100)	-	9 (100)	4 (100)	5 (100)	3 (75.0)	4 (100)	2 (100)	31 (96.9)
Blood and lymphatic system disorders	0	0	-	3 (33.3)	2 (50.0)	0	0	0	1 (50.0)	6 (18.8)
Lymphopenia	0	0	-	1 (11.1)	0	0	0	0	1 (50.0)	2 (6.3)
Gastrointestinal disorders	2 (100)	2 (100)	-	9 (100)	4 (100)	4 (80.0)	3 (75.0)	4 (100)	2 (100)	30 (93.8)
Abdominal pain	1 (50.0)	0	-	3 (33.3)	0	0	1 (25.0)	0	1 (50.0)	6 (18.8)
Abdominal pain upper	0	1 (50.0)	-	0	2 (50.0)	0	0	0	1 (50.0)	4 (12.5)
Constipation	0	0	-	1 (11.1)	0	1 (20.0)	0	1 (25.0)	0	3 (9.4)
Diarrhoea	2 (100)	2 (100)	-	8 (88.9)	3 (75.0)	3 (60.0)	2 (50.0)	1 (25.0)	2 (100)	23 (71.9)
Flatulence	0	0	-	1 (11.1)	1 (25.0)	0	0	0	0	2 (6.3)
Gastrooesophageal reflux disease	0	1 (50.0)	-	0	0	1 (20.0)	0	0	1 (50.0)	3 (9.4)
Nausea	1 (50.0)	0	-	4 (44.4)	1 (25.0)	2 (40.0)	2 (50.0)	4 (100)	0	14 (43.8)
Vomiting	0	2 (100)	-	2 (22.2)	1 (25.0)	0	1 (25.0)	3 (75.0)	0	9 (28.1)
General disorders and administration site conditions	2 (100)	0	-	6 (6.76)	2 (50.0)	5 (100)	1 (25.0)	2 (50.0)	1 (50.0)	19 (59.4)
Asthenia	0	0	-	1 (11.1)	0	1 (20.0)	0	0	0	2 (6.3)
Fatigue	0	0	-	5 (55.6)	1 (25.0)	3 (60.0)	1 (25.0)	2 (50.0)	0	12 (37.5)
Mucosal inflammation	0	0	-	2 (22.2)	0	0	1 (25.0)	0	1 (50.0)	4 (12.5)
Oedema peripheral	1 (50.0)	0	-	1 (11.1)	0	0	0	0	0	2 (6.3)
Pyrexia	0	0	-	0	1 (25.0)	1 (20.0)	0	0	0	2 (6.3)
Infections and infestations	2 (100)	0	-	2 (22.2)	1 (25.0)	0	1 (25.0)	0	1 (50.0)	7 (21.9)
Bronchitis	0	0	-	0	1 (25.0)	0	1 (25.0)	0	0	2 (6.3)
Urinary tract infection	1 (50.0)	0	-	0	0	0	0	0	1 (50.0)	2 (6.3)
Investigations	1 (50.0)	0	-	4 (44.4)	3 (75.0)	2 (40.0)	0	1 (25.0)	0	11 (34.4)
Alanine aminotransferase increased	1 (50.0)	0	-	2 (22.2)	0	1 (20.0)	0	0	0	4 (12.5)
Aspartate aminotransferase increased	0	0	-	2 (22.2)	0	1 (20.0)	0	0	0	3 (9.4)
Electrocardiogram QT prolonged	0	0	-	0	2 (50.0)	0	0	0	0	2 (6.3)
Weight decreased	0	0	-	0	1 (25.0)	0	0	1 (25.0)	0	2 (6.3)
Metabolism and nutrition disorders	1 (50.0)	0	-	4 (44.4)	0	2 (40.0)	0	3 (75.0)	0	10 (31.3)
Decreased appetite	1 (50.0)	0	-	3 (33.3)	0	1 (20.0)	0	2 (50.0)	0	7 (21.9)
Hypophosphataemia	0	0	-	1 (11.1)	0	1 (20.0)	0	0	0	2 (6.3)
Musculoskeletal and connective tissue disorders	0	1 (50.0)	-	3 (33.3)	1 (25.0)	1 (20.0)	3 (75.0)	1 (25.0)	2 (100)	12 (37.5)
Arthralgia	0	0	-	0	0	0	2 (50.0)	0	0	2 (6.3)
Back pain	0	0	-	0	0	0	1 (25.0)	1 (25.0)	1 (50.0)	3 (9.4)
Musculoskeletal pain	0	0	-	2 (22.2)	0	0	0	0	0	2 (6.3)
Pain in extremity	0	1 (50.0)	-	0	0	1 (20.0)	0	0	0	2 (6.3)

Table 7. Number (%) of Subjects Reporting Treatment-Emergent Non-Serious Adverse Events (All Causalities) With Percentage ≥5, Safety Population

System Organ Class Preferred Term[a]	BOSU 400 mg + CAPE 1000 mg (N=2)	BOSU 400 mg + CAPE 750 mg (N=2)	BOSU 400 mg + CAPE 625 mg (N=0)	BOSU 300 mg + CAPE 1000 mg (N=9)	BOSU 300 mg + CAPE 750 mg (N=4)	BOSU 300 mg + CAPE 625 mg (N=5)	BOSU 200 mg + CAPE 1000 mg (N=4)	BOSU 200 mg + CAPE 750 mg (N=4)	BOSU 200 mg + CAPE 625 mg (N=2)	Total (N=32)
Nervous system disorders	1 (50.0)	1 (50.0)	-	4 (44.4)	2 (50.0)	2 (40.0)	1 (25.0)	3 (75.0)	1 (50.0)	15 (46.9)
Dizziness	0	0	-	1 (11.1)	0	2 (40.0)	0	0	0	3 (9.4)
Headache	0	0	-	2 (22.2)	1 (25.0)	0	0	1 (25.0)	0	4 (12.5)
Neuropathy peripheral	0	0	-	0	0	1 (20.0)	0	1 (25.0)	0	2 (6.3)
Peripheral sensory neuropathy	0	0	-	0	0	0	0	2 (50.0)	1 (50.0)	3 (9.4)
Psychiatric disorders	0	1 (50.0)	-	2 (22.2)	0	2 (40.0)	1 (25.0)	1 (25.0)	1 (50.0)	8 (25.0)
Depression	0	0	-	1 (11.1)	0	0	1 (25.0)	0	0	2 (6.3)
Insomnia	0	1 (50.0)	-	1 (11.1)	0	1 (20.0)	0	0	0	3 (9.4)
Renal and urinary disorders	1 (50.0)	0	-	2 (22.2)	0	0	0	2 (50.0)	0	5 (15.6)
Urinary incontinence	0	0	-	2 (22.2)	0	0	0	0	0	2 (6.3)
Respiratory thoracic and mediastinal disorders	1 (50.0)	1 (50.0)	-	3 (33.3)	1 (25.0)	1 (20.0)	1 (25.0)	2 (50.0)	1 (50.0)	11 (34.4)
Cough	0	1 (50.0)	-	2 (22.2)	0	1 (20.0)	1 (25.0)	0	1 (50.0)	6 (18.8)
Dyspnoea	0	1 (50.0)	-	1 (11.1)	1 (25.0)	1 (20.0)	0	2 (50.0)	0	6 (18.8)
Skin and subcutaneous tissue disorders	1 (50.0)	1 (50.0)	-	5 (55.6)	1 (25.0)	1 (20.0)	3 (75.0)	2 (50.0)	2 (100)	16 (50.0)
Dry skin	0	0	-	0	0	0	1 (25.0)	0	1 (50.0)	2 (6.3)
Erythema	0	1 (50.0)	-	1 (11.1)	0	0	0	0	0	2 (6.3)
Palmar-plantar erythrodysaesthesia syndrome	1 (50.0)	1 (50.0)	-	3 (33.3)	1 (25.0)	0	2 (50.0)	1 (25.0)	1 (50.0)	10 (31.3)
Pruritis	1 (50.0)	0	-	0	0	0	0	0	1 (50.0)	2 (6.3)
Rash	1 (50.0)	0	-	1 (11.1)	0	1 (20.0)	0	0	0	3 (9.4)

BOSU = bosutinib; CAPE = capecitabine; N = total number of subjects; QT = QT electrocardiogram interval.

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

Table 8. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events With Percentage ≥5, Safety Population

System Organ Class Preferred Term[a]	BOSU 400 mg + CAPE 1000 mg (N=2)	BOSU 400 mg + CAPE 750 mg (N=2)	BOSU 400 mg + CAPE 625 mg (N=0)	BOSU 300 mg + CAPE 1000 mg (N=9)	BOSU 300 mg + CAPE 750 mg (N=4)	BOSU 300 mg + CAPE 625 mg (N=5)	BOSU 200 mg + CAPE 1000 mg (N=4)	BOSU 200 mg + CAPE 750 mg (N=4)	BOSU 200 mg + CAPE 625 mg (N=2)	Total (N=32)
Any adverse event	2 (100)	2 (100)	-	9 (100)	3 (75.0)	4 (80.0)	3 (75.0)	4 (100)	2 (100)	29 (90.6)
Blood and lymphatic system disorders	0	0	-	2 (22.2)	2 (50.0)	0	0	0	0	4 (12.5)
Leukopenia	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Lymphopenia	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Neutropenia	0	0	-	0	1 (25.0)	0	0	0	0	1 (3.1)
Thrombocytopenia	0	0	-	0	1 (25.0)	0	0	0	0	1 (3.1)
Cardiac disorders	1 (50.0)	0	-	0	1 (25.0)	0	0	0	0	2 (6.3)
Atrial fibrillation	1 (50.0)	0	-	0	0	0	0	0	0	1 (3.1)
Nodal rhythm	0	0	-	0	1 (25.0)	0	0	0	0	1 (3.1)
Gastrointestinal disorders	2 (100)	2 (100)	-	9 (100)	3 (75.0)	4 (80.0)	2 (50.0)	3 (75.0)	2 (100)	27 (84.4)
Abdominal pain	1 (50.0)	0	-	1 (11.1)	0	0	0	0	0	2 (6.3)
Abdominal pain upper	0	1 (50.0)	-	0	1 (25.0)	0	0	0	0	2 (6.3)
Constipation	0	0	-	1 (11.1)	0	1 (20.0)	0	1 (25.0)	0	3 (9.4)
Diarrhoea	2 (100)	2 (100)	-	8 (88.9)	2 (50.0)	3 (60.0)	1 (25.0)	1 (25.0)	2 (100)	21 (65.6)
Flatulence	0	0	-	1 (11.1)	1 (25.0)	0	0	0	0	2 (6.3)
Gastritis	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Gastrooesophageal reflux disease	0	1 (50.0)	-	0	0	1 (20.0)	0	0	1 (50.0)	3 (9.4)
Haematochezia	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Nausea	1 (50.0)	0	-	4 (44.4)	1 (25.0)	2 (40.0)	2 (50.0)	3 (75.0)	0	13 (40.6)
Stomatitis	0	0	-	0	0	0	0	0	1 (50.0)	1 (3.1)
Vomiting	0	2 (100)	-	2 (22.2)	1 (25.0)	0	0	3 (75.0)	0	8 (25.0)
General disorders and administration site conditions	1 (50.0)	0	-	5 (55.6)	1 (25.0)	2 (40.0)	1 (25.0)	2 (50.0)	1 (50.0)	13 (40.6)
Asthenia	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Chest pain	1 (50.0)	0	-	0	0	0	0	0	0	1 (3.1)
Fatigue	0	0	-	4 (44.4)	1 (25.0)	1 (20.0)	1 (25.0)	2 (50.0)	0	9 (28.1)
Mucosal inflammation	0	0	-	2 (22.2)	0	0	1 (25.0)	0	1 (50.0)	4 (12.5)
Malaise	0	0	-	0	0	1 (20.0)	0	0	0	1 (3.1)
Oedema	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Oedema peripheral	1 (50.0)	0	-	0	0	0	0	0	0	1 (3.1)
Xerosis	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Immune system disorders	0	0	-	0	1 (25.0)	0	0	0	0	1 (3.1)
Hypersensitivity	0	0	-	0	1 (25.0)	0	0	0	0	1 (3.1)
Infections and infestations	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Paronychia	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)

Table 8. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events With Percentage ≥5, Safety Population

System Organ Class Preferred Term[a]	BOSU 400 mg + CAPE 1000 mg (N=2)	BOSU 400 mg + CAPE 750 mg (N=2)	BOSU 400 mg + CAPE 625 mg (N=0)	BOSU 300 mg + CAPE 1000 mg (N=9)	BOSU 300 mg + CAPE 750 mg (N=4)	BOSU 300 mg + CAPE 625 mg (N=5)	BOSU 200 mg + CAPE 1000 mg (N=4)	BOSU 200 mg + CAPE 750 mg (N=4)	BOSU 200 mg + CAPE 625 mg (N=2)	Total (N=32)
Investigations	1 (50.0)	0	-	3 (33.3)	2 (50.0)	1 (20.0)	0	1 (25.0)	0	8 (25.0)
Alanine aminotransferase increased	1 (50.0)	0	-	2 (22.2)	0	1 (20.0)	0	0	0	4 (12.5)
Aspartate aminotransferase increased	0	0	-	2 (22.2)	0	1 (20.0)	0	0	0	3 (9.4)
Ejection fraction decreased	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Electrocardiogram QT prolonged	0	0	-	0	2 (50.0)	0	0	0	0	2 (6.3)
Weight decreased	0	0	-	0	0	0	0	1 (25.0)	0	1 (3.1)
Metabolism and nutrition disorders	1 (50.0)	0	-	3 (33.3)	0	0	0	3 (75.0)	0	7 (21.9)
Decreased appetite	1 (50.0)	0	-	2 (22.2)	0	0	0	2 (50.0)	0	5 (15.6)
Dehydration	0	0	-	0	0	0	0	1 (25.0)	0	1 (3.1)
Hypokalaemia	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Hypomagnesaemia	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Hypophosphataemia	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Musculoskeletal and connective tissue disorders	0	1 (50.0)	-	2 (22.2)	0	1 (20.0)	0	0	1 (50.0)	5 (15.6)
Joint stiffness	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Muscle spasms	0	0	-	0	0	0	0	0	1 (50.0)	1 (3.1)
Muscular weakness	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Pain in extremity	0	1 (50.0)	-	0	0	1 (20.0)	0	0	0	2 (6.3)
Nervous system disorders	1 (50.0)	1 (50.0)	-	2 (22.2)	1 (25.0)	0	0	2 (50.0)	1 (50.0)	8 (25.0)
Dysgeusia	0	0	-	0	1 (25.0)	0	0	0	0	1 (3.1)
Headache	0	0	-	1 (11.1)	0	0	0	1 (25.0)	0	2 (6.3)
Memory impairment	1 (50.0)	0	-	0	0	0	0	0	0	1 (3.1)
Neuralgia	0	1 (50.0)	-	0	0	0	0	0	0	1 (3.1)
Paraesthesia	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Peripheral motor neuropathy	0	0	-	0	0	0	0	1 (25.0)	0	1 (3.1)
Peripheral sensory neuropathy	0	0	-	0	0	0	0	2 (50.0)	1 (50.0)	3 (9.4)
Renal and urinary disorders	0	0	-	0	0	0	0	1 (25.0)	0	1 (3.1)
Proteinuria	0	0	-	0	0	0	0	1 (25.0)	0	1 (3.1)
Renal impairment	0	0	-	0	0	0	0	1 (25.0)	0	1 (3.1)
Respiratory thoracic and mediastinal disorders	1 (50.0)	1 (50.0)	-	1 (11.1)	0	0	0	1 (25.0)	0	4 (12.5)
Cough	0	1 (50.0)	-	0	0	0	0	0	0	1 (3.1)
Dyspnoea	1 (50.0)	0	-	0	0	0	0	1 (25.0)	0	2 (6.3)
Epistaxis	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Pleural effusion	1 (50.0)	0	-	0	0	0	0	0	0	1 (3.1)
Rales	1 (50.0)	0	-	0	0	0	0	0	0	1 (3.1)

Table 8. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events With Percentage ≥5, Safety Population

System Organ Class Preferred Term[a]	BOSU 400 mg + CAPE 1000 mg (N=2)	BOSU 400 mg + CAPE 750 mg (N=2)	BOSU 400 mg + CAPE 625 mg (N=0)	BOSU 300 mg + CAPE 1000 mg (N=9)	BOSU 300 mg + CAPE 750 mg (N=4)	BOSU 300 mg + CAPE 625 mg (N=5)	BOSU 200 mg + CAPE 1000 mg (N=4)	BOSU 200 mg + CAPE 750 mg (N=4)	BOSU 200 mg + CAPE 625 mg (N=2)	Total (N=32)
Skin and subcutaneous tissue disorders	1 (50.0)	1 (50.0)	-	3 (33.3)	1 (25.0)	1 (20.0)	3 (75.0)	2 (50.0)	2 (100)	14 (43.8)
Alopecia	0	0	-	0	0	0	0	1 (25.0)	0	1 (3.1)
Dry skin	0	0	-	0	0	0	1 (25.0)	0	1 (50.0)	2 (6.3)
Erythema	0	1 (50.0)	-	0	0	0	0	0	0	1 (3.1)
Night sweats	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Palmar-plantar erythrodysaesthesia syndrome	1 (50.0)	1 (50.0)	-	3 (33.3)	1 (25.0)	0	2 (50.0)	1 (25.0)	1 (50.0)	10 (31.3)
Pruritis	1 (50.0)	0	-	0	0	0	0	0	0	1 (3.1)
Rash	1 (50.0)	0	-	1 (11.1)	0	1 (20.0)	0	0	0	3 (9.4)
Skin fissures	0	0	-	0	0	0	0	0	1 (50.0)	1 (3.1)
Skin hyperpigmentation	0	0	-	0	0	0	0	1 (25.0)	0	1 (3.1)
Urticaria	0	0	-	0	0	0	1 (25.0)	0	0	1 (3.1)
Vascular disorders	0	0	-	1 (11.1)	0	0	0	1 (25.0)	0	2 (6.3)
Hot flush	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Hypotension	0	0	-	0	0	0	0	1 (25.0)	0	1 (3.1)

AEs and SAEs results not being separated out in this table.
AEs = adverse events; BOSU = bosutinib; CAPE = capecitabine; N = total number of subjects; SAEs = serious adverse events; QT = QT electrocardiogram interval.
a. Body system totals were not necessarily the sum of the individual adverse events since a subject might report ≥2 different adverse events in the same body system.

SAEs were reported for 10 (31.3%) subjects (Table 10). Of these, 2 subjects experienced treatment-related SAEs (treatment-related SAEs in 1 subject included atrial fibrillation, chest pain, and dyspnea and the treatment-related SAE in the other subject was renal impairment). The only SAEs that occurred in >1 subject were bronchitis (n=2) and neoplasm malignant (n=2). SAEs are summarized in Table 9 and Table 10.

Table 9. Number (%) of Subjects Reporting All Causality and Treatment-Related Serious Adverse Events, Safety Population

System Organ Class Preferred Term	BOSU 400 mg + CAPE 1000 mg (N=2)		BOSU 400 mg + CAPE 750 mg (N=2)		BOSU 400 mg + CAPE 625 mg (N=0)		BOSU 300 mg + CAPE 1000 mg (N=9)		BOSU 300 mg + CAPE 750 mg (N=4)		BOSU 300 mg + CAPE 625 mg (N=5)	
	All Adverse Events	Related Adverse Events	All Adverse Events	Related Adverse Events	All Adverse Events	Related Adverse Events	All Adverse Events	Related Adverse Events	All Adverse Events	Related Adverse Events	All Adverse Events	Related Adverse Events
Any study event	1 (50.0)	1 (50.0)	0	0	-	-	3 (33.3)	0	0	0	2 (40.0)	0
Blood and lymphatic system disorders	0	0	0	0	-	-	0	0	0	0	1 (20.0)	0
Anaemia	0	0	0	0	-	-	0	0	0	0	1 (20.0)	0
Cardiac disorders	1 (50.0)	1 (50.0)	0	0	-	-	0	0	0	0	0	0
Atrial fibrillation	1 (50.0)	1 (50.0)	0	0	-	-	0	0	0	0	0	0
Gastrointestinal disorders	0	0	0	0	-	-	1 (11.1)	0	0	0	1 (20.0)	0
Constipation	0	0	0	0	-	-	0	0	0	0	1 (20.0)	0
Gastrointestinal obstruction	0	0	0	0	-	-	1 (11.1)	0	0	0	0	0
General disorders and administration site conditions	1 (50.0)	1 (50.0)	0	0	-	-	0	0	0	0	1 (20.0)	0
Asthenia	0	0	0	0	-	-	0	0	0	0	1 (20.0)	0
Chest pain	1 (50.0)	1 (50.0)	0	0	-	-	0	0	0	0	0	0
Infections and infestations	0	0	0	0	-	-	1 (11.1)	0	0	0	0	0
Bronchitis	0	0	0	0	-	-	1 (11.1)	0	0	0	0	0
Neoplasms benign, malignant and unspecified (inclusiding cysts and polyps)	0	0	0	0	-	-	2 (22.2)	0	0	0	0	0
Glioblastoma multiforme	0	0	0	0	-	-	1 (11.1)	0	0	0	0	0
Neoplasm malignant	0	0	0	0	-	-	1 (11.1)	0	0	0	0	0
Pancreatic carcinoma	0	0	0	0	-	-	0	0	0	0	0	0
Nervous system disorders	0	0	0	0	-	-	0	0	0	0	1 (20.0)	0
Hemiparesis	0	0	0	0	-	-	0	0	0	0	1 (20.0)	0
Renal and urinary disorders	0	0	0	0	-	-	0	0	0	0	0	0
Renal impairment	0	0	0	0	-	-	0	0	0	0	0	0
Respiratory thoracic and mediastinal disorders	1 (50.0)	1 (50.0)	0	0	-	-	1 (11.1)	0	0	0	0	0
Acute respiratory distress syndrome	0	0	0	0	-	-	1 (11.1)	0	0	0	0	0
Dyspnoea	1 (50.0)	1 (50.0)	0	0	-	-	0	0	0	0	0	0

BOSU = bosutinib; CAPE = capecitabine; N = number of subjects.

Table 10. Number (%) of Subjects Reporting All Causality and Treatment-Related Serious Adverse Events, Safety Population

System Organ Class Preferred Term	BOSU 200 mg + CAPE 1000 mg (N=4)		BOSU 200 mg + CAPE 750 mg (N=4)		BOSU 200 mg + CAPE 625 mg (N=2)		Total (N=32)	
	All Adverse Events	Related Adverse Events	All Adverse Events	Related Adverse Events	All Adverse Events	Related Adverse Events	All Adverse Events	Related Adverse Events
Any study event	2 (50.0)	0	2 (50.0)	1 (25.0)	0	0	10 (31.3)	2 (6.3)
Blood and lymphatic system disorders	0	0	0	0	0	0	1 (3.1)	0
Anaemia	0	0	0	0	0	0	1 (3.1)	0
Cardiac disorders	0	0	0	0	0	0	1 (3.1)	1 (3.1)
Atrial fibrillation	0	0	0	0	0	0	1 (3.1)	1 (3.1)
Gastrointestinal disorders	0	0	0	0	0	0	2 (6.3)	0
Constipation	0	0	0	0	0	0	1 (3.1)	0
Gastrointestinal obstruction	0	0	0	0	0	0	1 (3.1)	0
General disorders and administration site conditions	0	0	0	0	0	0	2 (6.3)	1 (3.1)
Asthenia	0	0	0	0	0	0	1 (3.1)	0
Chest pain	0	0	0	0	0	0	1 (3.1)	1 (3.1)
Infections and infestations	1 (25.0)	0	0	0	0	0	2 (6.3)	0
Bronchitis	1 (25.0)	0	0	0	0	0	2 (6.3)	0
Neoplasms benign, malignant and unspecified	1 (25.0)	0	1 (25.0)	0	0	0	4 (12.5)	0
Glioblastoma multiforme	0	0	0	0	0	0	1 (3.1)	0
Neoplasm malignant	1 (25.0)	0	0	0	0	0	2 (6.3)	0
Pancreatic carcinoma	0	0	1 (25.0)	0	0	0	1 (3.1)	0
Nervous system disorders	0	0	0	0	0	0	1 (3.1)	0
Hemiparesis	0	0	0	0	0	0	1 (3.1)	0
Renal and urinary disorders	0	0	1 (25.0)	1 (25.0)	0	0	1 (3.1)	1 (3.1)
Renal impairment	0	0	1 (25.0)	1 (25.0)	0	0	1 (3.1)	1 (3.1)
Respiratory thoracic and mediastinal disorders	0	0	0	0	0	0	2 (6.3)	1 (3.1)
Acute respiratory distress syndrome	0	0	0	0	0	0	1 (3.1)	0
Dyspnoea	0	0	0	0	0	0	1 (3.1)	1 (3.1)

BOSU = bosutinib; CAPE = capecitabine; N = number of subjects.

Discontinuations due to Adverse Events: A total of 7 subjects had discontinued study treatment due to AEs (Table 11). The AEs leading to discontinuation of study treatment included asthenia, fatigue, bronchitis, GBM multiforme, neoplasm malignant, hemiparesis, acute respiratory distress syndrome, and palmar-plantar erythrodysesthesia syndrome. All discontinuations for these AEs occurred in 1 subject each with the exception of the AE of neoplasm malignant, for which discontinuation occurred in 2 subjects. Of the AEs leading to treatment discontinuation, 2 were considered to be treatment-related (palmar-plantar erythrodysesthesia syndrome [n=1] and fatigue [n=1]).

Table 11. Number (%) of Subjects Reporting Adverse Events Causing Discontinuation of Study Medication, Safety Population

System Organ Class[a] Preferred Term	BOSU 400 mg + CAPE 1000 mg (N=2)	BOSU 400 mg + CAPE 750 mg (N=2)	BOSU 400 mg + CAPE 625 mg (N=0)	BOSU 300 mg + CAPE 1000 mg (N=9)	BOSU 300 mg + CAPE 750 mg (N=4)	BOSU 300 mg + CAPE 625 mg (N=5)	BOSU 200 mg + CAPE 1000 mg (N=4)	BOSU 200 mg + CAPE 750 mg (N=4)	BOSU 200 mg + CAPE 625 mg (N=2)	Total (N=32)
Any adverse event	0	0	-	3 (33.3)	0	1 (20.0)	3 (75.0)	0	0	7 (21.9)
General disorders and administration site conditions	0	0	-	0	0	1 (20.0)	1 (25.0)	0	0	2 (6.3)
Asthenia	0	0	-	0	0	1 (20.0)	0	0	0	1 (3.1)
Fatigue	0	0	-	0	0	0	1 (25.0)	0	0	1 (3.1)
Infections and infestations	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Bronchitis	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	0	0	-	2 (22.2)	0	0	1 (25.0)	0	0	3 (9.4)
Glioblastoma multiforme	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Neoplasm malignant	0	0	-	1 (11.1)	0	0	1 (25.0)	0	0	2 (6.3)
Nervous system disorders	0	0	-	0	0	1 (20.0)	0	0	0	1 (3.1)
Hemiparesis	0	0	-	0	0	1 (20.0)	0	0	0	1 (3.1)
Respiratory thoracic and mediastinal disorders	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Acute respiratory distress syndrome	0	0	-	1 (11.1)	0	0	0	0	0	1 (3.1)
Skin and subcutaneous tissue disorders	0	0	-	0	0	0	1 (25.0)	0	0	1 (3.1)
Palmar plantar erythrodysaesthesia syndrome	0	0	-	0	0	0	1 (25.0)	0	0	1 (3.1)

BOSU = bosutinib; CAPE = capecitabine; N = total number of subjects

a. Body system totals were 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: Six subjects who received study treatment died during the study (Table 12). Reasons for deaths were pancreatic cancer (n=1), bronchitic infection (n=1; see erratum), disease progression (n=3), and GBM multiforme (n=1). None of the deaths in this study were considered by the Investigator to be related to study treatment.

Table 12. Summary of Deaths, Intent-to-Treat Population

Characteristic	BOSU 400 mg + CAPE 1000 mg (N=2)	BOSU 400 mg + CAPE 750 mg (N=2)	BOSU 400 mg + CAPE 625 mg (N=0)	BOSU 300 mg + CAPE 1000 mg (N=9)	BOSU 300 mg + CAPE 750 mg (N=4)	BOSU 300 mg + CAPE 625 mg (N=5)	BOSU 200 mg + CAPE 1000 mg (N=4)	BOSU 200 mg + CAPE 750 mg (N=4)	BOSU 200 mg + CAPE 625 mg (N=2)	Total (N=32)
Number of subjects who died										
No	2 (100)	2 (100)	-	6 (66.7)	4 (100)	4 (80.0)	3 (75.0)	3 (75.0)	2 (100)	26 (81.3)
Yes	0	0	-	3 (33.3)	0	1 (20.0)	1 (25.0)	1 (25.0)	0	6 (18.8)
Number of subjects who died within 28 days of last dose[a]										
No	0	0	-	1 (33.3)	0	0	0	0	0	1 (16.7)
Yes	0	0	-	2 (66.7)	0	1 (100)	1 (100)	1 (100)	0	5 (83.3)
Reason of death[a]										
Locally advanced pancreatic cancer	0	0	-	0	0	0	0	1 (100)	0	1 (16.7)
Bronchitic infection	0	0	-	1 (33.3)	0	0	0	0	0	1 (16.7)
Right hemiparesis due to disease progression	0	0	-	0	0	1 (100)	0	0	0	1 (16.7)
Disease progression	0	0	-	0	0	0	1 (100)	0	0	1 (16.7)
Disease progression	0	0	-	1 (33.3)	0	0	0	0	0	1 (16.7)
Glioblastoma multiforme	0	0	-	1 (33.3)	0	0	0	0	0	1 (16.7)

Based on the data collected on the following pages of the CRF: death record, conclusion of treatment, and conclusion of study.
BOSU = bosutinib; CAPE = capecitabine; CRF = case report form; N = number of subjects.
a. Percentages were based on the number of subjects who died.

Laboratory Evaluations: Grade 3 or 4 laboratory values (at least 1) at Baseline, on-treatment, and follow-up were reported for 1 subject at Baseline, 9 subjects on treatment, and 3 subjects at Follow-up. The subject with Grade 3 or 4 laboratory values at Baseline had abnormal partial thromboplastin time (PTT) and prothrombin time. Grade 3 or 4 laboratory values during the on-treatment period included abnormal values for sodium (n=3), international normalized ratio (INR), PTT, phosphorous, calcium, ALT, and prothrombin time (n=2 subjects each), and glucose, aspartate aminotransferase (AST), and hemoglobin (n=1 subject each). Grade 3 or 4 abnormal laboratory values during the follow-up period were reported for ALT, AST, bilirubin, and PTT (1 subject each).

ECG Data: No subjects had QT electrocardiogram interval or QT interval corrected for heart rateintervals >500 msec. One subject in the bosutinib 300 mg + capecitabine 750 mg/m^2 BID cohort had an increase in QT of >60 msec from Baseline. However, change from Baseline using QTc values for this subject did not meet this criterion. Two subjects experienced Grade 2 QT interval prolongation which was noted to be treatment-related for both subjects. These subjects were in the bosutinib 300 mg + capecitabine 750 mg/m^2 BID cohort. The AEs from both subjects were reported to have resolved.

CONCLUSIONS:

- The MTD was determined to be bosutinib 300 mg daily + Ccapecitabine 1000 mg/m^2 BID.

- Two subjects met criteria for DLT (cohorts: bosutinib 400 mg + capecitabine 750 mg/m^2 BID and bosutinib 400 mg + capecitabine 1000 mg/m^2 BID). Observed treatment-related DLTs included neuralgia, pruritus, rash, and increased ALT (all Grade 3).

- The most frequently observed treatment-related TEAEs across all treatment groups were diarrhea (n=21; 65.6%), nausea (n=13; 40.6%), palmar-plantar erythrodysesthesia syndrome (n=10; 31.3%), fatigue (n=9; 28.1%), and vomiting (n=8; 25.0%).

- Grade 3 or 4 laboratory values observed during treatment included abnormal values for sodium (n=3), INR, PTT, phosphorous, calcium, ALT, and prothrombin time (n=2 subjects each), and glucose, AST, and hemoglobin (n=1 subject each).

- Dosing delays for bosutinib and capecitabine due to AEs were common (11 [34.4%] subjects for bosutinib and 16 [50.0%] subjects for capecitabine). Dose reductions of capecitabine or bosutinib due to AEs were reported for 4 subjects (12.5%) and 3 subjects (9.4%), respectively.

- Treatment-related QT interval prolongation was observed in 2 subjects (bosutinib 300 mg + capecitabine 750 mg/m^2 BID cohort).

- Of the 30 subjects in the PP population, the BOR included: 2 subjects (6.7%) with a response of PR, 12 subjects (40.0%) with a response of SD (duration of SD ≤24 weeks [n=10], duration of SD >24 weeks [n=2]), 15 subjects (50.0%) with a response of PD,

and 1 subject (3.3%) with a response of indeterminate. No subject had a BOR of CR. The results were similar for the ITT population.

- Further translational biomarker analyses are needed to better define the breast tumor biomarkers that predict sensitivity to Sarcoma family kinase inhibitors, such as bosutinib, to further optimize the opportunity for successful clinical development of bosutinib for the treatment of subjects with breast cancer. Therefore, the study did not proceed to Part 2 and was ended at completion of Part 1.