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 (SKI-606)

PROTOCOL NO.: 3160A4-2203 (B1871007)

PROTOCOL TITLE: A Phase 1/2 Study of SKI-606 Administered as a Single Agent in Japanese Subjects With Philadelphia Chromosome Positive Leukemias

Study Centers: A total of 22 centers in Japan took part in the study and enrolled subjects.

Study Initiation, Primary Completion and Final Completion Dates:

Study Initiation Date: 03 December 2007

Primary Completion Date: 05 March 2013

Final Completion Date: 17 June 2015

Phase of Development: Phase 1/2

Study Objectives:

Part 1 (Dose Escalation Component):

Primary Objectives:

- Safety confirmation of 600 mg daily or establishment of maximum tolerated dose (MTD) lower than 600 mg, in subjects with chronic phase (CP) imatinib-resistant/refractory or imatinib-intolerant chronic myelogenous leukemia (CML);
- Evaluate the overall pharmacokinetic (PK) parameters in this population.

Secondary Objective:

- Determine the rate of major cytogenetic response (MCyR) in CP subjects at various dose levels of bosutinib.

Part 2 (Efficacy Component):

Primary Objective:

- Determine the rate of attaining MCyR in subjects entering with imatinib-resistant/refractory or imatinib-intolerant CP CML.

Secondary Objectives:

- Estimate the time to and duration of MCyR in subjects entering with imatinib-resistant/refractory or imatinib-intolerant CP CML;
- Estimate the time to and duration of complete hematologic response (CHR) in the imatinib-resistant/refractory or imatinib-intolerant groups;
- Estimate MCyR in CP CML subjects entering with imatinib-resistant/refractory or imatinib-intolerant followed by resistant/refractory or intolerant to dasatinib or nilotinib;
- Estimate the time to and duration of MCyR by resistant/refractory or intolerant to dasatinib or nilotinib CP CML;
- Overall survival (OS) and progression free survival (PFS) rates at 1 and 2 years were explored;
- Estimate CHR rate in accelerated or blast phase CML subjects with imatinib-resistant/refractory or intolerant to imatinib;
- Estimate overall hematologic response (OHR) rate in accelerated or blast phase CML subjects with imatinib-resistant/refractory or intolerant followed by resistant/refractory or intolerant to dasatinib or nilotinib;
- Assess the safety of bosutinib during prolonged oral exposure in a leukemic population;
- Determine the population PK parameters of this population.

METHODS

Study Design:

This was an open-label, continuous daily dosing, 2-part safety and efficacy study of bosutinib in subjects with Philadelphia Chromosome positive (Ph^+) CML.

Part 1: This was designed as a dose-escalation study in imatinib-resistant/refractory or imatinib-intolerant CP CML subjects, to confirm the safety of bosutinib at dose-levels from 400 mg to 600 mg. As summarized in the Study Flowchart of Part 1 (Table 1), safety evaluations were conducted at the end of the first 28 days of bosutinib administration.

Details on dose administration and dose-escalation rules are provided in section study treatment of this document.

Part 2: After having confirmed the safety of bosutinib 600 mg daily or established the MTD lower than 600 mg in Part 1, Part 2, an efficacy study of bosutinib 500 mg began. The study explored the hypotheses that oral daily dosing of bosutinib at 500 mg attained:

- MCyR in CP CML subjects with imatinib-resistant/refractory or intolerant to imatinib (second-line: primary cohort);

- CHR in accelerated or blast phase CML subjects with resistant/refractory or intolerant to imatinib (second-line: advanced cohort);

Bone marrow examination and cytogenetics were performed every 3 months for CP CML subjects. Accelerated or blast phase CML subjects underwent marrow examination every 28 days for the first 3 months and every 3 months thereafter, until the End of the Study.

After discontinuation of bosutinib treatment, survival, progression, and initiation of other anti-tumor treatment were followed up every 3 months.

The timing of procedures is described in Table 1 and Table 2.

Table 1. Study Flowchart (Part 1)

Study Procedures	Screening[a]								End of Treatment (28-42 Days After Last Dose)
Week		**1**		**2**	**3**	**4**	**8**	**12**	**q12w[b]**	
Study Days	**–14 to –1**	**1**	**7**	**14**	**21**	**28**	**56**	**84**	**168, 252 and 336**	
Cycle Day		**1**	**7**	**14**	**21**	**28**	**56**	**84**	**84**	
Study Visit Window			**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Dose bosutinib[c]		----------Continuous daily dosing----------								
Informed consent[d]	X									
Inclusion/exclusion	X									
Medical history/cancer history	X									
PRBC and platelet transfusion Hx	X[e]	X[f]		X	X	X	X	X	X	X
Chest X-ray	X						X	When clinically indicated		X
Physical examination[g]	X	X[f]						X	X	X
Digital ECG[h]	X		X		X					X
ECHO or MUGA	X	When clinically indicated							Week 24 only	X
ECOG performance status	X		X	X			X	X	X	X
Long term follow-up		After bosutinib discontinuation, every 3 months for survival, progression and other anti-tumor Tx								
SAEs and AEs (reported from the signing of the ICF)	X	----------								X
Concomitant treatments[i]	X	----------								
Serum pregnancy test (for women of childbearing potential)	X	As indicated by history/clinical evidence								X
Urinalysis[j]	X					X		X	X	X
Chemistry[k]	X		X	X	X	X	X	X	X	X
LFTs[k]	X		X	X		X	X	X	X	X
Creatinine kinase and amylase/lipase[l]	X			X					X	
CBC and differential[m]	X	X[f]	X	X	X	X	X	X	X	X
Coagulation tests[n]	X		X			X	X	X	X	
PCR for Bcr-Abl	X					X[o]	X[o]	X	X	X
Bone marrow aspirate[p]	X							X	X[o]	X
Cytogenetics, morphology and blast %	X							X	X	X
Site response assessment[q]								X	X	X
Bcr-Abl sequencing	X									X[r]

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; Bcr-Abl = fusion transcript or protein resulting from the 9:22 chromosomal translocation responsible for formation of the Philadelphia chromosome; BUN = blood urea nitrogen; CBC = complete blood count; CHR = complete hematologic response; CK = creatinine kinase; CORE = Computerized Randomization and Enrollment System; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; Hb = hemoglobin; Ht = hematocrit; ICF = informed consent form; INR = international normalized ratio; IRB = Institutional Review Board; LDH = lactate dehydrogenase; LFT = liver function test; MUGA = multiple gated

Table 1. Study Flowchart (Part 1)

acquisition scan; NEL = no evidence of leukemia; OAT = oral anticoagulant therapy (such as warfarin); PCR = polymerase chain reaction; PI = principal investigator; PRBC = packed red blood cells; PT = prothrombin time; QTc = corrected QT; RBC = red blood cell count; SAE = serious adverse event; ULN = upper limit of normal.

a. Screening visit within 14 days before the first dose of bosutinib.
b. Subjects benefiting from bosutinib treatment were eligible for continued treatment beyond 52 weeks with procedures continuing every 12 weeks.
c. The subject had to receive the first dose of bosutinib no more than 2 business days after being enrolled in the CORE system. Day 2 dose was withheld.
d. Signed and dated IRB-approved informed consent before any protocol-specific screening procedures were performed. Procedures performed as standard of care prior to signed and dated ICF, and within the 14 day screening window could be used for study entry. Bone marrow was excepted.
e. The approximate number and volume of transfusions of both blood and platelets given during the previous 28 days were collected. If the subject was referred to the institution, subject/referring physician recollection was sufficient.
f. Repeated if not performed within 3 days before the first dose of bosutinib.
g. Vital signs (supine blood pressure, heart rate and axillary temperature), height and weight.
h. Triplicate ECGs were performed at Screening, on Day 1 prior to treatment and at hours 1, 2, 3, 4, 6, 8, 24, and 48 postdose, and on Day 8 prior to treatment and at Hour 6 postdose and on Day 15 prior to treatment and at hours 1, 2, 3, 4, 6, 8, and 24 postdose, on Day 21 prior to treatment and at hours 2, 4, 6, and 20-23 postdose and End of Treatment visit. End of treatment ECG had to occur at least 7 days after the last dose to allow assessment of QTc after clearance of most of the bosutinib from the blood. Digital ECG recorders were used, and provided by the Sponsor through a third party vendor. An additional set of triplicate ECGs had to be done if a clinically significant decrease in ejection fraction was detected while on study by ECHO or MUGA. ECG data was sent to an independent central laboratory for a central review.
i. All medications from 28 days before the first dose of bosutinib were collected.
j. Qualitative examination: pH, specific gravity, protein/albumin, glucose/sugar, ketones/acetone, hemoglobin/blood.
k. Blood chemistries included sodium, potassium, chloride, calcium, phosphorus, magnesium, glucose, serum creatinine, and BUN. Uric acid performed until the subject achieved CHR or NEL.
l. LFTs done as part of a panel that included chemistry and LFTs when possible. LFTs included total protein, albumin, AST, ALT, LDH, ALP, total and direct bilirubin (if total >2.0 × ULN). Amylase and lipase and CK also included at indicated times.
m. Hematology included CBC including a 5-part differential (abnormalities confirmed by manual differentials), platelet count, ANC, RBC, Hb, and Ht. Phase of disease at screening assignment was based on first day of dosing CBC results. In the case of grade 4 hematologic toxicity, it was recommended that CBC be repeated at least every 2-3 days until recovered to ≤ Grade 2 toxicity.
n. The coagulation tests included PT (expressed as INR), APTT and fibrinogen (if PT/APTT abnormal, screening only). At Screening, test availability documented within 14 days before the first dose of bosutinib if the subject did not take OAT within the past 30 days, and within 3 days before the first dose of bosutinib if the subject took OAT within the past 30 days.
o. The 4 and 8 week PCRs omitted in situations in which Investigator did not believe the subject was experiencing clinical benefit (ie 90% peripheral blasts).
p. Bone marrow aspirate collected for morphology and cytogenetic analysis. Screening bone marrow obtained any time up to 28 days before the first dose of test article (Day –28). Bone marrow aspirates performed every 12 weeks in Year 1, every 24 weeks in Years 2 and 3, and yearly (q48 weeks) for after Year 4, and as clinically indicated. Additional bone marrow testing included the sequencing of Bcr-Abl (could be done on peripheral blood if adequate marrow was not available) to determine mutation status. A marrow sample submitted at any time progression from best response occurred, and for confirmation of progression. This time point could, or could not, coincide with cessation of treatment. (ie, if a subject progressed from complete hematologic response to partial hematologic response, they lost their best response but could not yet discontinue bosutinib).
q. Site assessments were the PI's determination of time point responses.
r. Bcr-Abl sequencing done at study end if subject ended for progression. Peripheral blood was acceptable for sequencing if bone marrow was not available.

Table 2. Study Flowchart (Part 2)

Study Procedures	**Screening**[a]								**End of Treatment (28-42 Days After Last Dose)**
Week		**1**		**2**	**3**	**4**	**8**	**12**	**q12w**[b]	
Study Days	**–14 to –1**	**1**	**7**	**14**	**21**	**28**	**56**	**84**	**168, 252 and 336**	
Cycle Day		**1**	**7**	**14**	**21**	**28**	**56**	**84**	**84**	
Study Visit Window			**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Dose bosutinib[c]		----------Continuous daily dosing----------								
Informed consent[d]	X									
Inclusion/exclusion	X									
Medical history/cancer history	X									
PRBC and platelet transfusion Hx	X[e]	X[f]		X	X	X	X	X	X	X
Chest X-ray	X						X	When clinically indicated		X
Physical examination[g]	X	X[f]						X	X	X
Digital ECG[h]	X	X		X[h]	X			X	X	X
ECHO or MUGA	X	When clinically indicated							Week 24 only	X
ECOG performance status	X		X	X			X	X	X	X
Long term follow-up		After bosutinib discontinuation, every 3 months for survival, progression and other anti-tumor Tx								
SAEs and AEs (reported from the signing of the ICF)	X	----------								X
Concomitant treatments[i]	X	----------								
Serum pregnancy test (for women of childbearing potential)	X	As indicated by history/clinical evidence								X
Urinalysis[j]	X					X		X	X	X
Chemistry[k]	X		X	X	X	X	X	X	X	X
LFTs[k]	X		X	X		X	X	X	X	X
Creatinine kinase and amylase/lipase[l]	X			X					X	
CBC and differential[m]	X	X[f]	X	X	X	X	X	X	X	X
Coagulation tests[n]	X		X			X	X	X	X	
PCR for Bcr-Abl	X					X[o]	X[o]	X	X	X
Bone marrow aspirate[p]	X					X*	X*	X	X[p]	X
Cytogenetics, morphology and blast %	X					X*	X*	X	X	X
Site response assessment[q]						X*	X*	X	X	X
Bcr-Abl sequencing	X									X[r]

* Advanced subjects only (accelerated phase CML/blast phase CML). Bone marrow aspiration was done monthly (3×) on advanced phase subjects until a return to CP was achieved (whichever came first).

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; Bcr-Abl = fusion transcript or protein resulting from the 9:22 chromosomal translocation responsible for formation of the Philadelphia

Table 2. Study Flowchart (Part 2)

chromosome; BUN = blood urea nitrogen; CBC = complete blood count; CHR = complete hematologic response; CK = creatinine kinase; CML = chronic myelogenous leukemia; CORE = Computerized Randomization and Enrollment System; CP = chronic phase; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; Hb = hemoglobin; Ht = hematocrit; ICF = informed consent form; INR = international normalized ratio; IRB = Institutional Review Board; LDH = lactate dehydrogenase; LFT = liver function test; MUGA = multiple gated acquisition scan; NEL = no evidence of leukemia; OAT = oral anticoagulant therapy (such as warfarin); PCR = polymerase chain reaction; PRBC = packed red blood cells.

a. Screening visit within 14 days before the first dose of bosutinib.
b. Subjects benefiting from bosutinib treatment were eligible for continued treatment beyond 52 weeks with procedures continuing every 12 weeks performed.
c. The subject received the first dose of bosutinib no more than 2 business days after being enrolled in the CORE system.
d. Signed and dated IRB-approved informed consent before any protocol-specific screening procedures were performed. Procedures performed as standard of care prior to signed and dated ICF, and within the 14 day screening window could be used for study entry. Bone marrow was excepted.
e. The approximate number and volume of transfusions of both blood and platelets given during the previous 28 days were collected. If the subject was referred to the institution, subject/referring physician recollection was sufficient.
f. Repeated if not performed within 3 days before the first dose of bosutinib.
g. Vital signs (supine blood pressure, heart rate and axillary temperature), height and weight.
h. Triplicate ECGs were performed at Screening, on Day 1 prior to treatment and at Hours 2, 4 and 6 postdose, on Day 14 prior to treatment, on Day 21 prior to treatment and at Hours 2, 4, 6, and 20-23 postdose, on Day 84 prior to treatment, on Day 168 prior to treatment and on Day 252 prior to treatment and End of Treatment visit for except exploratory cohort, at Screening, on Day 1 prior to treatment and at hour 4 postdose, on Day 21 prior to treatment, on Day 84 prior to treatment, on Day 168 prior to treatment and on Day 252 prior to treatment and End of Treatment visit for exploratory cohort. End of treatment ECG occurred at least 7 days after the last dose to allow assessment of QTc after clearance of most of the bosutinib from the blood. Digital ECG recorders were used, and provided by the Sponsor through a third party vendor. An additional set of triplicate ECGs done if a clinically significant decrease in ejection fraction was detected while on study by ECHO or MUGA. ECG data was sent to an independent central laboratory for a central review.
i. All medications from 28 days before the first dose of bosutinib were collected.
j. Qualitative examination: pH, specific gravity, protein/albumin, glucose/sugar, ketones/acetone, hemoglobin/blood.
k. Blood chemistries to include sodium, potassium, chloride, calcium, phosphorus, magnesium, glucose, serum creatinine, and BUN. Uric acid performed until the subject achieved CHR or NEL.
l. LFTs done as part of a panel that included chemistry and LFTs when possible. LFTs included total protein, albumin, AST, ALT, LDH, ALP, total and direct bilirubin (if total >2.0 × ULN). Amylase and lipase and CK included at indicated times.
m. Hematology included CBC including a 5-part differential (abnormalities confirmed by manual differentials), platelet count, ANC, RBC, Hb, and Ht. Phase of disease at screening assignment was based on first day of dosing CBC results. In the case of grade 4 hematologic toxicity, it was recommended that CBC be repeated at least every 2-3 days until recovered to ≤ Grade 2 toxicity.
n. The coagulation tests included PT (expressed as INR), APTT and fibrinogen (if PT/APTT abnormal, screening only). At Screening, test availability documented within 14 days before the first dose of bosutinib if the subject did not take OAT within the past 30 days, and within 3 days before the first dose of bosutinib if the subject took OAT within the past 30 days.
o. The 4 and 8 week PCRs omitted in situations in which Investigator did not believe the subject was experiencing clinical benefit (ie 90% peripheral blasts).
p. Bone marrow aspirate collected for morphology and cytogenetic analysis. Screening bone marrow obtained any time up to 28 days before the first dose of test article (Day –28). Bone marrow aspirates was performed every 12 weeks in Year 1, every 24 weeks in Years 2 and 3 and yearly.
q. Site Assessments were the PI's determination of time point responses.
r. Bcr-Abl sequencing done at study end if subject ended for progression. Peripheral blood was acceptable for sequencing if bone marrow was not available.

Number of Subjects (Planned and Analyzed):

Part 1: This was planned to consist of 3 cohorts, with 3 to 6 subjects planned for 400 mg, 500 mg, and 600 mg, respectively. A total of 17 subjects (400 mg: 7 subjects, 500 mg: 7 subjects, 600 mg: 3 subjects) were enrolled and treated with bosutinib.

Part 2: This was planned to consist of 45 subjects, with ≥25 subjects planned for primary cohort, ≤10 subjects for advanced cohort and 10 subjects for exploratory cohort. A total of 46 subjects (second-line: 35 subjects consisted of 28 subjects in the primary cohort and 7 subjects in the advanced cohort; third-line: 11 subjects) were enrolled and treated with bosutinib 500 mg.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Subjects with cytogenetic or polymerase chain reaction based diagnosis of CP of Ph^+ CML (Part 1), any phase of Ph^+ CML (Part 2), whose disease was resistant/refractory to full-dose imatinib or were intolerant of any dose of imatinib, or whose disease was resistant/refractory to full-dose imatinib or were intolerant of any dose of imatinib as a first-line treatment and resistant/refractory to full-dose dasatinib or nilotinib, or were intolerant of any dose of dasatinib or nilotinib. Subjects were also required to have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 for CP subjects, and 0, 1 or 2 for advanced stage subjects and to be aged ≥20 years and <75 years for Part 1 and ≥20 years for Part 2.

Exclusion Criteria: Subjects with philadelphia chromosome negative chronic myelogenous leukemia, those who had ongoing requirement for warfarin or other oral anticoagulant therapy (Part 1), ongoing requirement for hydroxyurea (Part 1), ongoing clinical requirement for administration of a strong inhibitor or inducer of CYP-3A4 (Part 1) were excluded from the study.

Study Treatment:

Bosutinib was orally administered with water and food as a single dose on Day 1 and as continuous once-daily dosing from Day 3 (Part 1). The dose on Day 2 was skipped in Part 1 only to provide an appropriate 48 hour PK profile.

Part 1: To confirm the safety of 600 mg daily or to establish the MTD lower than 600 mg, 3 to 6 subjects were to be evaluated for treatment-emergent toxicities at 400 mg, 500 mg, and 600 mg.

Part 2: The starting dose was 500 mg and dose escalation up to 600 mg was allowed for the lack of efficacy.

Subjects in both parts, deemed by the Investigator and the Sponsor to be benefiting from the compound, were allowed to continue on bosutinib until disease progression, unacceptable toxicity, or withdrawal of consent occurred.

Efficacy, Pharmacokinetic and Safety Endpoints:

Part 1 (Dose Escalation Component):

Primary Endpoints:

- MTD of bosutinib in subjects with CP imatinib-resistant/refractory or imatinib-intolerant CML, measured as incidence and severity of dose-limiting toxicities (DLTs) at each dose level (400 mg, 500 mg, and 600 mg);
- Overall PK parameters in this population.

Secondary Endpoint:

- The rate of attaining MCyR in CP subjects at various dose levels of bosutinib.

Pharmacokinetic Endpoints:

- PK parameters including observed maximum concentration (C_{max}), time of maximum concentration (T_{max}), area under the concentration-time curve (AUC), terminal elimination half-life ($t_{½}$), apparent oral clearance (CL/F), apparent volume of distribution (V_z/F) and the accumulation ratio (R) were calculated.

Part 2 (Efficacy Component):

Primary Efficacy Endpoint:

- The rate of attaining MCyR in subjects with imatinib-resistant/refractory or imatinib-intolerant CP CML, who have completed at least 24 weeks of follow-up, or obtained MCyR prior to 24 weeks.

Secondary Efficacy Endpoints:

- Time to McyR, duration of McyR, and maintenance rate of MCyR.
- The rate of attaining CHR, Time to CHR, and Duration of CHR;
- PFS;
- Time to treatment failure (TTF);
- OS.

Pharmacokinetic Endpoints:

- Population PK parameters were estimated in this population.

Safety Evaluations: The safety variables included incidence and severity of DLTs in Part 1 and adverse events (AEs) at each dose level in Part 1 and in Part 2, changes in laboratory test results, electrocardiogram, and chest X-ray, concomitant medications used for management of AEs, and changes in ECOG performance status or physical examination (as summarized in Table 1 and Table 2).

Statistical Methods:

Analysis Populations: The following 6 analysis populations were analyzed in the study:

- All-treated population was defined as all enrolled subjects who had received at least 1 dose of bosutinib.
- Evaluable populations were defined for cytogenetic, hematologic, and molecular responses, respectively, as a subset of the all-treated population, ie, all enrolled subjects who had received at least 1 dose of bosutinib and had an adequate baseline efficacy assessment for pertinent response.
- The per-protocol (PP) population was defined as a subset of the evaluable population, ie, all enrolled subjects who received at least 1 dose of bosutinib, had no major protocol violation, had an adequate baseline efficacy assessment, and had an adequate post-baseline efficacy assessment unless the subject had early progression or died.
- The safety population was defined as all subjects who had received at least 1 dose of bosutinib. This population excluded only those subjects who had never received bosutinib.
- The PK concentration population was defined as all enrolled subjects who had received ≥1 dose of bosutinib and had at least 1 concentration data.
- The PK parameter population was defined as all enrolled subjects who received ≥1 dose of bosutinib and had at least 1 of the PK parameters of interest.

Efficacy Analysis: The statistical analysis performed for efficacy endpoints was based on the all-treated, evaluable, and PP populations. The analysis based on the all-treated population was considered primary. The primary efficacy endpoint was analyzed based on all 3 populations. The secondary efficacy endpoints were analyzed based on the all-treated and evaluable populations, except that TTF, PFS and OS were analyzed based only on the all-treated population.

Categorical endpoints included the MCyR, CHR, major hematologic response (MHR), OHR, major molecular response (MMR), and accelerated phase (AP)/ blast phase (BP) transformation rates. The number of subjects with a response were reported. The observed rate and the exact 2-sided 95% confidence interval (CI) for the rate was also provided.

Time-to-event endpoints included the time to response, duration of response, TTF, PFS, and OS. The number of subjects with each event and censoring were reported. The distributions

of time-to-event were estimated using the Kaplan-Meier method. The quartile (25%, 50%, and 75%) time-to-event and the corresponding 2-sided 95% CIs were reported. For the TTF, PFS, and OS analyses, the rates at Week 48 and at Week 96 and the corresponding 2-sided 95% CIs were also presented.

Safety Analysis: Safety data were tabulated using descriptive statistics and no formal statistical testing was planned. Safety data was analyzed on the basis of available data in safety population.

Pharmacokinetic Analysis: The PK analyses were based on the PK concentration and PK parameter populations. Bosutinib plasma concentration profiles were summarized for each sampling point and each dose group (Part 1 only). The concentration-time curves were drawn for each subject (Part 1 only). Summaries of bosutinib concentrations and majority of PK parameters included n, mean, standard deviation, coefficient of variance (CV) %, minimum, median, maximum and geometric mean of data. For certain parameters, particularly those associated with time observations such as T_{max}, total population (n), median, and range (minimum, maximum) were included. The actual times of sample collection were used in the PK analyses.

RESULTS

Subject Disposition and Demography:

Subject disposition is summarized in Table 3. In Part 1, 17 subjects were enrolled and treated with bosutinib. In Part 2, 46 subjects (second-line: 35 subjects, third-line: 11 subjects) were enrolled and treated with bosutinib. Forty-five (45) (86.5%) subjects in the total second-line subjects and 11 (100%) subjects in the exploratory third-line cohort were lost to follow-up which includes the completion of the study. In the total second-line median duration of treatment in weeks was 137.14 weeks (range: 1.14 to 372.43 weeks) and median duration of follow-up in weeks was 149.93 weeks (range: 3.14 to 372.43 weeks). In the exploratory third-line cohort, the median duration of treatment in weeks was 131.43 weeks (range: 13.00 to 160.14 weeks) and median duration of follow-up in weeks was 131.43 weeks (range: 105.43 to 160.14 weeks).

Table 3. Subject Disposition: All-Treated Population

	Part 1 Second-Line 400 mg N=7	Part 1 Second-Line 500 mg N=7	Part 1 Second-Line 600 mg N=3	Part 2 Primary Second-Line 500 mg N=28	Part 2 Advanced Second-Line 500 mg N=7	Total Second-Line N=52	Part 2 Exploratory Third-Line 500 mg N=11	Total N=63
Deceased	0	0	0	2 (7.1)	5 (71.4)	7 (13.5)	0	7 (11.1)
Lost to follow-up	7 (100)	7 (100)	3 (100)	26 (92.9)	2 (28.6)	45 (86.5)	11 (100)	56 (88.9)
Duration of treatment in weeks								
N	7	7	3	28	7	52	11	63
Mean	204.98	165.45	253.10	161.53	31.84	155.73	110.91	147.90
Standard deviation	174.03	169.71	130.05	115.05	65.09	134.72	52.80	125.19
Minimum	1.86	1.71	103.00	1.14	1.14	1.14	13.00	1.14
Maximum	372.43	359.86	332.29	312.00	179.00	372.43	160.14	372.43
Median	270.14	88.00	324.00	238.00	8.00	137.14	131.43	131.43
Duration of follow-up in weeks								
N	7	7	3	28	7	52	11	63
Mean	225.73	195.33	254.90	190.88	68.53	183.39	131.06	174.26
Standard deviation	150.96	145.11	130.33	81.01	63.11	110.34	20.33	102.39
Minimum	7.14	3.14	104.43	34.57	17.29	3.14	105.43	3.14
Maximum	372.43	362.00	332.29	312.14	179.43	372.43	160.14	372.43
Median	270.14	112.14	328.00	238.00	25.14	149.93	131.43	132.00

Duration of treatment in weeks is computed as ([date of last dose - date of first dose + 1]/7).
Duration of follow-up in weeks is computed as ([date of last available subject contact - date of first dose + 1]/7).
N = number of subjects.

The reasons for discontinuation of treatment and discontinuation of study are summarized in Table 4 and Table 5 respectively. The summary of subject populations is presented in Table 6.

Table 4. Reasons for Conclusion of Treatment Phase: Safety Population

Conclusion Status Reason[a] n (%)	Treatment							
	Part 1 Second-Line 400 mg N=7	Part 1 Second-Line 500 mg N=7	Part 1 Second-Line 600 mg N=3	Part 2 Primary Second-Line 500 mg N=28	Part 2 Advanced Second-Line 500 mg N=7	Total Second-Line N=52	Part 2 Exploratory Third-Line 500 mg N=11	Total N=63
Total	7 (100)	7 (100)	3 (100)	28 (100)	7 (100)	52 (100)	11 (100)	63 (100)
Completed	3 (42.9)	3 (42.9)	2 (66.7)	14 (50.0)	0	22 (42.3)	7 (63.6)	29 (46.0)
Other:study completed	3 (42.9)	3 (42.9)	2 (66.7)	14 (50.0)	0	22 (42.3)	7 (63.6)	29 (46.0)
Discontinued	4 (57.1)	4 (57.1)	1 (33.3)	14 (50.0)	7 (100)	30 (57.7)	4 (36.4)	34 (54.0)
Adverse event	1 (14.3)	1 (14.3)	0	10 (35.7)	2 (28.6)	14 (26.9)	2 (18.2)	16 (25.4)
Death	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Disease progression	1 (14.3)	1 (14.3)	0	1 (3.6)	5 (71.4)	8 (15.4)	1 (9.1)	9 (14.3)
Investigator request	1 (14.3)	1 (14.3)	0	1 (3.6)	0	3 (5.8)	1 (9.1)	4 (6.3)
Other	0	0	1 (33.3)	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Subject request	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Symptomatic deterioration	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)

N = number of subjects; n = number of subjects meeting criteria.
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.

Table 5. Reasons for Conclusion of Participation: All-Treated Population

Conclusion Status Reason[a] n (%)	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Total	7 (100)	7 (100)	3 (100)	28 (100)	7 (100)	52 (100)	11 (100)	63 (100)
Completed	6 (85.7)	6 (85.7)	3 (100)	26 (92.9)	2 (28.6)	43 (82.7)	10 (90.9)	53 (84.1)
Study completed	6 (85.7)	6 (85.7)	3 (100)	26 (92.9)	2 (28.6)	43 (82.7)	10 (90.9)	53 (84.1)
Discontinued	1 (14.3)	1 (14.3)	0	2 (7.1)	5 (71.4)	9 (17.3)	1 (9.1)	10 (15.9)
Death	0	0	0	2 (7.1)	5 (71.4)	7 (13.5)	0	7 (11.1)
Investigator request	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Other	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Subject request	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)

N = number of subjects; n = number of subjects meeting criteria.
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.

Table 6. Summary of Subject Population: All Consented Subjects

Population (N)	Part 1 Second-Line 400 mg	Part 1 Second-Line 500 mg	Part 1 Second-Line 600 mg	Part 2 Primary Second-Line 500 mg	Part 2 Advanced Second-Line 500 mg	Total Second-Line	Part 2 Exploratory Third-Line 500 mg	Total
Enrolled subjects	7	7	3	28	7	52	11	63
Subjects treated with bosutinib	7	7	3	28	7	52	11	63
Analysis populations								
All-treated population	7	7	3	28	7	52	11	63
Evaluable population								
Cytogenetic assessment	6	7	3	28	7	51	11	62
Hematologic assessment	7	7	3	28	7	52	11	63
Molecular assessment	4	7	2	28	7	48	11	59
Per-protocol population								
Cytogenetic assessment	5	6	3	24	7	45	11	56
Safety population	7	7	3	28	7	52	11	63

N = number of subjects.

Of the 63 subjects, 24 (38.1%) subjects were female and 39 (61.9%) subjects were male (Table 7). The median age was 55 years (range: 20 to 78 years).

All 52 second-line subjects had received prior imatinib therapy. In these subjects, the reasons for discontinuation of prior imatinib therapy were imatinib-intolerant in 32 (61.5%) subjects and imatinib-resistant/refractory in 20 (38.5%) subjects. In the primary cohort, 24 (85.7%) subjects were imatinib-intolerant and 4 (14.3%) subjects were imatinib-resistant/refractory.

In the exploratory cohort of third-line subjects, 9 (81.8%) subjects had received prior dasatinib therapy and 2 (18.2 %) subjects had received prior nilotinib therapy. The reasons for discontinuation of prior dasatinib/nilotinib therapy were dasatinib/nilotinib intolerant in 8 (72.7%) subjects and dasatinib/nilotinib resistant/refractory in 3 (27.3%) subjects.

Table 7. Demographic and Baseline Characteristics: All-Treated Population

Characteristic (n, %)	Treatment							
	Part 1 Second-Line 400 mg	Part 1 Second-Line 500 mg	Part 1 Second-Line 600 mg	Part 2 Primary Second-Line 500 mg	Part 2 Advanced Second-Line 500 mg	Total Second-Line	Part 2 Exploratory Third-Line 500 mg	Total
Age (years)								
N	7	7	3	28	7	52	11	63
Mean	42.14	53.57	51.00	53.86	66.57	53.79	51.18	53.33
SD	11.14	18.72	23.81	14.59	8.10	15.49	11.07	14.77
Minimum	31.00	20.00	24.00	26.00	55.00	20.00	34.00	20.00
Maximum	59.00	73.00	69.00	78.00	78.00	78.00	69.00	78.00
Median	41.00	62.00	60.00	56.50	66.00	58.00	49.00	55.00
Age category								
<65 years	7 (100)	4 (57.1)	2 (66.7)	20 (71.4)	3 (42.9)	36 (69.2)	9 (81.8)	45 (71.4)
≥65 years	0	3 (42.9)	1 (33.3)	8 (28.6)	4 (57.1)	16 (30.8)	2 (18.2)	18 (28.6)
Sex								
Female	3 (42.9)	2 (28.6)	2 (66.7)	12 (42.9)	1 (14.3)	20 (38.5)	4 (36.4)	24 (38.1)
Male	4 (57.1)	5 (71.4)	1 (33.3)	16 (57.1)	6 (85.7)	32 (61.5)	7 (63.6)	39 (61.9)
Race								
Japanese	7 (100)	7 (100)	3 (100)	28 (100)	7 (100)	52 (100)	11 (100)	63 (100)

N = number of subjects; n = number of subjects meeting criteria; SD = standard deviation.

Efficacy and Pharmacokinetic Results:

At 400 mg and at 500 mg bosutinib, 1 of 6 evaluable subjects each had a DLT (liver injury, Grade 3, and hepatic function abnormal, Grade 4, respectively). No DLTs were reported among 3 evaluable subjects at 600 mg bosutinib, and thus, safety of bosutinib up to 600 mg was confirmed (ie, primary endpoint of Part 1 was met).

Therefore, the starting dose of 500 mg bosutinib for Part 2 was assumed appropriate for the Japanese population under study.

Part 1: The percentage of participants with MCyR up to Week 24 is shown in Table 8. The cumulative MCyR rate up to Week 24 was 42.9% (95% CI: 9.9%, 81.6%), 57.1% (95% CI: 18.4%, 90.1%), and 33.3% (95% CI: 0.8%, 90.6%) in the subjects treated with 400 mg, 500 mg, and 600 mg, respectively. The maintained MCyR rate (numerator includes subjects without baseline response who were in response at Week 24 and subjects with baseline complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR) who had a post-baseline response either maintained or improved at Week 24) in the all treated population is summarized in Table 9.

Table 8. Major Cytogenetic Response Rate up to Week 24: All-Treated Population

Major Cytogenetic Response Rate, as: R/E (%) (95% CI)[a]	Treatment							
	Part 1 Second-Line 400 mg (N=7)	Part 1 Second-Line 500 mg (N=7)	Part 1 Second-Line 600 mg (N=3)	Part 2 Primary Second-Line 500 mg (N=28)	Part 2 Advanced Second-Line 500 mg (N=7)	Total Second-Line (N=52)	Part 2 Exploratory Third-Line 500 mg (N=11)	Total (N=63)
Number of subjects with CCyR at Baseline, n (%)[b]	0/7	0/7	1/3 (33.3)	10/28 (35.7)	0/7	11/52 (21.2)	6/11 (54.5)	17/63 (27.0)
Primary analysis								
Cumulative MCyR up to Week 24	3/7 (42.9) (9.9, 81.6)	4/7 (57.1) (18.4, 90.1)	1/3 (33.3) (0.8, 90.6)	10/28 (35.7) (18.6, 55.9)	3/7 (42.9) (9.9, 81.6)	21/52 (40.4) (27.0, 54.9)	2/11 (18.2) (2.3, 51.8)	23/63 (36.5) (24.7, 49.6)
Complete response	2/7 (28.6) (3.7, 71.0)	4/7 (57.1) (18.4, 90.1)	1/3 (33.3) (0.8, 90.6)	8/28 (28.6) (13.2, 48.7)	1/7 (14.3) (0.4, 57.9)	16/52 (30.8) (18.7, 45.1)	1/11 (9.1) (0.2, 41.3)	17/63 (27.0) (16.6, 39.7)
Partial response	1/7 (14.3) (0.4, 57.9)	0/7 (0.0, 41.0)	0/3 (0.0, 70.8)	2/28 (7.1) (0.9, 23.5)	2/7 (28.6) (3.7, 71.0)	5/52 (9.6) (3.2, 21.0)	1/11 (9.1) (0.2, 41.3)	6/63 (9.5) (3.6, 19.6)
MCyR at Week 24	3/7 (42.9) (9.9, 81.6)	3/7 (42.9) (9.9, 81.6)	1/3 (33.3) (0.8, 90.6)	10/28 (35.7) (18.6, 55.9)	1/7 (14.3) (0.4, 57.9)	18/52 (34.6) (22.0, 49.1)	2/11 (18.2) (2.3, 51.8)	20/63 (31.7) (20.6, 44.7)
Complete response	2/7 (28.6) (3.7, 71.0)	3/7 (42.9) (9.9, 81.6)	1/3 (33.3) (0.8, 90.6)	8/28 (28.6) (13.2, 48.7)	0/7 (0.0, 41.0)	14/52 (26.9) (15.6, 41.0)	1/11 (9.1) (0.2, 41.3)	15/63 (23.8) (14.0, 36.2)
Partial response	1/7 (14.3) (0.4, 57.9)	0/7 (0.0, 41.0)	0/3 (0.0, 70.8)	2/28 (7.1) (0.9, 23.5)	1/7 (14.3) (0.4, 57.9)	4/52 (7.7) (2.1, 18.5)	1/11 (9.1) (0.2, 41.3)	5/63 (7.9) (2.6, 17.6)
Sensitivity analysis								
Cumulative MCyR up to Week 24	3/7 (42.9) (9.9, 81.6)	4/7 (57.1) (18.4, 90.1)	1/2 (50.0) (1.3, 98.7)	10/18 (55.6) (30.8, 78.5)	3/7 (42.9) (9.9, 81.6)	21/41 (51.2) (35.1, 67.1)	2/5 (40.0) (5.3, 85.3)	23/46 (50.0) (34.9, 65.1)
Complete response	2/7 (28.6) (3.7, 71.0)	4/7 (57.1) (18.4, 90.1)	1/2 (50.0) (1.3, 98.7)	8/18 (44.4) (21.5, 69.2)	1/7 (14.3) (0.4, 57.9)	16/41 (39.0) (24.2, 55.5)	1/5 (20.0) (0.5, 71.6)	17/46 (37.0) (23.2, 52.5)
Partial response	1/7 (14.3) (0.4, 57.9)	0/7 (0.0, 41.0)	0/2 (0.0, 84.2)	2/18 (11.1) (1.4, 34.7)	2/7 (28.6) (3.7, 71.0)	5/41 (12.2) (4.1, 26.2)	1/5 (20.0) (0.5, 71.6)	6/46 (13.0) (4.9, 26.3)
MCyR at Week 24	3/7 (42.9) (9.9, 81.6)	3/7 (42.9) (9.9, 81.6)	1/2 (50.0) (1.3, 98.7)	10/18 (55.6) (30.8, 78.5)	1/7 (14.3) (0.4, 57.9)	18/41 (43.9) (28.5, 60.3)	2/5 (40.0) (5.3, 85.3)	20/46 (43.5) (28.9, 58.9)
Complete response	2/7 (28.6) (3.7, 71.0)	3/7 (42.9) (9.9, 81.6)	1/2 (50.0) (1.3, 98.7)	8/18 (44.4) (21.5, 69.2)	0/7 (0.0, 41.0)	14/41 (34.1) (20.1, 50.6)	1/5 (20.0) (0.5, 71.6)	15/46 (32.6) (19.5, 48.0)
Partial response	1/7 (14.3) (0.4, 57.9)	0/7 (0.0, 41.0)	0/2 (0.0, 84.2)	2/18 (11.1) (1.4, 34.7)	1/7 (14.3) (0.4, 57.9)	4/41 (9.8) (2.7, 23.1)	1/5 (20.0) (0.5, 71.6)	5/46 (10.9) (3.6, 23.6)

CCyR = complete cytogenetic response; CI = confidence interval; MCyR = major cytogenetic response (complete + partial); N = number of subjects; n = number of subjects meeting pre-specified criteria.

a. R - number of responders; E - number of evaluable subjects. Percentages (%) were based on number of evaluable subjects within each treatment group and

Table 8. Major Cytogenetic Response Rate up to Week 24: All-Treated Population

the corresponding 95% CIs were calculated by the exact method. The best response of post-baseline was selected for each evaluable subject.

b. For primary analysis, subjects with CCyR at Baseline were counted as non-responder and were included in the denominator. For sensitivity analysis, they were considered as non-evaluable subjects and were excluded from the denominator.

Table 9. Maintained Major Cytogenetic Response Rate: All-Treated Population

Maintained Major Cytogenetic Response Rate, as: R/E (%) (95% CI)[a]	Treatment							
	Part 1 Second-Line 400 mg (N=7)	Part 1 Second-Line 500 mg (N=7)	Part 1 Second-Line 600 mg (N=3)	Part 2 Primary Second-Line 500 mg (N=28)	Part 2 Advanced Second-Line 500 mg (N=7)	Total Second-Line (N=52)	Part 2 Exploratory Third-Line 500 mg (N=11)	Total (N=63)
Number of subjects with CCyR at Baseline, n (%)	0/7	0/7	1/3 (33.3)	10/28 (35.7)	0/7	11/52 (21.2)	6/11 (54.5)	17/63 (27.0)
Number of subjects with PCyR at Baseline, n (%)	1/7 (14.3)	3/7 (42.9)	1/3 (33.3)	3/28 (10.7)	1/7 (14.3)	9/52 (17.3)	1/11 (9.1)	10/63 (15.9)
Maintained MCyR at Week 24	3/7 (42.9)	3/7 (42.9)	3/3 (100)	18/28 (64.3)	1/7 (14.3)	28/52 (53.8)	7/11 (63.6)	35/63 (55.6)
	(9.9, 81.6)	(9.9, 81.6)	(29.2, 100)	(44.1, 81.4)	(0.4, 57.9)	(39.5, 67.8)	(30.8, 89.1)	(42.5, 68.1)
Complete response	2/7 (28.6)	3/7 (42.9)	2/3 (66.7)	16/28 (57.1)	0/7	23/52 (44.2)	6/11 (54.5)	29/63 (46.0)
	(3.7, 71.0)	(9.9, 81.6)	(9.4, 99.2)	(37.2, 75.5)	(0.0, 41.0)	(30.5, 58.7)	(23.4, 83.3)	(33.4, 59.1)
Partial response	1/7 (14.3)	0/7	1/3 (33.3)	2/28 (7.1)	1/7 (14.3)	5/52 (9.6)	1/11 (9.1)	6/63 (9.5)
	(0.4, 57.9)	(0.0, 41.0)	(0.8, 90.6)	(0.9, 23.5)	(0.4, 57.9)	(3.2, 21.0)	(0.2, 41.3)	(3.6, 19.6)

CCyR = complete cytogenetic response; CI = confidence interval; PCyR = partial cytogenetic response; MCyR = major cytogenetic response (complete + partial);N = number of subjects; n = number of subjects meeting pre-specified criteria.

a. R - number of responders; E - number of evaluable subjects. Percentages (%) were based on number of evaluable subjects within each treatment group and the corresponding 95% CIs were calculated by the exact method.

Part 2 – Primary Efficacy Endpoint Results: The MCyR results in the evaluable population were identical to that in the all-treated population as no subjects excluded from the all-treated population in Part 2. The per-protocol population was also identical to the all-treated population in the advanced cohort and the exploratory cohort.

In the primary cohort, CCyR was reported in 8 (28.6%) subjects and PCyR was reported in 2 (7.1%) subjects at Week 24. The cumulative MCyR rate up to Week 24 in the all-treated population was 35.7% (10/28 subjects, 95% CI: 18.6%, 55.9%). The MCyR rate at Week 24 and cumulative MCyR rate through the study were 35.7% and 46.4%, respectively.

Part 2 - Secondary Efficacy Endpoint Results:

Major Cytogenetic Response:

In the primary cohort, the time to MCyR in the all-treated population is summarized in Table 10. The median time to MCyR was 12.3 weeks. Note that the first post-baseline evaluation time point for MCyR was Week 12 in CP subjects.

The duration of MCyR in the all-treated population is summarized in Table 11. Of the 13 subjects who attained MCyR, 1 subject lost MCyR, therefore, the median duration of MCyR was not estimable.

The cumulative MCyR rate up to Week 24 in the all-treated population was 18.2% (2/11 subjects, 95% CI: 2.3%, 51.8%) (Table 8).

Table 10. Time to Major Cytogenetic Response: All-Treated Population - Responders Only

Time to MCyR	Treatment							
	Part 1 Second-Line 400 mg (N=7)	**Part 1 Second-Line 500 mg (N=7)**	**Part 1 Second-Line 600 mg (N=3)**	**Part 2 Primary Second-Line 500 mg (N=28)**	**Part 2 Advanced Second-Line 500 mg (N=7)**	**Total Second-Line (N=52)**	**Part 2 Exploratory Third-Line 500 mg (N=11)**	**Total (N=63)**
Number of subjects with MCyR, n (%)	4 (57.1)	4 (57.1)	2 (66.7)	13 (46.4)	3 (42.9)	26 (50.0)	2 (18.2)	28 (44.4)
Time to MCyR in weeks (95% CI)								
25% quartile	12.1 (NE)	7.9 (4.3, 12.0)	12.1 (12.1, 36.4)	12.0 (11.9, 12.3)	4.0 (4.0, 12.0)	12.0 (11.6, 12.1)	12.1 (12.1, 24.1)	12.0 (11.6, 12.1)
50% quartile (median)	12.1 (12.1, 48.3)	11.8 (4.3, 12.0)	24.3 (12.1, 36.4)	12.3 (12.0, 24.1)	5.0 (4.0, 12.0)	12.1 (12.0, 12.3)	18.1 (12.1, 24.1)	12.1 (12.0, 12.3)
75% quartile	30.2 (12.1, 48.3)	12.0 (11.6, 12.0)	36.4 (12.1, 36.4)	24.1 (12.3, 36.0)	12.0 (4.0, 12.0)	24.1 (12.1, 36.0)	24.1 (12.1, 24.1)	24.1 (12.1, 36.0)

CI = confidence interval; MCyR = major cytogenetic response; N = number of subjects; n = number of subjects meeting pre-specified criteria NE = not estimable.

Table 11. Duration of Major Cytogenetic Response: All-Treated Population - Responders Only

Duration of MCyR	Treatment							
	Part 1 Second-Line 400 mg (N=7)	**Part 1 Second-Line 500 mg (N=7)**	**Part 1 Second-Line 600 mg (N=3)**	**Part 2 Primary Second-Line 500 mg (N=28)**	**Part 2 Advanced Second-Line 500 mg (N=7)**	**Total Second-Line (N=52)**	**Part 2 Exploratory Third-Line 500 mg (N=11)**	**Total (N=63)**
Number of subjects with MCyR, n (%)	4 (57.1)	4 (57.1)	2 (66.7)	13 (46.4)	3 (42.9)	26 (50.0)	2 (18.2)	28 (44.4)
Number of subjects who lost MCyR[a]	0	0	0	1 (7.7)	2 (66.7)	3 (11.5)	0	3 (10.7)
Number of censored subjects	4 (100)	4 (100)	2 (100)	12 (92.3)	1 (33.3)	23 (88.5)	2 (100)	25 (89.3)
Duration of MCyR in weeks (95% CI)								
25% quartile	NE	NE	NE	NE (12.3, NE)	9.1 (9.1, 167.3)	NE (167.3, NE)	NE	NE (167.3, NE)
50% quartile (median)	NE	NE	NE	NE	88.2 (9.1, 167.3)	NE	NE	NE
75% quartile	NE	NE	NE	NE	167.3 (9.1, 167.3)	NE	NE	NE

CI = confidence interval; MCyR = major cytogenetic response; N = number of subjects; n = number of subjects meeting pre-specified criteria NE = not estimable.
a. Percentages (%) were based on number of subjects with MCyR within each treatment group.

Hematologic Response:

Confirmed complete hematologic response (cCHR) in the all-treated population is summarized in Table 12. In the advanced phase second-line cohort, there were no subjects who attained cCHR up to Week 24.

The time to cCHR in the all-treated population is summarized in Table 13. The median time to cCHR was 5.3 weeks in the primary cohort, 84.0 weeks in the advanced cohort, 4.7 weeks in the total second-line, 2.4 weeks (95% CI: 1.1%, 8.1%) in the third-line CP and 12.4 weeks (95% CI: not estimable [NE]) in the third-line AP/BP.

The duration of cCHR in the all-treated population is summarized in Table 14. Of the 22 subjects with cCHR in the primary cohort, 5 subjects lost cCHR. In the advanced cohort, 1 subject attained cCHR but lost cCHR. Of the 33 subjects with cCHR in the total second-line, 12 subjects lost cCHR. The median duration of cCHR was not estimable. Of the 9 subjects with cCHR in the third-line CP, 4 subjects lost cCHR.

In the exploratory cohort of third-line AP/BP subjects, 1 subject attained cCHR but lost cCHR. The median duration of cCHR in the third-line CP was NE. The duration of cCHR in the third-line AP/BP was 36.1 weeks (95%CI: NE).

The major/overall hematologic response results of the third-line AP/BP subject (up to Week 24) are presented in Table 15.

Table 12. Complete Hematologic Response Rate: All-Treated Population

Complete Hematologic Response Rate, as: R/E (%) (95% CI)[a]	Treatment								
	Part 1 Second-Line 400 mg (N=7)	Part 1 Second-Line 500 mg (N=7)	Part 1 Second-Line 600 mg (N=3)	Part 2 Primary Second-Line 500 mg (N=28)	Part 2 Advanced Second-Line 500 mg (N=7)	Total Second-Line (N=52)	Part 2 Third-Line CP 500 mg (N=10)	Part 2 Third-Line AP/BP 500 mg N=1	Total N=63
Cumulative cCHR up to Week 24	4/7 (57.1) (18.4, 90.1)	2/7 (28.6) (3.7, 71.0)	2/3 (66.7) (9.4, 99.2)	20/28 (71.4) (51.3, 86.8)	0/7 (0.0, 41.0)	28/52 (53.8) (39.5, 67.8)	8/10 (80.0) (44.4, 97.5)	1/1 (100) (2.5, 100)	37/63 (58.7) (45.6, 71.0)
cCHR at Week 24	3/7 (42.9) (9.9, 81.6)	2/7 (28.6) (3.7, 71.0)	2/3 (66.7) (9.4, 99.2)	16/28 (57.1) (37.2, 75.5)	0/7 (0.0, 41.0)	23/52 (44.2) (30.5, 58.7)	7/10 (70.0) (34.8, 93.3)	1/1 (100) (2.5, 100)	31/63 (49.2) (36.4, 62.1)

Subjects who had a CHR at Baseline were included in the denominator, and if the CHR was subsequently confirmed at post-baseline, the subject was counted as responder and contribute to the numerator.

AP = accelerated phase; BP = blast phase; CP = chronic phase; cCHR = confirmed complete hematologic response; CI = confidence interval; CP = chronic phase; N = number of subjects.

a. R - number of responders; E - number of evaluable subjects. Percentages (%) were based on number of evaluable subjects within each treatment group and the corresponding 95% CIs were calculated by the exact method.

Table 13. Time to Complete Hematologic Response : All-Treated Population - Responders Only

Time to Complete Hematologic Response	Treatment								
	Part 1 Second-Line 400 mg (N=7)	**Part 1 Second-Line 500 mg (N=7)**	**Part 1 Second-Line 600 mg (N=3)**	**Part 2 Primary Second-Line 500 mg (N=28)**	**Part 2 Advanced Second-Line 500 mg (N=7)**	**Total Second-Line (N=52)**	**Part 2 Third-Line CP 500 mg (N=10)**	**Part 2 Third-Line AP/BP 500 mg (N=1)**	**Total N=63**
Number of subjects with cCHR, n (%)	4 (57.1)	3 (42.9)	3 (100)	22 (78.6)	1 (14.3)	33 (63.5)	9 (90.0)	1 (100)	43 (68.3)
Time to cCHR in weeks (95% CI)									
25% quartile	1.1 (1.0, 2.1)	1.1 (1.1, 43.1)	1.1 (1.1, 66.1)	1.1 (1.0, 4.9)	84.0 (NE)	1.1 (1.1, 2.1)	1.1 (1.0, 8.1)	12.4 (NE)	1.1 (1.1, 2.1)
50% quartile (median)	1.6 (1.0, 4.4)	11.6 (1.1, 43.1)	1.1 (1.1, 66.1)	5.3 (2.0, 11.9)	84.0 (NE)	4.7 (2.0, 8.0)	2.4 (1.1, 8.1)	12.4 (NE)	4.7 (2.0, 8.1)
75% quartile	3.3 (1.1, 4.4)	43.1 (1.1, 43.1)	66.1 (1.1, 66.1)	12.1 (5.7, 16.0)	84.0 (NE)	12.1 (6.1, 35.9)	8.1 (2.1, 84.1)	12.4 (NE)	12.1 (7.9, 23.9)

AP = accelerated phase; BP = blast phase; cCHR = confirmed complete hematologic response; CI = confidence interval; CP = chronic phase; N = number of subjects; n = number of subjects meeting pre-specified criteria; NE = not estimable.

Table 14. Duration of Complete Hematologic Response: All-Treated Population - Responders Only

Duration of Complete Hematologic Response	Treatment								
	Part 1 Second-Line 400 mg (N=7)	**Part 1 Second-Line 500 mg (N=7)**	**Part 1 Second-Line 600 mg (N=3)**	**Part 2 Primary Second-Line 500 mg (N=28)**	**Part 2 Advanced Second-Line 500 mg (N=7)**	**Total Second-Line (N=52)**	**Part 2 Third-Line CP 500 mg (N=10)**	**Part 2 Third-Line AP/BP 500 mg (N=10)**	**Total N=63**
Number of subjects with cCHR, n (%)	4 (57.1)	3 (42.9)	3 (100)	22 (78.6)	1 (14.3)	33 (63.5)	9 (90.0)	1 (100)	43 (68.3)
Number of subjects who lost cCHR[a]	2 (50.0)	2 (66.7)	2 (66.7)	5 (22.7)	1 (100.0)	12 (36.4)	4 (44.4)	1 (100)	17 (39.5)
Number of censored subjects	2 (50.0)	1 (33.3)	1 (33.3)	17 (77.3)	0	21 (63.6)	5 (55.6)	0	26 (60.5)
Duration of cCHR in weeks (95% CI)									
25% quartile	57.0 (19.9, NE)	8.1 (8.1, NE)	55.1 (55.1, NE)	107.1 (52.1, NE)	95.3 (NE)	94.1 (52.1, NE)	28.1 (11.4, NE)	36.1 (NE)	55.1 (28.1, 100.9)
50% quartile (median)	NE (19.9, NE)	100.9 (8.1, NE)	59.1 (55.1, NE)	NE	95.3 (NE)	NE (96.1, NE)	NE (28.1, NE)	36.1 (NE)	NE (96.1, NE)
75% quartile	NE (94.1, NE)	NE (8.1, NE)	NE (55.1, NE)	NE	95.3 (NE)	NE	NE 36.6, NE)	36.1 (NE)	NE

AP = accelerated phase; BP = blast phase; cCHR = confirmed complete hematologic response; CI = confidence interval; CP = chronic phase; N = number of subjects; n = number of subjects meeting pre-specified criteria ; NE = not estimable.
a. Percentages (%) were based on number of subjects with CHR within each treatment group.

Table 15. Major/Overall Hematologic Response Rate: All-treated Population - Accelerated/Blast Phase CML Subjects Only

Major/Overall Hematologic Response Rate, R/E (%) (95% CI)[a]	Treatment
	Part 2 Third-line AP/BP 500 mg (N=1)
Cumulative cMHR up to Week 24	1/1 (100) (2.5, 100)
cMHR at Week 24	1/1 (100) (2.5, 100)
Cumulative cOHR up to Week 24	1/1 (100) (2.5, 100)
cOHR at Week 24	1/1 (100) (2.5, 100)

Confirmed MHR/OHR rate. Subjects who had a MHR/OHR at Baseline were included in the denominator, and if the MHR/OHR was subsequently confirmed at post-baseline, the subject was counted as responder and contribute to the numerator.
AP = accelerated phase; BP = blast phase; cMHR = confirmed major hematologic response; cOHR = confirmed overall hematologic response CI = confidence interval; MHR = major hematologic response; N = number of subjects; OHR = overall hematologic response.
a. R - number of responders; E - number of evaluable subjects. Percentages (%) were based on number of evaluable subjects within each treatment group and the corresponding 95% CIs were calculated by the exact method.

Time to Treatment Failure: The TTF was assessed as the secondary endpoint in all 3 cohorts and results are presented in Table 16.

In the primary cohort, treatment failure was reported in 14 (50%) subjects. The estimated probability of no treatment failure was 57.1% at Week 144. The median TTF was 253.9 weeks. In the advanced cohort, treatment failure was reported in 7 (100%) subjects. The estimated probability of no treatment failure was 14.3% at Week 144. The median TTF was 10.0 weeks.

In the total second-line, treatment failure was reported in 30 (57.7%) subjects. The median TTF was 139.7 weeks (95%CI: 39.7, NE). The estimated probability of no treatment failure was 50.0% at Week 144. In the exploratory third-line cohort, treatment failure was reported in 4 (36.4%) subjects. The estimated probability of no treatment failure was 63.6% at Week 144 (approximately 3 years).

Table 16. Time to Treatment Failure: All-Treated Population

TTF	Treatment							
	Part 1 Second-Line 400 mg (N=7)	**Part 1 Second-Line 500 mg (N=7)**	**Part 1 Second-Line 600 mg (N=3)**	**Part 2 Primary Second-Line 500 mg (N=28)**	**Part 2 Advanced Second-Line 500 mg (N=7)**	**Total Second-Line (N=52)**	**Part 2 Exploratory Third-Line 500 mg (N=11)**	**Total (N=63)**
Number of subjects with treatment failure, n (%)	4 (57.1)	4 (57.1)	1 (33.3)	14 (50.0)	7 (100)	30 (57.7)	4 (36.4)	34 (54.0)
Number of censored subjects, n (%)	3 (42.9)	3 (42.9)	2 (66.7)	14 (50.0)	0	22 (42.3)	7 (63.6)	29 (46.0)
TTF in weeks (95% CI)								
25% quartile	3.3 (2.1, NE)	3.3 (3.0, NE)	103.1 (103.1, NE)	29.9 (16.1, 166.6)	2.6 (1.1, 13.0)	19.1 (4.6, 39.7)	77.4 (14.1, NE)	22.0 (10.0,76.0)
50% quartile (median)	270.1 (3.3, NE)	88.1 (3.3, NE)	NE (103.1, NE)	253.9 (76.0, NE)	10.0 (2.6, 22.3)	139.7 (39.7, NE)	NE (77.4, NE)	179.1 (76.0, NE)
75% quartile	NE (68.3, NE)	NE (34.6, NE)	NE (103.1, NE)	NE (253.9, NE)	22.3 (4.6, 179.1)	NE	NE	NE
TTF rate[a] at Week 48, %	71.4 (38.0, 100)	57.1 (20.5, 93.8)	100 (100, 100)	67.9 (50.6, 85.2)	14.3 (0.0, 40.2)	61.5 (48.3, 74.8)	81.8 (59.0, 100)	65.1 (53.3, 76.9)
TTF rate[a] at Week 96, %	57.1 (20.5, 93.8)	42.9 (6.2, 79.5)	100 (100, 100)	60.7 (42.6, 78.8)	14.3 (0.0, 40.2)	53.8 (40.3, 67.4)	72.7 (46.4, 99.0)	57.1 (44.9, 69.4)
TTF rate at Week 144, %	57.1 (20.5, 93.8)	42.9 (6.2, 79.5)	66.7 (13.3, 100)	57.1 (38.8, 75.5)	14.3 (0.0, 40.2)	50.0 (36.4, 63.6)	63.6 (35.2, 92.1)	52.4 (40.0, 64.7)
TTF rate at Week 192, %	57.1 (20.5, 93.8)	42.9 (6.2, 79.5)	66.7 (13.3, 100)	53.6 (35.1, 72.0)	NE	46.2 (32.6, 59.7)	NE	48.4 (35.8, 60.9)
TTF rate at Week 240, %	57.1 (20.5, 93.8)	42.9 (6.2, 79.5)	66.7 (13.3, 100)	53.6 (35.1, 72.0)	NE	46.2 (32.6, 59.7)	NE	48.4 (35.8, 60.9)
TTF rate at Week 288, %	42.9 (6.2, 79.5)	42.9 (6.2, 79.5)	66.7 (13.3, 100)	45.9 (24.9, 67.0)	NE	39.9 (25.7, 54.2)	NE	41.8 (28.1, 55.6)
TTF rate at Week 336, %	42.9 (6.2, 79.5)	42.9 (6.2, 79.5)	NE	NE	NE	39.9 (25.7, 54.2)	NE	41.8 (28.1, 55.6)

CI = confidence interval; N = number of subjects; n = number of subjects meeting pre-specified criteria; NE = not estimable; TTF = time to treatment failure.
a. TTF rate indicates the probability of no treatment failure.

Progression Free Survival: The PFS was assessed as a secondary endpoint in all cohorts. The PFS in the all-treated population is summarized in Table 17.

In the primary cohort, disease progression or death was reported in 1 (3.6%) subject. The estimated PFS rate was 94.4% at Week 144. The median time to PFS was NE. In the advanced cohort, disease progression or death was reported in 6 (85.7%) subjects. The estimated PFS rate was 21.4% at Week 144. The median time to PFS was 13.0 weeks.

In the total second-line, PFS events were reported in 9 (17.3%) subjects. The estimated PFS rate was 81.8% (95% CI: 70.1%, 93.5%) at Week 144. The median PFS was NE.

In the exploratory cohort of third-line, PFS events were reported in 1 subject (9.1%). The estimated PFS rate was 88.9% (95% CI: 68.4%, 100%) at Week 144. The median PFS was NE.

Table 17. Progression-Free Survival: All-Treated Population

PFS	Treatment							
	Part 1 Second-Line 400 mg (N=7)	Part 1 Second-Line 500 mg (N=7)	Part 1 Second-Line 600 mg (N=3)	Part 2 Primary Second-Line 500 mg (N=28)	Part 2 Advanced Second-Line 500 mg (N=7)	Total Second-Line (N=52)	Part 2 Exploratory Third-Line 500 mg (N=11)	Total (N=63)
Number of subjects with progression or who died, n (%)	1 (14.3)	1 (14.3)	0	1 (3.6)	6 (85.7)	9 (17.3)	1 (9.1)	10 (15.9)
Number of censored subjects, n (%)	6 (85.7)	6 (85.7)	3 (100)	27 (96.4)	1 (14.3)	43 (82.7)	10 (90.9)	53 (84.1)
PFS in weeks (95% CI)								
25% quartile	NE (2.1, NE)	NE (88.1, NE)	NE	NE	2.6 (1.1, 24.0)	NE (88.1, NE)	NE (77.4, NE)	NE (95.1, NE)
50% quartile (median)	NE	NE (88.1, NE)	NE	NE	13.0 (2.6, 179.1)	NE	NE	NE
75% quartile	NE	NE	NE	NE	24.0 (4.6, 179.1)	NE	NE	NE
PFS rate at Week 48, %	85.7 (59.8, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)	21.4 (0.0, 56.3)	87.6 (78.3, 96.9)	100 (100, 100)	89.8 (82.0, 97.6)
PFS rate at Week 96, %	85.7 (59.8, 100)	75.0 (32.6, 100)	100 (100, 100)	94.4 (83.9, 100)	21.4 (0.0, 56.3)	81.8 (70.1, 93.5)	88.9 (68.4, 100)	82.9 (72.6, 93.3)
PFS rate at Week 144, %	85.7 (59.8, 100)	75.0 (32.6, 100)	100 (100, 100)	94.4 (83.9, 100)	21.4 (0.0, 56.3)	81.8 (70.1, 93.5)	88.9 (68.4, 100)	82.9 (72.6, 93.3)
PFS rate at Week 192, %	85.7 (59.8, 100)	75.0 (32.6, 100)	100 (100, 100)	94.4 (83.9, 100)	NE	78.5 (65.6, 91.4)	NE	79.6 (67.8, 91.4)
PFS rate at Week 240, %	85.7 (59.8, 100)	75.0 (32.6, 100)	100 (100, 100)	94.4 (83.9, 100)	NE	78.5 (65.6, 91.4)	NE	79.6 (67.8, 91.4)
PFS rate at Week 288, %	85.7 (59.8, 100)	75.0 (32.6, 100)	100 (100, 100)	94.4 (83.9, 100)	NE	78.5 (65.6, 91.4)	NE	79.6 (67.8, 91.4)
PFS rate at Week 336, %	85.7 (59.8, 100)	75.0 (32.6, 100)	NE	NE	NE	78.5 (65.6, 91.4)	NE	79.6 (67.8, 91.4)

The determination of disease progression was based on the Investigator's assessment.
CI = confidence interval; N = number of subjects; n = number of subjects meeting pre-specified criteria; NE = not estimable; PFS = progression free survival.

Overall Survival: OS was assessed as a secondary endpoint in all cohorts. The OS in the all-treated population is summarized in Table 18. In the primary cohort, death was reported in 2 (7.1%) subject. The estimated OS rate was 96.4% at Week 144. In the advanced cohort, death was reported in 5 (71.4%) subjects. The estimated OS rate was 28.6% at Week 144. In the total second-line, death was reported in 7 (13.5%) subjects. The estimated OS rate was 87.6% (95% CI: 78.3%, 96.9%) at Week 144.

There was no death in the exploratory cohort of third-line subjects. The estimated OS rate at Week 144 was 100%.

Table 18. Overall Survival: All-Treated Population

OS	Treatment							
	Part 1 Second-Line 400 mg (N=7)	**Part 1 Second-Line 500 mg (N=7)**	**Part 1 Second-Line 600 mg (N=3)**	**Part 2 Primary Second-Line 500 mg (N=28)**	**Part 2 Advanced Second-Line 500 mg (N=7)**	**Total Second-Line (N=52)**	**Part 2 Exploratory Third-Line 500 mg (N=11)**	**Total (N=63)**
Number of deaths, n (%)	0	0	0	2 (7.1)	5 (71.4)	7 (13.5)	0	7 (11.1)
Number of censored subjects, n (%)	7 (100)	7 (100)	3 (100)	26 (92.9)	2 (28.6)	45 (86.5)	11 (100)	56 (88.9)
OS in weeks (95% CI)								
25% quartile	NE	NE	NE	NE (253.9, NE)	21.4 (17.3, 106.0)	NE (253.9, NE)	NE	NE (253.9, NE)
50% quartile (Median)	NE	NE	NE	NE	25.1 (21.4, NE)	NE	NE	NE
75% quartile	NE	NE	NE	NE	NE (23.7, NE)	NE	NE	NE
OS rate at Week 48, %	100 (100, 100)	100 (100, 100)	100 (100, 100)	96.4 (89.6, 100)	42.9 (6.2, 79.5)	90.0 (81.7, 98.3)	100 (100, 100)	91.8 (84.9, 98.7)
OS rate at Week 96, %	100 (100, 100)	100 (100, 100)	100 (100, 100)	96.4 (89.6, 100)	42.9 (6.2, 79.5)	90.0 (81.7, 98.3)	100 (100, 100)	91.8 (84.9, 98.7)
OS rate at Week 144, %	100 (100, 100)	100 (100, 100)	100 (100, 100)	96.4 (89.6, 100)	28.6 (0.0, 62.0)	87.6 (78.3, 96.9)	100 (100, 100)	89.9 (82.2, 97.6)
OS rate at Week 192, %	100 (100, 100)	100 (100, 100)	100 (100, 100)	96.4 (89.6, 100)	NE	87.6 (78.3, 96.9)	NE	89.9 (82.2, 97.6)
OS rate at Week 240, %	100 (100, 100)	100 (100, 100)	100 (100, 100)	96.4 (89.6, 100)	NE	87.6 (78.3, 96.9)	NE	89.9 (82.2, 97.6)
OS rate at Week 288, %	100 (100, 100)	100 (100, 100)	100 (100, 100)	82.7 (57.0, 100)	NE	82.2 (68.6, 95.7)	NE	84.3 (71.4, 97.1)
OS rate at Week 336, %	100 (100, 100)	100 (100, 100)	NE	NE	NE	82.2 (68.6, 95.7)	NE	84.3 (71.4, 97.1)

CI = confidence interval; N = number of subjects; n = number of subjects meeting pre-specified criteria; NE = not estimable; OS = overall survival.

Part 1 - Primary Pharmacokinetics Endpoints Results: PK analysis (Part 1) was conducted as of the interim data release on 13 July 2011. Plasma samples were available for non-compartmental analysis from 17 subjects receiving oral bosutinib doses of 400 mg, 500 mg, and 600 mg from Part 1. The plasma concentrations from 1 subject on Day 8 and 1 subject on Day 15 were excluded from the summary of concentrations and the plasma concentrations from 5 subjects on Day 15 were not obtained due to temporarily dose discontinuations. These subjects were excluded from PK analysis. Individual and mean plasma concentrations time of bosutinib after single ascending oral doses of bosutinib, once-daily ascending oral doses of bosutinib on Day 8, or once-daily ascending oral doses of bosutinib on Day 15.

The PK analyses indicated that after single or multiple doses of 400 mg, 500 mg, or 600 mg of bosutinib, absorption was relatively slow, with a median T_{max} of approximately 4 hours.

PK results for bosutinib are summarized after single oral doses of 400 mg, 500 mg, and 600 mg on Day 1 in Table 19 and for bosutinib 400 mg, 500 mg, and 600 mg after once-daily dosing on Day 15 are presented in Table 20. On Day 1, following single doses of bosutinib 400 mg, 500 mg, and 600 mg, the mean C_{max} of bosutinib were 131 ng/mL (CV =23%), 128 ng/mL (CV =18%), and 155 ng/mL (CV =29%), respectively. The corresponding steady state mean C_{max} on Day 15 were 129 ng/mL (CV =19%), 226 ng/mL (CV =22%), and 214 ng/mL (CV was not calculated) for the 400 mg, 500 mg, and 600 mg, respectively. After a single oral dose of bosutinib on Day 1, mean AUC were 2474 ng•h/mL (CV =20%), 2720 ng•h/mL (CV =21%) and 2760 ng•h/mL (CV =23%) after the 400 mg, 500 mg, and 600 mg, respectively. The corresponding steady state mean AUC (AUC_{ss}) were 2235 ng•h/mL (CV =10%), 3690 ng•h/mL (CV =26%), and 3371 ng•h/mL (CV was not calculated), respectively. Multiple dose exposure was 1.67 to 2.46-fold higher than single dose exposure (mean accumulation ratio, R = AUC_{ss} on Day 15/area under the concentration-time curve from 0 to 24 hours [AUC_{24}] on Day 1) at doses of 400 mg, 500 mg, and 600 mg.

V_z/F was large with mean values ranged from 4035 L to 5707 L, and the CV was 16% to 38%. CL/F ranged from 167 L/h to 224 L/h (CV =20% to 21%). Mean $t_{½}$ after a single dose on Day 1 was 17 hours. These values should be taken with caution because the blood samples were collected for 48 hours and $t_{½}$, V_z/F and CL/F results are likely to change if assessed for blood samples collected over a longer period.

After a single dose and multiple oral daily doses, bosutinib exposure generally increased with increasing dose. However, C_{max} and AUC at the 500 mg, and 600 mg doses were not well separated. This was likely due to high variability and small number of subjects.

Table 19. Pharmacokinetic Parameters of Bosutinib After Once - Daily Ascending Oral Doses of Bosutinib to Subjects With Leukemia on Day 1

Parameters (Mean ± SD)	Bosutinib 400 mg	Bosutinib 500 mg	Bosutinib 600 mg
N	7	7	3
C_{max} (ng/mL)	131±29.7	128±23.1	155±44.4
T_{max} (h)[a]	4.00 (3.97-7.90)	3.95 (3.00-5.98)	3.98 (3.97-4.03)
$t_{½}$ (h)	16.82±2.37	16.90±2.47	17.27±3.64
AUC_{24} (ng•h/mL)	1503±309.7	1617±262.0	1692±563.7
AUC_t (ng•h/mL)	2091±406.1	2283±429.9	2347±651.7
AUC (ng•h/mL)	2474±482.7	2720±560.4	2760±625.9
CL/F (L/h)	167±34.6	190±37.8	224±45.7
V_z/F (L)	4035±879.8	4570±713.8	5707±2187

AUC_{24} = area under the concentration-time curve from 0 to 24 hours; AUC_t = area under the concentration-time curve to the last observable concentration at time t; AUC = area under the concentration-time curve from 0 to infinite time; CL/F = apparent oral dose clearance; C_{max}= maximum concentration; N = total population; SD = standard deviation; T_{max} = time of maximum concentration; $t_{½}$ = terminal elimination half-life; V_z/F = apparent volume of distribution.
a. Median (minimum - maximum).

Table 20. Pharmacokinetic Parameters of Bosutinib After Once - Daily Ascending Oral Doses of Bosutinib to Subjects With Leukemia on Day 15

Parameters (Mean ± SD)	Bosutinib 400 mg	Bosutinib 500 mg	Bosutinib 600 mg
N	5	4	2
C_{max} (ng/mL)	129±24.4	226±49.5	214
T_{max} (h)[a]	4.03 (3.92 - 8.00)	3.95 (3.93 - 7.98)	4.00 (3.98 - 4.02)
AUC_{ss} (ng•h/mL)	2235±220.1	3690±962.1	3371
CL_{ss}/F (L/h)	180±17.4	144±41.8	179
R	1.67±0.369	2.16±0.556	2.46

AUC_{24} = area under the concentration time curve from 0 to 24 hours; AUCss = area under the concentration-time curve within the dosage interval at steady state; CL_{ss}/F = apparent oral dose clearance at steady state; C_{max}= maximum concentration; R = accumulation ratio (AUC_{ss} on Day 15/AUC_{24} on Day 1); SD = standard deviation; T_{max} = time of maximum concentration.
a. Median (minimum - maximum).

Safety Results:

Part 1 – Primary Endpoint Results:

Dose-Limiting Toxicity: The occurrence of DLT was assessed during the first 28 days of treatment. Subjects had to take at least 18 of 27 planned doses (66%, omitting a dose on Day 2) to be evaluable.

In Part 1, 1 of 6 evaluable subjects had a DLT (liver injury, Grade 3) at 400 mg, and 1 of 6 evaluable subjects had a DLT (hepatic function abnormal, Grade 4) at 500 mg both were considered related to study treatment. No DLTs were reported among 3 evaluable subjects at 600 mg. Thus, safety of bosutinib up to 600 mg was confirmed and bosutinib 500 mg as the starting dose for part 2 of a previous open-label, continuous daily dosing, two-part safety and

efficacy study (A Phase 1/2 Study of SKI-606 in Philadelphia Chromosome Positive Leukemias [NCT00261846]) was assumed to be appropriate in Japanese subjects as the starting dose for Part 2.

Serious Adverse Events: Table 21 provides the incidence of all-causality serious adverse events (SAEs) by system organ class and preferred term. SAEs were reported in 21 (33.3%) subjects in total; 19 (36.5%) subjects in the total second-line subjects and 2 (18.2%) subjects in the third-line subjects. The treatment-related SAEs were reported in 14 (26.9%) subjects in the total second-line subjects as presented in Table 22. No drug related SAEs were reported in the third-line subjects.

Table 21. Number (%) of Subjects Reporting Serious Adverse Events : Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Any adverse event	2 (28.6)	3 (42.9)	1 (33.3)	10 (35.7)	3 (42.9)	19 (36.5)	2 (18.2)	21 (33.3)
Blood and lymphatic system disorders	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Thrombocytopenia	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Cardiac disorders	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Acute myocardial infarction	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Eye disorders	0	0	0	2 (7.1)	0	2 (3.8)	1 (9.1)	3 (4.8)
Cataract	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Macular fibrosis	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Macular hole	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Gastrointestinal disorders	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Diarrhoea	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Vomiting	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
General disorders and administration site conditions	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Fatigue	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Hepatobiliary disorders	1 (14.3)	1 (14.3)	0	0	0	2 (3.8)	0	2 (3.2)
Hepatic function abnormal	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Liver injury	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Infections and infestations	1 (14.3)	0	0	4 (14.3)	0	5 (9.6)	1 (9.1)	6 (9.5)
Diverticulitis	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Enterocolitis infectious	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Gastroenteritis	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Pertussis	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Pneumonia pneumococcal	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Urinary tract infection	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Injury, poisoning and procedural complications	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Spinal compression fracture	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)

Table 21. Number (%) of Subjects Reporting Serious Adverse Events : Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Musculoskeletal and connective tissue disorders	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Osteonecrosis	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	1 (3.6)	1 (14.3)	2 (3.8)	0	2 (3.2)
Bladder cancer	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Bladder neoplasm	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Blast cell crisis	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Nervous system disorders	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Cerebral haemorrhage	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Posterior reversible encephalopathy syndrome	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Psychiatric disorders	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Completed suicide	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Renal and urinary disorders	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Renal impairment	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Respiratory, thoracic and mediastinal disorders	0	2 (28.6)	0	2 (7.1)	1 (14.3)	5 (9.6)	0	5 (7.9)
Alveolitis allergic	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Dyspnoea	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Pleural effusion	0	1 (14.3)	0	0	1 (14.3)	2 (3.8)	0	2 (3.2)
Pleurisy	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Skin and subcutaneous tissue disorders	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Drug eruption	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Rash	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)

Table 21. Number (%) of Subjects Reporting Serious Adverse Events : Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63

Classifications of serious adverse events are based on the Medical Dictionary for Regulatory Activities.
N = number of subjects.

a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different adverse events within the higher level category.

Table 22. Number (%) of Subjects Reporting Drug Related Serious Adverse Events : Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Any adverse event	1 (14.3)	3 (42.9)	0	8 (28.6)	2 (28.6)	14 (26.9)	0	14 (22.2)
Blood and lymphatic system disorders	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Thrombocytopenia	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Gastrointestinal disorders	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Diarrhoea	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Vomiting	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
General disorders and administration site conditions	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Fatigue	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Hepatobiliary disorders	1 (14.3)	1 (14.3)	0	0	0	2 (3.8)	0	2 (3.2)
Hepatic function abnormal	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Liver injury	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Infections and infestations	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Pertussis	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Musculoskeletal and connective tissue disorders	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Osteonecrosis	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Bladder cancer	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Bladder neoplasm	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Nervous system disorders	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Cerebral haemorrhage	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Posterior reversible encephalopathy syndrome	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Renal and urinary disorders	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Renal impairment	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)

Table 22. Number (%) of Subjects Reporting Drug Related Serious Adverse Events : Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Respiratory, thoracic and mediastinal disorders	0	2 (28.6)	0	0	1 (14.3)	3 (5.8)	0	3 (4.8)
Alveolitis allergic	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Pleural effusion	0	1 (14.3)	0	0	1 (14.3)	2 (3.8)	0	2 (3.2)
Skin and subcutaneous tissue disorders	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Drug eruption	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Rash	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities.
N = number of subjects.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different adverse events within the higher level category.

Adverse Events: Table 23 and Table 24 provide the incidence of all-causality and treatment-related, treatment-emergent AEs by system organ class and preferred term in ≥5% subjects in any of the cohorts.

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Any adverse event	7 (100)	7 (100)	3 (100)	28 (100)	7 (100)	52 (100)	11 (100)	63 (100)
Blood and lymphatic system disorders	4 (57.1)	4 (57.1)	2 (66.7)	17 (60.7)	4 (57.1)	31 (59.6)	6 (54.5)	37 (58.7)
Anaemia	1 (14.3)	1 (14.3)	0	7 (25.0)	4 (57.1)	13 (25.0)	0	13 (20.6)
Eosinophilia	0	0	0	3 (10.7)	0	3 (5.8)	1 (9.1)	4 (6.3)
Iron deficiency anaemia	0	0	0	3 (10.7)	0	3 (5.8)	0	3 (4.8)
Leukopenia	1 (14.3)	2 (28.6)	0	5 (17.9)	3 (42.9)	11 (21.2)	2 (18.2)	13 (20.6)
Lymphopenia	2 (28.6)	2 (28.6)	2 (66.7)	11 (39.3)	2 (28.6)	19 (36.5)	5 (45.5)	24 (38.1)
Neutropenia	2 (28.6)	2 (28.6)	1 (33.3)	4 (14.3)	3 (42.9)	12 (23.1)	2 (18.2)	14 (22.2)
Thrombocytopenia	2 (28.6)	3 (42.9)	1 (33.3)	8 (28.6)	3 (42.9)	17 (32.7)	2 (18.2)	19 (30.2)
Cardiac disorders	0	2 (28.6)	0	4 (14.3)	0	6 (11.5)	1 (9.1)	7 (11.1)
Acute myocardial infarction	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Pericardial effusion	0	1 (14.3)	0	3 (10.7)	0	4 (7.7)	0	4 (6.3)
Ventricular extrasystoles	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Congenital, familial and genetic disorders	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Hydrocele	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Ear and labyrinth disorders	2 (28.6)	0	0	2 (7.1)	1 (14.3)	5 (9.6)	0	5 (7.9)
Deafness	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Vertigo	2 (28.6)	0	0	0	0	2 (3.8)	0	2 (3.2)
Eye disorders	2 (28.6)	2 (28.6)	0	10 (35.7)	3 (42.9)	17 (32.7)	1 (9.1)	18 (28.6)
Cataract	0	1 (14.3)	0	2 (7.1)	0	3 (5.8)	1 (9.1)	4 (6.3)
Conjunctival haemorrhage	0	1 (14.3)	0	1 (3.6)	1 (14.3)	3 (5.8)	0	3 (4.8)
Conjunctival hyperaemia	1 (14.3)	0	0	0	1 (14.3)	2 (3.8)	0	2 (3.2)
Conjunctivitis allergic	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Dry eye	1 (14.3)	0	0	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Ocular hyperaemia	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Papilloedema	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Vision blurred	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Gastrointestinal disorders	7 (100)	7 (100)	3 (100)	27 (96.4)	7 (100)	51 (98.1)	11 (100)	62 (98.4)
Abdominal discomfort	1 (14.3)	0	0	2 (7.1)	0	3 (5.8)	0	3 (4.8)
Abdominal distension	0	1 (14.3)	2 (66.7)	3 (10.7)	1 (14.3)	7 (13.5)	0	7 (11.1)
Abdominal pain	1 (14.3)	0	1 (33.3)	0	0	2 (3.8)	1 (9.1)	3 (4.8)
Abdominal pain upper	1 (14.3)	1 (14.3)	0	5 (17.9)	0	7 (13.5)	2 (18.2)	9 (14.3)
Anal fissure	0	1 (14.3)	0	0	1 (14.3)	2 (3.8)	0	2 (3.2)
Cheilitis	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Chronic gastritis	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Constipation	0	2 (28.6)	0	3 (10.7)	2 (28.6)	7 (13.5)	0	7 (11.1)
Dental caries	3 (42.9)	2 (28.6)	0	4 (14.3)	0	9 (17.3)	2 (18.2)	11 (17.5)
Diarrhoea	7 (100)	7 (100)	3 (100)	26 (92.9)	7 (100)	50 (96.2)	10 (90.9)	60 (95.2)
Dry mouth	0	0	1 (33.3)	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Dyspepsia	0	1 (14.3)	0	1 (3.6)	1 (14.3)	3 (5.8)	2 (18.2)	5 (7.9)
Enterocolitis	0	0	0	2 (7.1)	1 (14.3)	3 (5.8)	0	3 (4.8)
Gastric polyps	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Gastritis	1 (14.3)	0	0	6 (21.4)	0	7 (13.5)	0	7 (11.1)
Gastritis erosive	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Gastrooesophageal reflux disease	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Gingival swelling	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Haemorrhoids	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Leukoplakia oral	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Nausea	2 (28.6)	3 (42.9)	1 (33.3)	12 (42.9)	1 (14.3)	19 (36.5)	5 (45.5)	24 (38.1)
Oesophagitis	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Pancreatitis	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Pancreatitis acute	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Periodontal disease	1 (14.3)	0	0	2 (7.1)	0	3 (5.8)	0	3 (4.8)
Proctalgia	0	0	0	3 (10.7)	1 (14.3)	4 (7.7)	0	4 (6.3)
Stomatitis	1 (14.3)	3 (42.9)	1 (33.3)	5 (17.9)	1 (14.3)	11 (21.2)	1 (9.1)	12 (19.0)

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Toothache	0	1 (14.3)	0	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Vomiting	1 (14.3)	2 (28.6)	3 (100)	14 (50.0)	3 (42.9)	23 (44.2)	1 (9.1)	24 (38.1)
General disorders and administration site conditions	4 (57.1)	3 (42.9)	3 (100)	14 (50.0)	2 (28.6)	26 (50.0)	3 (27.3)	29 (46.0)
Chest discomfort	0	0	2 (66.7)	0	1 (14.3)	3 (5.8)	0	3 (4.8)
Chills	0	0	1 (33.3)	0	0	1 (1.9)	1 (9.1)	2 (3.2)
Fatigue	1 (14.3)	1 (14.3)	1 (33.3)	4 (14.3)	0	7 (13.5)	1 (9.1)	8 (12.7)
Injection site reaction	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Malaise	1 (14.3)	0	0	2 (7.1)	0	3 (5.8)	1 (9.1)	4 (6.3)
Oedema peripheral	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Peripheral swelling	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Pyrexia	1 (14.3)	2 (28.6)	1 (33.3)	7 (25.0)	1 (14.3)	12 (23.1)	0	12 (19.0)
Hepatobiliary disorders	2 (28.6)	2 (28.6)	2 (66.7)	6 (21.4)	0	12 (23.1)	3 (27.3)	15 (23.8)
Hepatic function abnormal	0	2 (28.6)	2 (66.7)	4 (14.3)	0	8 (15.4)	2 (18.2)	10 (15.9)
Hepatotoxicity	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Liver disorder	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Liver injury	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Immune system disorders	0	0	1 (33.3)	2 (7.1)	0	3 (5.8)	0	3 (4.8)
Seasonal allergy	0	0	1 (33.3)	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Infections and infestations	5 (71.4)	6 (85.7)	3 (100)	23 (82.1)	2 (28.6)	39 (75.0)	9 (81.8)	48 (76.2)
Bronchitis	1 (14.3)	1 (14.3)	0	2 (7.1)	0	4 (7.7)	0	4 (6.3)
Carbuncle	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Cellulitis	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Conjunctivitis	0	0	0	2 (7.1)	1 (14.3)	3 (5.8)	1 (9.1)	4 (6.3)
Cystitis	0	0	1 (33.3)	2 (7.1)	0	3 (5.8)	1 (9.1)	4 (6.3)
Diarrhoea infectious	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Enterocolitis bacterial	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Enterocolitis infectious	1 (14.3)	0	0	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Enterocolitis viral	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Epididymitis	0	1 (14.3)	0	0	0	1 (1.9)	1 (9.1)	2 (3.2)
Folliculitis	1 (14.3)	0	0	2 (7.1)	0	3 (5.8)	0	3 (4.8)
Gastroenteritis	1 (14.3)	1 (14.3)	1 (33.3)	5 (17.9)	0	8 (15.4)	1 (9.1)	9 (14.3)
Gastroenteritis viral	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Gingivitis	1 (14.3)	2 (28.6)	1 (33.3)	1 (3.6)	1 (14.3)	6 (11.5)	1 (9.1)	7 (11.1)
Herpes zoster	0	1 (14.3)	0	2 (7.1)	0	3 (5.8)	0	3 (4.8)
Influenza	1 (14.3)	1 (14.3)	0	3 (10.7)	0	5 (9.6)	0	5 (7.9)
Nasopharyngitis	4 (57.1)	5 (71.4)	3 (100.0)	18 (64.3)	0	30 (57.7)	6 (54.5)	36 (57.1)
Otitis media	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Periodontitis	0	0	0	3 (10.7)	0	3 (5.8)	0	3 (4.8)
Pharyngitis	1 (14.3)	0	0	3 (10.7)	1 (14.3)	5 (9.6)	0	5 (7.9)
Pulpitis dental	1 (14.3)	1 (14.3)	0	0	0	2 (3.8)	0	2 (3.2)
Respiratory tract infection	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Skin infection	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Tinea versicolour	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Tonsillitis	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Upper respiratory tract infection	1 (14.3)	0	0	0	0	1 (1.9)	1 (9.1)	2 (3.2)
Urinary tract infection	1 (14.3)	0	0	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Injury, poisoning and procedural complications	2 (28.6)	0	2 (66.7)	7 (25.0)	1 (14.3)	12 (23.1)	2 (18.2)	14 (22.2)
Allergic transfusion reaction	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Arthropod sting	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Contusion	1 (14.3)	0	0	2 (7.1)	0	3 (5.8)	0	3 (4.8)
Foot fracture	0	0	2 (66.7)	0	0	2 (3.8)	0	2 (3.2)
Ligament injury	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Meniscus injury	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Post-traumatic neck syndrome	0	0	0	0	0	0	1 (9.1)	1 (1.6)

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Rib fracture	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Spinal compression fracture	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Tendon injury	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Thermal burn	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Investigations	5 (71.4)	6 (85.7)	2 (66.7)	23 (82.1)	4 (57.1)	40 (76.9)	7 (63.6)	47 (74.6)
Alanine aminotransferase increased	3 (42.9)	4 (57.1)	0	13 (46.4)	0	20 (38.5)	4 (36.4)	24 (38.1)
Amylase decreased	0	1 (14.3)	1 (33.3)	0	0	2 (3.8)	0	2 (3.2)
Amylase increased	0	0	0	5 (17.9)	1 (14.3)	6 (11.5)	1 (9.1)	7 (11.1)
Aspartate aminotransferase increased	4 (57.1)	2 (28.6)	0	9 (32.1)	0	15 (28.8)	4 (36.4)	19 (30.2)
Blood albumin decreased	0	1 (14.3)	1 (33.3)	2 (7.1)	0	4 (7.7)	0	4 (6.3)
Blood albumin increased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Blood alkaline phosphatase increased	0	2 (28.6)	0	7 (25.0)	0	9 (17.3)	2 (18.2)	11 (17.5)
Blood bilirubin increased	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Blood calcium decreased	0	1 (14.3)	1 (33.3)	0	0	2 (3.8)	0	2 (3.2)
Blood calcium increased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Blood chloride decreased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Blood cholinesterase decreased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Blood creatine phosphokinase decreased	0	2 (28.6)	1 (33.3)	0	0	3 (5.8)	0	3 (4.8)
Blood creatine phosphokinase increased	1 (14.3)	1 (14.3)	0	4 (14.3)	0	6 (11.5)	2 (18.2)	8 (12.7)
Blood creatinine increased	1 (14.3)	2 (28.6)	2 (66.7)	2 (7.1)	1 (14.3)	8 (15.4)	0	8 (12.7)
Blood fibrinogen increased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Blood lactate dehydrogenase increased	1 (14.3)	0	1 (33.3)	2 (7.1)	0	4 (7.7)	2 (18.2)	6 (9.5)

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Blood potassium decreased	0	1 (14.3)	1 (33.3)	0	0	2 (3.8)	0	2 (3.2)
Blood potassium increased	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Blood sodium decreased	0	2 (28.6)	1 (33.3)	0	0	3 (5.8)	0	3 (4.8)
Blood urea increased	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Blood uric acid increased	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Blood urine present	0	1 (14.3)	1 (33.3)	0	0	2 (3.8)	0	2 (3.2)
C-reactive protein increased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Electrocardiogram QT prolonged	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Gamma-glutamyltransferase increased	1 (14.3)	2 (28.6)	0	6 (21.4)	0	9 (17.3)	1 (9.1)	10 (15.9)
Glucose urine present	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Haemoglobin decreased	0	3 (42.9)	1 (33.3)	2 (7.1)	0	6 (11.5)	0	6 (9.5)
International normalised ratio decreased	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
International normalised ratio increased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Lipase increased	0	2 (28.6)	0	8 (28.6)	1 (14.3)	11 (21.2)	4 (36.4)	15 (23.8)
Liver function test abnormal	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Lymphocyte count decreased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Neutrophil count decreased	0	1 (14.3)	0	1 (3.6)	0	2 (3.8)	1 (9.1)	3 (4.8)
Platelet count decreased	0	1 (14.3)	0	2 (7.1)	0	3 (5.8)	0	3 (4.8)
Protein total decreased	0	1 (14.3)	1 (33.3)	0	0	2 (3.8)	0	2 (3.2)
Protein urine present	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Prothrombin time prolonged	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Prothrombin time shortened	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Renal function test abnormal	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Specific gravity urine abnormal	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Weight decreased	0	0	1 (33.3)	6 (21.4)	2 (28.6)	9 (17.3)	0	9 (14.3)
Weight increased	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
White blood cell count decreased	1 (14.3)	1 (14.3)	0	1 (3.6)	0	3 (5.8)	1 (9.1)	4 (6.3)
White blood cell count increased	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Metabolism and nutrition disorders	4 (57.1)	6 (85.7)	1 (33.3)	16 (57.1)	4 (57.1)	31 (59.6)	1 (9.1)	32 (50.8)
Decreased appetite	1 (14.3)	3 (42.9)	1 (33.3)	6 (21.4)	3 (42.9)	14 (26.9)	1 (9.1)	15 (23.8)
Dehydration	0	0	0	1 (3.6)	1 (14.3)	2 (3.8)	0	2 (3.2)
Gout	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Hyperglycaemia	2 (28.6)	0	1 (33.3)	1 (3.6)	0	4 (7.7)	0	4 (6.3)
Hyperkalaemia	0	0	0	1 (3.6)	1 (14.3)	2 (3.8)	0	2 (3.2)
Hyperlipidaemia	0	0	0	4 (14.3)	0	4 (7.7)	0	4 (6.3)
Hypertriglyceridaemia	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Hyperuricaemia	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Hypoalbuminaemia	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Hypocalcaemia	1 (14.3)	1 (14.3)	0	0	0	2 (3.8)	0	2 (3.2)
Hypokalaemia	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Hypophosphataemia	2 (28.6)	3 (42.9)	0	7 (25.0)	1 (14.3)	13 (25.0)	0	13 (20.6)
Musculoskeletal and connective tissue disorders	3 (42.9)	2 (28.6)	1 (33.3)	9 (32.1)	1 (14.3)	16 (30.8)	4 (36.4)	20 (31.7)
Arthralgia	1 (14.3)	0	0	1 (3.6)	1 (14.3)	3 (5.8)	2 (18.2)	5 (7.9)
Arthritis	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Back pain	1 (14.3)	0	0	1 (3.6)	0	2 (3.8)	1 (9.1)	3 (4.8)
Intervertebral disc protrusion	0	1 (14.3)	0	2 (7.1)	0	3 (5.8)	0	3 (4.8)
Muscle spasms	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Muscular weakness	0	0	0	3 (10.7)	0	3 (5.8)	0	3 (4.8)
Musculoskeletal pain	1 (14.3)	0	0	0	0	1 (1.9)	1 (9.1)	2 (3.2)

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Musculoskeletal stiffness	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Myalgia	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Pain in extremity	1 (14.3)	1 (14.3)	0	0	0	2 (3.8)	1 (9.1)	3 (4.8)
Plantar fasciitis	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Rheumatoid arthritis	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	1 (33.3)	4 (14.3)	1 (14.3)	6 (11.5)	0	6 (9.5)
Blast cell crisis	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Ear neoplasm	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Nervous system disorders	1 (14.3)	2 (28.6)	2 (66.7)	9 (32.1)	1 (14.3)	15 (28.8)	5 (45.5)	20 (31.7)
Depressed level of consciousness	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Dizziness	0	0	1 (33.3)	1 (3.6)	0	2 (3.8)	1 (9.1)	3 (4.8)
Dysgeusia	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Headache	1 (14.3)	1 (14.3)	1 (33.3)	1 (3.6)	0	4 (7.7)	1 (9.1)	5 (7.9)
Hypoaesthesia	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Intercostal neuralgia	1 (14.3)	0	0	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Neuropathy peripheral	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Paraesthesia	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Peripheral sensory neuropathy	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Sensory disturbance	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Somnolence	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Psychiatric disorders	0	1 (14.3)	1 (33.3)	4 (14.3)	0	6 (11.5)	0	6 (9.5)
Confusional state	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Insomnia	0	1 (14.3)	0	3 (10.7)	0	4 (7.7)	0	4 (6.3)
Renal and urinary disorders	1 (14.3)	0	0	7 (25.0)	0	8 (15.4)	2 (18.2)	10 (15.9)
Haematuria	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Pollakiuria	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Renal impairment	0	0	0	3 (10.7)	0	3 (5.8)	0	3 (4.8)
Urogenital haemorrhage	1 (14.3)	0	0	0	0	1 (1.9)	1 (9.1)	2 (3.2)
Reproductive system and breast disorders	1 (14.3)	0	0	1 (3.6)	0	2 (3.8)	1 (9.1)	3 (4.8)
Benign prostatic hyperplasia	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Pelvic pain	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Respiratory, thoracic and mediastinal disorders	2 (28.6)	4 (57.1)	1 (33.3)	9 (32.1)	2 (28.6)	18 (34.6)	3 (27.3)	21 (33.3)
Alveolitis allergic	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Cough	1 (14.3)	1 (14.3)	0	0	0	2 (3.8)	0	2 (3.2)
Dyspnoea	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Epistaxis	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Haemoptysis	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Hyperventilation	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Nasal congestion	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Nasal dryness	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Oropharyngeal pain	0	0	1 (33.3)	2 (7.1)	0	3 (5.8)	1 (9.1)	4 (6.3)
Pleural effusion	0	2 (28.6)	0	4 (14.3)	1 (14.3)	7 (13.5)	2 (18.2)	9 (14.3)
Pleurisy	0	1 (14.3)	0	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Productive cough	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Rhinorrhoea	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Upper respiratory tract inflammation	1 (14.3)	0	0	4 (14.3)	0	5 (9.6)	0	5 (7.9)
Skin and subcutaneous tissue disorders	6 (85.7)	6 (85.7)	3 (100)	25 (89.3)	3 (42.9)	43 (82.7)	7 (63.6)	50 (79.4)
Acne	1 (14.3)	0	0	3 (10.7)	0	4 (7.7)	0	4 (6.3)
Alopecia	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Drug eruption	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Dry skin	1 (14.3)	1 (14.3)	0	1 (3.6)	1 (14.3)	4 (7.7)	1 (9.1)	5 (7.9)

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-line 400 mg N=7	Part 1 Second-line 500 mg N=7	Part 1 Second-line 600 mg N=3	Part 2 Primary Second-line 500 mg N=28	Part 2 Advanced Second-line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-line 500 mg N=11	Total N=63
Eczema	1 (14.3)	2 (28.6)	0	3 (10.7)	0	6 (11.5)	0	6 (9.5)
Eczema asteatotic	0	0	1 (33.3)	3 (10.7)	0	4 (7.7)	0	4 (6.3)
Erythema	0	1 (14.3)	0	1 (3.6)	0	2 (3.8)	1 (9.1)	3 (4.8)
Erythema nodosum	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Generalised erythema	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Hyperkeratosis	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Leukoderma	1 (14.3)	1 (14.3)	0	1 (3.6)	0	3 (5.8)	0	3 (4.8)
Night sweats	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Palmar-plantar erythrodysaesthesia syndrome	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Photosensitivity reaction	1 (14.3)	0	0	0	0	1 (1.9)	2 (18.2)	3 (4.8)
Pigmentation disorder	0	0	0	2 (7.1)	0	2 (3.8)	1 (9.1)	3 (4.8)
Pruritus	1 (14.3)	1 (14.3)	0	4 (14.3)	0	6 (11.5)	2 (18.2)	8 (12.7)
Rash	3 (42.9)	6 (85.7)	3 (100)	16 (57.1)	3 (42.9)	31 (59.6)	5 (45.5)	36 (57.1)
Seborrhoeic dermatitis	1 (14.3)	0	0	4 (14.3)	0	5 (9.6)	0	5 (7.9)
Urticaria	3 (42.9)	1 (14.3)	0	0	0	4 (7.7)	0	4 (6.3)
Xeroderma	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Vascular disorders	1 (14.3)	1 (14.3)	1 (33.3)	6 (21.4)	0	9 (17.3)	0	9 (14.3)
Haemorrhage	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Hypertension	1 (14.3)	1 (14.3)	0	4 (14.3)	0	6 (11.5)	0	6 (9.5)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Non SAE and SAE results are not separated out.
N = number of subjects, SAE = serious adverse events.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different adverse events within the higher level category.

Table 24. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-Line 400 mg N=7	Part 1 Second-Line 500 mg N=7	Part 1 Second-Line 600 mg N=3	Part 2 Primary Second-Line 500 mg N=28	Part 2 Advanced Second-Line 500 mg N=7	Total Second-Line N=52	Part 2 Exploratory Third-Line 500 mg N=11	Total N=63
Any adverse event	7 (100)	7 (100)	3 (100)	28 (100)	7 (100)	52 (100)	11 (100)	63 (100)
Blood and lymphatic system disorders	3 (42.9)	4 (57.1)	2 (66.7)	14 (50.0)	4 (57.1)	27 (51.9)	6 (54.5)	33 (52.4)
Anaemia	1 (14.3)	1 (14.3)	0	7 (25.0)	4 (57.1)	13 (25.0)	0	13 (20.6)
Eosinophilia	0	0	0	3 (10.7)	0	3 (5.8)	1 (9.1)	4 (6.3)
Leukopenia	1 (14.3)	2 (28.6)	0	5 (17.9)	3 (42.9)	11 (21.2)	2 (18.2)	13 (20.6)
Lymphopenia	0	2 (28.6)	2 (66.7)	8 (28.6)	2 (28.6)	14 (26.9)	5 (45.5)	19 (30.2)
Neutropenia	2 (28.6)	2 (28.6)	1 (33.3)	4 (14.3)	3 (42.9)	12 (23.1)	2 (18.2)	14 (22.2)
Thrombocytopenia	2 (28.6)	3 (42.9)	1 (33.3)	8 (28.6)	3 (42.9)	17 (32.7)	2 (18.2)	19 (30.2)
Cardiac disorders	0	2 (28.6)	0	4 (14.3)	0	6 (11.5)	0	6 (9.5)
Pericardial effusion	0	1 (14.3)	0	3 (10.7)	0	4 (7.7)	0	4 (6.3)
Ventricular extrasystoles	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Ear and labyrinth disorders	1 (14.3)	0	0	1 (3.6)	1 (14.3)	3 (5.8)	0	3 (4.8)
Deafness	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Vertigo	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Eye disorders	1 (14.3)	0	0	4 (14.3)	3 (42.9)	8 (15.4)	0	8 (12.7)
Conjunctival haemorrhage	0	0	0	1 (3.6)	1 (14.3)	2 (3.8)	0	2 (3.2)
Conjunctival hyperaemia	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Dry eye	1 (14.3)	0	0	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Papilloedema	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Gastrointestinal disorders	7 (100)	7 (100)	3 (100)	26 (92.9)	7 (100)	50 (96.2)	11 (100)	61 (96.8)
Abdominal discomfort	1 (14.3)	0	0	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Abdominal distension	0	1 (14.3)	1 (33.3)	0	1 (14.3)	3 (5.8)	0	3 (4.8)
Abdominal pain	1 (14.3)	0	1 (33.3)	0	0	2 (3.8)	1 (9.1)	3 (4.8)
Abdominal pain upper	0	1 (14.3)	0	5 (17.9)	0	6 (11.5)	2 (18.2)	8 (12.7)
Anal fissure	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Cheilitis	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Chronic gastritis	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Constipation	0	1 (14.3)	0	1 (3.6)	2 (28.6)	4 (7.7)	0	4 (6.3)

Table 24. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-Line 400 mg N=7	Part 1 Second-Line 500 mg N=7	Part 1 Second-Line 600 mg N=3	Part 2 Primary Second-Line 500 mg N=28	Part 2 Advanced Second-Line 500 mg N=7	Total Second-Line N=52	Part 2 Exploratory Third-Line 500 mg N=11	Total N=63
Diarrhoea	7 (100)	7 (100)	3 (100)	25 (89.3)	7 (100)	49 (94.2)	10 (90.9)	59 (93.7)
Dry mouth	0	0	1 (33.3)	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Dyspepsia	0	1 (14.3)	0	1 (3.6)	1 (14.3)	3 (5.8)	1 (9.1)	4 (6.3)
Gastritis	0	0	0	6 (21.4)	0	6 (11.5)	0	6 (9.5)
Gastrooesophageal reflux disease	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Gingival swelling	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Leukoplakia oral	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Nausea	2 (28.6)	2 (28.6)	1 (33.3)	12 (42.9)	1 (14.3)	18 (34.6)	5 (45.5)	23 (36.5)
Oesophagitis	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Pancreatitis	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Pancreatitis acute	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Proctalgia	0	0	0	2 (7.1)	1 (14.3)	3 (5.8)	0	3 (4.8)
Stomatitis	0	3 (42.9)	1 (33.3)	4 (14.3)	1 (14.3)	9 (17.3)	1 (9.1)	10 (15.9)
Toothache	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Vomiting	1 (14.3)	2 (28.6)	2 (66.7)	14 (50.0)	3 (42.9)	22 (42.3)	1 (9.1)	23 (36.5)
General disorders and administration site conditions	4 (57.1)	3 (42.9)	3 (100)	9 (32.1)	2 (28.6)	21 (40.4)	3 (27.3)	24 (38.1)
Chest discomfort	0	0	2 (66.7)	0	1 (14.3)	3 (5.8)	0	3 (4.8)
Chills	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Fatigue	1 (14.3)	1 (14.3)	1 (33.3)	3 (10.7)	0	6 (11.5)	1 (9.1)	7 (11.1)
Malaise	1 (14.3)	0	0	1 (3.6)	0	2 (3.8)	1 (9.1)	3 (4.8)
Peripheral swelling	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Pyrexia	1 (14.3)	2 (28.6)	1 (33.3)	5 (17.9)	1 (14.3)	10 (19.2)	0	10 (15.9)
Hepatobiliary disorders	2 (28.6)	2 (28.6)	2 (66.7)	4 (14.3)	0	10 (19.2)	3 (27.3)	13 (20.6)
Hepatic function abnormal	0	2 (28.6)	2 (66.7)	3 (10.7)	0	7 (13.5)	2 (18.2)	9 (14.3)
Hepatotoxicity	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Liver disorder	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Liver injury	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)

Table 24. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-Line 400 mg N=7	Part 1 Second-Line 500 mg N=7	Part 1 Second-Line 600 mg N=3	Part 2 Primary Second-Line 500 mg N=28	Part 2 Advanced Second-Line 500 mg N=7	Total Second-Line N=52	Part 2 Exploratory Third-Line 500 mg N=11	Total N=63
Infections and infestations	3 (42.9)	5 (71.4)	1 (33.3)	13 (46.4)	2 (28.6)	24 (46.2)	3 (27.3)	27 (42.9)
Bronchitis	1 (14.3)	1 (14.3)	0	2 (7.1)	0	4 (7.7)	0	4 (6.3)
Cellulitis	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Conjunctivitis	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Cystitis	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Folliculitis	1 (14.3)	0	0	2 (7.1)	0	3 (5.8)	0	3 (4.8)
Gastroenteritis	0	1 (14.3)	0	3 (10.7)	0	4 (7.7)	0	4 (6.3)
Gingivitis	0	1 (14.3)	0	1 (3.6)	1 (14.3)	3 (5.8)	0	3 (4.8)
Herpes zoster	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Influenza	0	1 (14.3)	0	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Nasopharyngitis	2 (28.6)	3 (42.9)	0	9 (32.1)	0	14 (26.9)	2 (18.2)	16 (25.4)
Periodontitis	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Tinea versicolour	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Upper respiratory tract infection	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Investigations	5 (71.4)	6 (85.7)	2 (66.7)	22 (78.6)	4 (57.1)	39 (75.0)	6 (54.5)	45 (71.4)
Alanine aminotransferase increased	3 (42.9)	4 (57.1)	0	13 (46.4)	0	20 (38.5)	4 (36.4)	24 (38.1)
Amylase decreased	0	1 (14.3)	1 (33.3)	0	0	2 (3.8)	0	2 (3.2)
Amylase increased	0	0	0	5 (17.9)	1 (14.3)	6 (11.5)	1 (9.1)	7 (11.1)
Aspartate aminotransferase increased	4 (57.1)	2 (28.6)	0	9 (32.1)	0	15 (28.8)	4 (36.4)	19 (30.2)
Blood albumin decreased	0	1 (14.3)	1 (33.3)	1 (3.6)	0	3 (5.8)	0	3 (4.8)
Blood albumin increased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Blood alkaline phosphatase increased	0	2 (28.6)	0	7 (25.0)	0	9 (17.3)	2 (18.2)	11 (17.5)
Blood bilirubin increased	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Blood calcium decreased	0	1 (14.3)	1 (33.3)	0	0	2 (3.8)	0	2 (3.2)
Blood calcium increased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)

Table 24. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-Line 400 mg N=7	Part 1 Second-Line 500 mg N=7	Part 1 Second-Line 600 mg N=3	Part 2 Primary Second-Line 500 mg N=28	Part 2 Advanced Second-Line 500 mg N=7	Total Second-Line N=52	Part 2 Exploratory Third-Line 500 mg N=11	Total N=63
Blood chloride decreased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Blood cholinesterase decreased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Blood creatine phosphokinase decreased	0	2 (28.6)	1 (33.3)	0	0	3 (5.8)	0	3 (4.8)
Blood creatine phosphokinase increased	1 (14.3)	0	0	3 (10.7)	0	4 (7.7)	2 (18.2)	6 (9.5)
Blood creatinine increased	1 (14.3)	2 (28.6)	2 (66.7)	2 (7.1)	1 (14.3)	8 (15.4)	0	8 (12.7)
Blood fibrinogen increased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Blood lactate dehydrogenase increased	1 (14.3)	0	1 (33.3)	2 (7.1)	0	4 (7.7)	2 (18.2)	6 (9.5)
Blood potassium decreased	0	1 (14.3)	1 (33.3)	0	0	2 (3.8)	0	2 (3.2)
Blood sodium decreased	0	2 (28.6)	1 (33.3)	0	0	3 (5.8)	0	3 (4.8)
Blood urea increased	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Blood urine present	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Electrocardiogram QT prolonged	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Gamma-glutamyltransferase increased	0	2 (28.6)	0	3 (10.7)	0	5 (9.6)	1 (9.1)	6 (9.5)
Glucose urine present	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Haemoglobin decreased	0	3 (42.9)	1 (33.3)	2 (7.1)	0	6 (11.5)	0	6 (9.5)
International normalised ratio decreased	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
International normalised ratio increased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Lipase increased	0	2 (28.6)	0	7 (25.0)	1 (14.3)	10 (19.2)	4 (36.4)	14 (22.2)
Liver function test abnormal	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Lymphocyte count decreased	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)

Table 24. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-Line 400 mg N=7	Part 1 Second-Line 500 mg N=7	Part 1 Second-Line 600 mg N=3	Part 2 Primary Second-Line 500 mg N=28	Part 2 Advanced Second-Line 500 mg N=7	Total Second-Line N=52	Part 2 Exploratory Third-Line 500 mg N=11	Total N=63
Neutrophil count decreased	0	1 (14.3)	0	1 (3.6)	0	2 (3.8)	1 (9.1)	3 (4.8)
Platelet count decreased	0	1 (14.3)	0	2 (7.1)	0	3 (5.8)	0	3 (4.8)
Protein total decreased	0	1 (14.3)	1 (33.3)	0	0	2 (3.8)	0	2 (3.2)
Protein urine present	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Prothrombin time prolonged	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Prothrombin time shortened	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Renal function test abnormal	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Specific gravity urine abnormal	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Weight decreased	0	0	1 (33.3)	6 (21.4)	1 (14.3)	8 (15.4)	0	8 (12.7)
White blood cell count decreased	1 (14.3)	1 (14.3)	0	1 (3.6)	0	3 (5.8)	1 (9.1)	4 (6.3)
Metabolism and nutrition disorders	3 (42.9)	6 (85.7)	1 (33.3)	13 (46.4)	3 (42.9)	26 (50.0)	1 (9.1)	27 (42.9)
Decreased appetite	1 (14.3)	3 (42.9)	1 (33.3)	5 (17.9)	3 (42.9)	13 (25.0)	1 (9.1)	14 (22.2)
Dehydration	0	0	0	1 (3.6)	1 (14.3)	2 (3.8)	0	2 (3.2)
Hyperglycaemia	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Hypertriglyceridaemia	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Hyperuricaemia	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Hypoalbuminaemia	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Hypocalcaemia	1 (14.3)	1 (14.3)	0	0	0	2 (3.8)	0	2 (3.2)
Hypophosphataemia	1 (14.3)	3 (42.9)	0	7 (25.0)	1 (14.3)	12 (23.1)	0	12 (19.0)
Musculoskeletal and connective tissue disorders	1 (14.3)	0	1 (33.3)	6 (21.4)	0	8 (15.4)	2 (18.2)	10 (15.9)
Arthralgia	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Back pain	1 (14.3)	0	0	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Myalgia	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Rheumatoid arthritis	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)

Table 24. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-Line 400 mg N=7	Part 1 Second-Line 500 mg N=7	Part 1 Second-Line 600 mg N=3	Part 2 Primary Second-Line 500 mg N=28	Part 2 Advanced Second-Line 500 mg N=7	Total Second-Line N=52	Part 2 Exploratory Third-Line 500 mg N=11	Total N=63
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	1 (33.3)	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Ear neoplasm	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Nervous system disorders	0	2 (28.6)	2 (66.7)	6 (21.4)	0	10 (19.2)	5 (45.5)	15 (23.8)
Dizziness	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Dysgeusia	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Headache	0	1 (14.3)	1 (33.3)	1 (3.6)	0	3 (5.8)	1 (9.1)	4 (6.3)
Hypoaesthesia	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Neuropathy peripheral	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Paraesthesia	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Peripheral sensory neuropathy	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Sensory disturbance	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Somnolence	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Psychiatric disorders	0	1 (14.3)	0	2 (7.1)	0	3 (5.8)	0	3 (4.8)
Insomnia	0	1 (14.3)	0	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Renal and urinary disorders	1 (14.3)	0	0	5 (17.9)	0	6 (11.5)	1 (9.1)	7 (11.1)
Haematuria	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Renal impairment	0	0	0	3 (10.7)	0	3 (5.8)	0	3 (4.8)
Urogenital haemorrhage	1 (14.3)	0	0	0	0	1 (1.9)	1 (9.1)	2 (3.2)
Respiratory, thoracic and mediastinal disorders	1 (14.3)	4 (57.1)	1 (33.3)	5 (17.9)	2 (28.6)	13 (25.0)	3 (27.3)	16 (25.4)
Alveolitis allergic	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Cough	1 (14.3)	1 (14.3)	0	0	0	2 (3.8)	0	2 (3.2)
Epistaxis	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Haemoptysis	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Nasal congestion	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)
Oropharyngeal pain	0	0	1 (33.3)	0	0	1 (1.9)	1 (9.1)	2 (3.2)

Table 24. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-Line 400 mg N=7	Part 1 Second-Line 500 mg N=7	Part 1 Second-Line 600 mg N=3	Part 2 Primary Second-Line 500 mg N=28	Part 2 Advanced Second-Line 500 mg N=7	Total Second-Line N=52	Part 2 Exploratory Third-Line 500 mg N=11	Total N=63
Pleural effusion	0	2 (28.6)	0	4 (14.3)	1 (14.3)	7 (13.5)	2 (18.2)	9 (14.3)
Pleurisy	0	1 (14.3)	0	0	0	1 (1.9)	0	1 (1.6)
Productive cough	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Rhinorrhoea	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Skin and subcutaneous tissue disorders	4 (57.1)	5 (71.4)	3 (100)	24 (85.7)	3 (42.9)	39 (75.0)	6 (54.5)	45 (71.4)
Acne	1 (14.3)	0	0	3 (10.7)	0	4 (7.7)	0	4 (6.3)
Alopecia	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Drug eruption	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Dry skin	1 (14.3)	0	0	0	1 (14.3)	2 (3.8)	1 (9.1)	3 (4.8)
Eczema	1 (14.3)	1 (14.3)	0	2 (7.1)	0	4 (7.7)	0	4 (6.3)
Eczema asteatotic	0	0	1 (33.3)	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Erythema	0	1 (14.3)	0	1 (3.6)	0	2 (3.8)	0	2 (3.2)
Erythema nodosum	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Generalised erythema	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Hyperkeratosis	0	0	0	1 (3.6)	0	1 (1.9)	1 (9.1)	2 (3.2)
Leukoderma	1 (14.3)	1 (14.3)	0	1 (3.6)	0	3 (5.8)	0	3 (4.8)
Night sweats	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Palmar-plantar erythrodysaesthesia syndrome	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Photosensitivity reaction	1 (14.3)	0	0	0	0	1 (1.9)	2 (18.2)	3 (4.8)
Pigmentation disorder	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Pruritus	1 (14.3)	1 (14.3)	0	4 (14.3)	0	6 (11.5)	0	6 (9.5)
Rash	1 (14.3)	4 (57.1)	3 (100)	16 (57.1)	2 (28.6)	26 (50.0)	4 (36.4)	30 (47.6)
Seborrhoeic dermatitis	1 (14.3)	0	0	4 (14.3)	0	5 (9.6)	0	5 (7.9)
Urticaria	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Xeroderma	1 (14.3)	0	0	0	0	1 (1.9)	0	1 (1.6)
Vascular disorders	1 (14.3)	1 (14.3)	1 (33.3)	3 (10.7)	0	6 (11.5)	0	6 (9.5)
Haemorrhage	0	0	1 (33.3)	0	0	1 (1.9)	0	1 (1.6)

Table 24. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events (≥5% Subjects in Any of the Cohorts): Safety Population

System Organ Class[a] Preferred Term	Treatment							
	Part 1 Second-Line 400 mg N=7	Part 1 Second-Line 500 mg N=7	Part 1 Second-Line 600 mg N=3	Part 2 Primary Second-Line 500 mg N=28	Part 2 Advanced Second-Line 500 mg N=7	Total Second-Line N=52	Part 2 Exploratory Third-Line 500 mg N=11	Total N=63
Hypertension	1 (14.3)	1 (14.3)	0	2 (7.1)	0	4 (7.7)	0	4 (6.3)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Non SAE and SAE results are not separated out.
N = number of subjects; SAE = serious adverse events.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject might report ≥2 different adverse events within the higher level category.

Permanent Discontinuations due to Adverse Events: AEs leading to permanent discontinuation are summarized in Table 25.

AEs leading to treatment discontinuation were reported in 18 (28.6%) subjects in total; 16 (30.8%) subjects in the total second-line subjects and 2 (18.2%) subjects in the third-line subjects. In total, the most common AEs leading to treatment discontinuation (incidence ≥3%) were aspartate aminotransferase increased (6.3%), hepatic function abnormal (4.8%), alanine aminotransferase increased (4.8%) and thrombocytopenia (3.2%).

Table 25. Number (%) of Subjects Reporting Adverse Events Leading to Permanent Discontinuation: Safety Population

System Organ Class[a] Preferred Term	Part 1 Second-Line 400 mg N=7	Part 1 Second-Line 500 mg N=7	Part 1 Second-Line 600 mg N=3	Part 2 Primary Second-Line 500 mg N=28	Part 2 Advanced Second-Line 500 mg N=7	Total Second-Line N=52	Part 2 Exploratory Third-Line 500 mg N=11	Total N=63
Any adverse event	1 (14.3)	1 (14.3)	0	11 (39.3)	3 (42.9)	16 (30.8)	2 (18.2)	18 (28.6)
Blood and lymphatic system disorders	0	0	0	0	2 (28.6)	2 (3.8)	0	2 (3.2)
Thrombocytopenia	0	0	0	0	2 (28.6)	2 (3.8)	0	2 (3.2)
Hepatobiliary disorders	1 (14.3)	1 (14.3)	0	1 (3.6)	0	3 (5.8)	1 (9.1)	4 (6.3)
Hepatic function abnormal	0	1 (14.3)	0	1 (3.6)	0	2 (3.8)	1 (9.1)	3 (4.8)
Liver injury	1 (14.3)	0	0	0	0	1 (1.9)	0	1(1.6)
Investigations	0	0	0	6 (21.4)	0	6 (11.5)	1 (9.1)	7 (11.1)
Alanine aminotransferase increased	0	0	0	3 (10.7)	0	3 (5.8)	0	3 (4.8)
Aspartate aminotransferase increased	0	0	0	4 (14.3)	0	4 (7.7)	0	4 (6.3)
Lipase increased	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Liver function test abnormal	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Platelet count decreased	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	1 (3.6)	1 (14.3)	2 (3.8)	0	2 (3.2)
Bladder cancer	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Blast cell crisis	0	0	0	0	1 (14.3)	1 (1.9)	0	1 (1.6)
Nervous system disorders	0	0	0	2 (7.1)	0	2 (3.8)	0	2 (3.2)
Cerebral haemorrhage	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Posterior reversible encephalopathy syndrome	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Skin and subcutaneous tissue disorders	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Rash	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)

Table 25. Number (%) of Subjects Reporting Adverse Events Leading to Permanent Discontinuation: Safety Population

Classifications of adverse events were based on MedDRA.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.

a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different adverse events within the higher level category.

Temporary Discontinuations due to Adverse Events: AEs leading to dose delays were reported in 53 (84.1%) subjects in total; 44 (84.6%) subjects in the total second-line subjects and 9 (81.8%) subjects in the third-line exploratory cohort. In total, the most common AEs leading to dose delays (incidence ≥10%) were rash (23.8%), alanine aminotransferase increased (19.0%), thrombocytopenia (15.9%), lipase increased (15.9%), diarrhea (12.7%), neutropenia (11.1%) and aspartate aminotransferase increased (11.1%).

Death: A summary of deaths is provided in Table 26. Overall 7 subjects died, of these, 1 subject who received bosutinib 500 mg in the primary second-line died within 30 days of the last dose. The reason for death was an AE related to bosutinib (cerebral haemorrhage). Six (6) second-line subjects died after 30 days from the last dose. The reasons for death were AE unrelated to bosutinib in 3 subjects (pneumonia occurring 86 days after the last dose, pulmonary aspergillosis occurring 103 days after the last dose, and suicide occurring 686 days after the last dose) and disease progression in 3 subjects.

Table 26. Summary of Deaths: Safety Population

Deaths (n, %)	Part 1 Second-Line 400 mg N=7	Part 1 Second-Line 500 mg N=7	Part 1 Second-Line 600 mg N=3	Part 2 Primary Second-Line 500 mg N=28	Part 2 Advanced Second-Line 500 mg N=7	Total Second-line N=52	Part 2 Exploratory Third-Line 500 mg N=11	Total N=63
Number of all deaths	0	0	0	2 (7.1)	5 (71.4)	7 (13.5)	0	7 (11.1)
Number of deaths within 30 days of last dose	0	0	0	1 (3.6)	0	1 (1.9)	0	1 (1.6)
Number of deaths after 30 days from last dose	0	0	0	1 (3.6)	5 (71.4)	6 (11.5)	0	6 (9.5)
Reason for death[a]	0	0	0	2 (100)	5 (100)	7 (100)	0	7 (100)
Adverse event unrelated to test article	0	0	0	0	3 (60.0)	3 (42.9)	0	3 (42.9)
Adverse event related to test article	0	0	0	1 (50)		1 (14.3)		1 (14.3)
Disease progression	0	0	0	1 (50)	2 (40.0)	3 (42.9)	0	3 (42.9)
Cause-specific death rate								
Number of deaths due to disease progression	0	0	0	1 (3.6)	2 (28.6)	3 (5.8)	0	3 (4.8)

N = total number of subjects; n= number of subjects meeting pre-specified criteria.
a. Percentages were based on number of subjects who died in each group.

Clinical Laboratory Evaluation: A total of 53 subjects (84.1%) experienced Grade 3 or 4 abnormality in laboratory test results. The most common Grade 3 or 4 hematology test abnormalities (incidence ≥20%) were lymphocytes (33.3%), neutrophils (27.0%), and platelet count (23.8%). The most common Grade 3 or 4 blood chemistry test abnormalities (incidence ≥20%) were uric acid (31.7%), alanine aminotransferase (27.0%), and lipase (24.2%). There were no abnormalities that met the criteria for potential Hy's Law cases.

Vital Signs, Electrocardiogram, Physical Findings, and Other Observations Related to Safety:

Fourteen (14) subjects (23.0%) had a potentially clinically important (PCI) value in vital signs or body weight. Of which, 13 subjects (21.7%) were found to have PCI value of ≥10% change of body weight, in addition 1 (1.7%) subject had a heart rate value of <40 beats/min. No PCI values were reported in other vital signs (supine blood pressure and axillary temperature). An increase of QT interval by >0-30 msec was reported in 3 subjects in the 400 mg cohort, 10 subjects in the primary cohort and 7 subjects in the exploratory third-line cohort. An increase of QT interval by >30 msec was reported in 2 subjects in the exploratory third-line cohort. A total of 6 (12.2%) subjects experienced Grade 1 or 2 left ventricular ejection fraction abnormalities.

CONCLUSIONS:

The safety of bosutinib up to 600 mg was confirmed in Part 1 of the study and bosutinib 500 mg as the starting dose for part 2 of a previous open-label, continuous daily dosing, two-part safety and efficacy study (A Phase 1/2 Study of SKI-606 in Philadelphia Chromosome Positive Leukemias [NCT00261846]) was assumed to be appropriate in Japanese subjects as the starting dose for Part 2 of the study.

Overall, bosutinib given at 500 mg demonstrated efficacy in Japanese second-line CML subjects. A CCyR was observed in a third-line CML subject. Bosutinib demonstrated an acceptable safety profile at an oral daily dose of 500 mg in Japanese subjects with Ph^+ CML.