CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer Japan Inc.

Investigational Product: Bosutinib

Clinical Study Report Synopsis: Protocol B1871048

Protocol Title: A Phase 2, Open-Label, Single-Arm Study to Evaluate Efficacy and Safety of Bosutinib Monotherapy in Japanese Adult Patients With Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia

Investigators: Refer to CCI [redacted] for a list of investigators involved in this study.

Study Centers: This study was conducted at 20 centers in Japan. Refer to CCI [redacted] for a list of sites involved in this study.

Publications Based on the Study: None.

Study Initiation Date: 15 May 2017

Study Completion Date: 12 March 2019 (Data Cut-off Date)

Report Date: 01 July 2019

Previous Report Date(s): Not applicable

Phase of Development: Phase 2

Primary and Secondary Study Objectives and Endpoints:

The study objectives and endpoints of this study are presented in Table 1.

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Table 1. Study Objectives and Endpoints

Type	Objectives	Endpoints
Primary		
Efficacy	To evaluate MMR at 12 months (48 weeks) in newly diagnosed Japanese Ph+ CP CML patients harboring b2a2 and/or b3a2 transcripts	MMR at 12 months (48 weeks). All Ph+ CP CML patients harboring b2a2 and/or b3a2 transcripts were assessed and followed up for MMR as primary endpoint. MMR is defined as ≤0.1% BCR-ABL on the IS by RT-qPCR
Secondary[a]		
Efficacy	To evaluate MMR by 12 and 18 months	MMR by 12 and 18 months
	To estimate the proportion of patients demonstrating CCyR by 12 months	CCyR by 12 months
	To evaluate the duration of MMR and CCyR	Duration of MMR and CCyR
	To evaluate EFS	EFS
	To evaluate OS	OS
PK	To assess the population PK	Population PK parameters
	To assess correlations between trough concentrations of bosutinib and key efficacy and safety endpoints	Correlations between trough concentrations of bosutinib and key efficacy and safety endpoints
Safety	To characterize the safety profile of bosutinib in Japanese patients	Safety: AEs (as graded by NCI CTCAE Version 4.03); laboratory abnormalities (as graded by NCI CTCAE Version 4.03); vital signs (blood pressure, pulse rate); ECGs; ECHO or MUGA

Abbreviations: AE=adverse event; BCR-ABL=fusion transcript or protein resulting from the 9;22 chromosomal translocation responsible for formation of the Philadelphia chromosome; CCyR=complete cytogenetic response; CML=chronic myelogenous leukemia; CP=chronic phase; CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; ECHO=echocardiogram; EFS=event-free survival; IS=international scale; MMR=major molecular response; MUGA=multiple gated acquisition; NCI=National Cancer Institute; OS=overall survival; Ph=Philadelphia chromosome; PK=pharmacokinetic; RT-qPCR=quantitative reverse transcriptase polymerase chain reaction.

a. All the efficacy analyses for secondary objectives were performed using the same population as primary objective, unless otherwise indicated.

METHODS

Study Design: This was a Phase 2, open-label, single-arm study designed to evaluate the efficacy and safety of bosutinib alone in Japanese adult patients with newly diagnosed chronic phase (CP) chronic myelogenous leukemia (CML). The primary endpoint was major molecular response (MMR) at 12 months in newly diagnosed Japanese Philadelphia chromosome (Ph)+ CP CML patients harboring b2a2 and/or b3a2 transcripts. Patients received bosutinib treatment at a starting dose of 400 mg once daily (QD). The dose of bosutinib was allowed to be escalated (up to a maximum of 600 mg QD) for unsatisfactory response or reduced (down to 300 mg QD, and further to a minimum of 200 mg QD only when approved by the sponsor) for toxicity.

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This study had approximately 52 weeks of planned patient accrual. Each patient had 12 months (48 weeks) of Core Treatment Phase and the following ≥24 months (96 weeks) of Extension Phase. After treatment discontinuation, the patient entered Long-Term Follow-Up. The Extension Phase or Long-Term Follow-Up will continue until the end of the study.

The data in this study was collected till the primary completion date (12 March 2019).

Diagnosis and Main Criteria for Inclusion: Patients with diagnosis of CP CML of ≤6 months (from initial diagnosis), diagnosis of CP CML with molecular confirmation by detection of fusion transcript or protein resulting from the 9;22 chromosomal translocation responsible for formation of the Ph (BCR-ABL) rearrangement at Screening (cytogenetic assessment for Ph was not required for enrollment; however, patients with known Ph- CML prior to registration were not eligible for this study), aged ≥20 years, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and adequate renal and liver function were included in the study.

Patients who had any prior medical treatment for CML, including tyrosine kinase inhibitors, with the exception of hydroxyurea treatment, which was permitted for up to 6 months prior to registration, any past or current central nervous system involvement, including leptomeningeal leukemia, extramedullary disease only, major surgery or radiotherapy within 14 days prior to registration, history of clinically significant or uncontrolled cardiac disease were excluded from the study.

Study Treatment: Bosutinib tablets (100 mg dosage strength) were supplied by sponsor in high-density polyethylene bottles. The starting dose was 400 mg QD, orally, recommended to be taken in the morning with a meal and with approximately 200 mL of water. Available data show that both tolerance and absorption are greatly improved by taking bosutinib with a meal, including adequate dietary fats; no restriction was imposed on patients' food choices.

Patients swallowed the study drug whole and did not manipulate or chew the study drug prior to swallowing. Patients were instructed that if they missed a dose or vomited any time after taking a dose, they were not to "make it up" with an extra dose. Instead, the patients were to resume the subsequent doses as originally prescribed. Any missed dose could have been taken up to 12 hours prior to the next scheduled dose, otherwise it should have been skipped and dosing resumed with subsequent doses as prescribed.

The study drug information is provided in Table 2.

Table 2. Study Drug Information

Investigational Product Description	Vendor Lot Number	Sponsor Lot Number	Strength/Potency	Dosage Form
Bosutinib (SKI-606) 100 mg oval yellow film coated tablet commercial formulation	CCI	CCI	100 mg	Tablet

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Efficacy Evaluations:

Primary Efficacy Endpoint:

The primary endpoint was MMR at 12 months (48 weeks). All Philadelphia chromosome Ph+ CP CML patients harboring b2a2 and/or b3a2 transcripts were assessed and followed up for the MMR as the primary endpoint.

The MMR was defined as ≤0.1% BCR-ABL on the international scale by quantitative reverse transcriptase polymerase chain reaction.

The analysis of MMR rate included all patients with Ph+ CML harboring b2a2 and/or b3a2 transcripts. This was anticipated to represent approximately 95% of enrolled patients; 1-2% of patients could harbor other BCR-ABL transcripts not validated for MMR assessment.

MMR at 12 months (48 weeks) was counted only if the response was demonstrated at the 12-month (48-week) visit; any MMR gained and lost before the 12-month (48-week) visit was deemed a non-response as is the case where MMR is never achieved at or before 12 months (48 weeks).

The primary analysis was conducted 12 months after the last Ph+ CML patient harboring b2a2 and/or b3a2 transcripts was enrolled.

Secondary Efficacy Endpoints:

- Complete Cytogenetic Response (CCyR) by 12 months: The CCyR is defined as absence of detectable Ph.

- MMR by 12 and 18 months (MMR by 18 months is not presented in this study).

- Duration of MMR and CCyR: The duration of response (MMR and CCyR, respectively) was measured from the first date of response until the first date of confirmed loss of response, treatment discontinuation due to progressive disease (PD), or death due to disease progression within 28 days after the last dose. A loss of response was confirmed by a second consecutive loss at least 4 weeks later, treatment discontinuation due to PD or death due to PD within 28 days of the last dose. A PD was defined as investigator assessed progression. Treatment discontinuation due to PD or death due to PD within 28 days of the last dose without loss of response was considered a confirmed loss. An unconfirmed loss followed by treatment discontinuation due to suboptimal response was considered a confirmed loss.

- Event-Free Survival (EFS):

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The EFS was measured from the date of the first dose until the first occurrence of one of the following events, censored at the earlier of the last valid hematologic or cytogenetic assessment for those without events:

- Death due to any cause;
- Transformation to accelerated phase (AP) or blast phase (BP);
- Loss of complete hematologic response (CHR);
    - Loss of CHR was defined as the appearance of any of the following, confirmed by a second determination ≥4 weeks later (unless associated with CML-related treatment discontinuation):
        - White blood cell (WBC) count that rose to >20.0 × 10^9/L;
        - Platelet count that rose to ≥600 × 10^9/L;
        - Appearance of palpable spleen or other extramedullary involvement proven by biopsy;
        - Appearance of 5% myelocytes in the peripheral blood; or
        - Appearance of blasts or promyelocytes in the peripheral blood.
- Loss of CCyR; or
- For patients not achieving a CHR: doubling of WBC at least 1 month apart with the second value >20 × 10^9/L and maintained in subsequent assessments for at least 2 weeks.

- Overall Survival (OS): OS was measured from the date of the first dose until the occurrence of death due to any cause, censored at the last known alive date for those without events.

Pharmacokinetic Evaluations:

The objectives of the pharmacokinetic (PK) analyses were as follows:

- Objective 1: Aim was to use the PK model developed in the previous population PK reports to analyze the trough concentration data in this study to obtain population PK parameters of bosutinib;

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- Objective 2: Aim was to compare/correlate the distribution of the trough concentrations by demographic and clinical covariates at each of the 3 time points (or cumulative exposure); and

- Objective 3: Aim was to compare the distribution of the trough concentrations by presence of major adverse events (AEs) (all-causality) at each of the 3 time points (or cumulative exposure) and efficacy endpoints.

PK profiles of bosutinib were determined using a sparse sampling regimen. A total of 4 PK samples per patient were drawn. All patients provided predose blood samples on Day 1, Day 28, Day 56, and Day 84. All efforts were made to obtain the PK samples at the scheduled nominal time relative to dosing. Blood samples (3 mL) to provide a minimum of 1.0 mL plasma for PK analysis were collected into appropriately labeled tubes containing potassium ethylenediaminetetraacetic acid.

Bosutinib samples were assayed using a validated, sensitive and specific high-performance tandem mass spectrometry method.

Safety Evaluations:

Safety evaluations included collection of AEs, serious adverse events (SAEs), vital signs, physical examinations, 12-lead electrocardiogram (ECG), chest X-rays, echocardiogram/multiple gated acquisition scans, laboratory assessments, including pregnancy tests, potential cases of drug-induced liver injury, exposure to the investigational product during pregnancy or breastfeeding, and occupational exposure, medication errors and verification of concomitant treatments.

Statistical Methods:

Data Sets Analyzed:

The efficacy endpoints were analyzed based on modified as-treated population set. The safety endpoints were analyzed based on as-treated population set.

As-Treated Population: The as-treated population consisted of all enrolled patients who received at least 1 dose of the study drug. Since this was a single-arm Phase 2 study, as-treated population was also the full analysis set.

Modified As-Treated Population: The modified as-treated population consisted of all enrolled patients with Ph+ CP CML harboring b2a2 and/or b3a2 transcripts who received at least 1 dose of the study drug. This is the primary population for primary analysis of efficacy endpoints.

PK endpoints were analyzed based on PK analysis set.

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Analysis of Efficacy Endpoints:

Analysis of Primary Endpoint:

The MMR at 12 months (48 weeks) was analyzed using the hypothesis test of a 1-sample binomial proportion test with the normal approximation. The 2-sided asymptotic 90% confidence interval (CI) of MMR rate at 12 months (48 weeks) was also calculated.

The MMR at 12 months (48 weeks) was counted only if the response was demonstrated at the 12-month (48-week) visit; any MMR gained and lost before the 12-month (48-week) visit was deemed a non-response as is the case where the MMR was never achieved at or before 12 months (48 weeks).

Sixty (60) patients would provide 82% power to detect the null hypothesis (H_0) of MMR rate at 12 months ≤25% when the true rate under H_1 was ≥40% at 1-sided significance level of 0.05. Rejecting the null hypothesis and accepting the alternative hypothesis in the modified as-treated population (observing at least 21 responders out of the 60 total patients), was considered to be a successful demonstration of efficacy for this study.

Analysis of Secondary Endpoints:

Since this was a single-arm Phase 2 study, as-treated population was also the full analysis set.

The secondary endpoints mentioned in Table 1 were evaluated in the study.

Major Molecular Response by 12 and 18 Months:

Evaluations of MMR by 12 and 18 months were assessed using the frequency tables, respectively. The 2-sided asymptotic 90% CI was also calculated. For the analysis of MMR by 12 and 18 months, a patient was counted as a responder if the MMR occurred at or before 12 and 18 months, respectively, even if the MMR was subsequently lost at or before the 12-month and 18-month time points, respectively. A patient never achieving the MMR at or before 12 and 18 months was considered a non-responder, respectively.

Complete Cytogenetic Response:

Evaluations of CCyR by 12 months (48 weeks) was assessed using the frequency tables. The 2-sided 90% CI was also calculated. The CCyR rate by 12 months was defined as the proportion of patients demonstrating CCyR at or before 12 months (48 weeks). The percentage of Ph+ cells was calculated according to the following formula:

$$\text{Ceil}\ (100 \times \text{the number of Ph+ cells} / \text{the number of metaphases}),$$

where, ceil () denotes a ceiling function.

The proportion of patients who had confirmed loss of CCyR were also evaluated.

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Duration of Response:

The duration of MMR and CCyR were based on the estimations of the quartiles of duration and yearly rates using the Kaplan-Meier method.

For the analysis of MMR and CCyR, the proportion of patients who had confirmed loss of response were also evaluated, respectively.

The duration of MMR were planned to be analyzed for MMR responders in the modified as-treated population and those in as-treated population separately. The duration of CCyR were planned to be analyzed for CCyR responders in the modified as-treated population.

Event-Free Survival

EFS was planned to be analyzed using the cumulative incidence method adjusting for the competing risk of treatment discontinuation without the event, and yearly rates and percentiles were displayed. This was indicated as the on-treatment EFS. The transformation to AP and BP on treatment was considered as an event in the analysis of EFS. This means that if the first transformation to AP and BP was occurred after 28 days from the last dose, this was not to be considered as an event in the analysis of EFS.

As a reference, the EFS using the transformation to AP and BP occurred after 28 days from the last dose instead of the transformation to AP and BP on treatment was also assessed using the same analysis method. This was indicated as the off-treatment EFS.

The on-treatment EFS and off-treatment EFS were analyzed in the modified as-treated population.

Overall Survival

The analysis of OS was similar to that for duration of response.

The OS was planned to be analyzed in the modified as-treated population and as-treated population separately.

Analysis of Pharmacokinetic Endpoints:

The PK endpoints were analyzed using PK population set. The PK population was defined as any patient in the safety population of patients who had at least 1 concentration of bosutinib on-treatment.

Analysis of Safety Endpoints:

The safety population consisted of all enrolled patients, regardless of Ph status, who received at least 1 dose of the study drug. This means that the as-treated population was also the

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safety analysis set. Therefore, the as-treated population was presented in any tables, listings and figures instead of the safety analysis set.

All AEs were coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 at the analysis. The toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03.

The numbers of events and incidence rates were tabulated by preferred term and system organ class (SOC). AEs were presented with and without regard to causality. The frequency of overall toxicity, categorized by toxicity Grades 1 through Grade 5, were described. Additional tables were provided for AEs that were observed with higher frequency.

AE summaries included incidence of treatment-emergent adverse events (TEAEs) by MedDRA preferred term and SOC, SAEs including deaths, AEs that led to study drug discontinuation, characteristics of AEs that led to study drug discontinuation, AEs that led to study drug interruption, AEs that led to study drug reduction and AEs by maximum severity and relationship to study drug. Discontinuation due to AE and death data were also listed.

AEs and AE categories including cardiac, edema, effusion, gastrointestinal, hemorrhage, hypertension, infection, liver function, myelosuppression, rash, renal and vascular were summarized.

RESULTS

Subject Disposition and Demography:

A total of 64 patients were screened in this study (Table 3), of which 60 patients entered the study. As all the 60 patients had both Ph+ and b2a2 and/or b3a2 transcripts, the as-treated population and the modified as-treated population were identical.

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Table 3. Summary of Subject Evaluation Groups

	Bosutinib (N=60) n (%)
Screened: 64	
Screened Failure: 4	
As-Treated Population	60 (100.0)
Modified as-Treated Population	60 (100.0)
PK Analysis Set	60 (100.0)

Cutoff Date: 12Mar2019
The As-Treated Population is identical to Safety Analysis Set.
Percentages are based on As-Treated Population.
CCI [redacted]

Overall, 19 patients (31.7%) discontinued study treatment, of which 18 patients (30.0%) discontinued study treatment within 12 months. Forty-two (42) patients (70.0%) completed 12 months of Core Treatment Phase, of which 41 patients (68.3%) were remained in Treatment Phase at the time of data cut-off. The primary reason for the treatment discontinuation was due to AEs (18 patients [30.0%]). The 19 patients who discontinued study treatment entered into Long-Term Follow-Up Phase, of which 1 patient (1.7%) died during Long-Term Follow-Up Phase. A summary of patient disposition is provided in Table 4.

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Table 4. Summary of Disposition Events - As-Treated Population

Number (%) of Subjects	Bosutinib (N=60) Overall n (%)	Bosutinib (N=60) Within 12 months n (%)
Disposition Phase: TREATMENT		
Subjects Entered:	60 (100.0)	60 (100.0)
Discontinued	19 (31.7)	18 (30.0)
Adverse Event	18 (30.0)	17 (28.3)
Physician Decision	1 (1.7)	1 (1.7)
Completed	0	0
Ongoing	41 (68.3)	42 (70.0)
Disposition Phase: LONG-TERM FOLLOW-UP		
Subjects Entered:	19 (31.7)	18 (30.0)
Discontinued	1 (1.7)	0
Death	1 (1.7)	0
Completed	0	0
Ongoing	18 (30.0)	18 (30.0)

Cutoff Date: 12Mar2019
CCI [redacted]

A total of 36 male patients and 24 female patients were enrolled in the study. The median age of patients was 55.0 years (range: 20 to 83 years). Nineteen (19) patients (31.7%) enrolled in the study were ≥65 years of age. All the patients were Asian (Japanese).

Overall, the distribution of Sokal score was high risk (>1.2), intermediate risk (0.8-1.2), and low risk (<0.8). The majority of patients had low risk (45.0%) or intermediate risk (43.3%) Sokal score. The Ph status was positive for all patients. Among them, at Screening, the Ph status of 1 patient was not reported. However, the status was confirmed as a positive before the screening period. Most patients (48 patients [80.0%]) had no extramedullary disease; 12 patients (20.0%) had extramedullary disease. The majority of patients (59 patients [98.3%]) had no history of cardiac diseases. The majority of patients (58 patients [96.7%]) had ECOG performance status of 0.

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Efficacy Results:

Primary Efficacy Results:

The details of MMR at 12 months are presented in Table 5. The MMR at 12 months was 55.0% (90% CI: 44.4, 65.6) in the modified as-treated population, demonstrating that the proportion of patients achieving MMR at 12 months was statistically significantly higher for bosutinib (55.0%; 33/60) compared to the historical control (25%) under H_0 with 1-sided p-value of <0.0001. The primary objective of the protocol was met.

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Table 5. Summary of Major Molecular Response (MMR) at Month 12 - Modified as-Treated Population

	Bosutinib (N=60) n (%)
Molecular Response	
MMR	33 (55.0)
90% CI	[44.4, 65.6]
1-sided p-value	<.0001

Cutoff Date: 12Mar2019
Note: Percentages are based on the number of subjects. MMR is defined as <= 0.1% BCR-ABL ratio on the international scale (corresponding to >= 3 log reduction from standardized baseline) with a minimum of 3,000 ABL transcripts assessed by the central laboratory.
CCI [redacted]

The MMR at 12 months by Sokal risk group was 51.9% (90% CI: 36.0, 67.7), 61.5% (90% CI: 45.8, 77.2) and 42.9% (90% CI: 12.1, 73.6) for low, intermediate and high risk groups, respectively (Table 6).

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Table 6. Summary of Major Molecular Response (MMR) at Month 12 by Sokal Risk Group - Modified as-Treated Population

	Bosutinib (N=60) n (%)
Low Risk < 0.8	27
MMR	14 (51.9)
90% CI	[36.0, 67.7]
Intermediate Risk 0.8-1.2	26
MMR	16 (61.5)
90% CI	[45.8, 77.2]
High Risk > 1.2	7
MMR	3 (42.9)
90% CI	[12.1, 73.6]

Cutoff Date: 12Mar2019
Note: Percentages are based on the number of subjects in each group. MMR is defined as <= 0.1% BCR-ABL ratio on the international scale (corresponding to >= 3 log reduction from standardized baseline) with a minimum of 3,000 ABL transcripts assessed by the central laboratory.
CCI [redacted]

Secondary Efficacy Results:

Major Molecular Response by 12 Months:

The MMR by 12 months was 61.7% (90% CI: 51.3, 72.0) in the modified as-treated population.

Note: MMR by 18 months was not evaluated in the Core Treatment Phase analysis; the data for this endpoint were immature as not all patients still on-treatment but without achieving MMR had reached the Month 18 visit at the time of data cut-off. Therefore, the analysis of this endpoint is not presented.

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Complete Cytogenetic Response by 12 Months:

The CCyR by 12 months was 80.0% (90% CI: 71.5, 88.5) in the modified as-treated population.

Duration of Major Molecular Response:

Data for duration of MMR was not mature at the data cut-off date. Of the 40 (out of 60 patients) that achieved MMR anytime on-treatment in the modified as-treated population, no patients had events at the time of data cut-off (events defined as confirmed loss of MMR, treatment discontinuation due to disease progression, and deaths that occurred due to disease progression within 28 days after last dose).

Duration of Complete Cytogenetic Response:

Data for duration of CCyR was not mature at the data cut-off date. Of the 48 patients (out of 60 patients) that achieved CCyR anytime on-treatment in the modified as-treated population, no patients had events at the time of the data cut-off (events defined as confirmed loss of CCyR, treatment discontinuation due to disease progression, and deaths that occurred due to disease progression within 28 days after last dose).

Event-Free Survival:

Data for on-treatment EFS was not mature at the data cut-off date; no on-treatment deaths were reported. Of 60 patients in the modified as-treated population, 1 patient had events of interest (defined as either death, transformation to AP or BP, doubling of WBC without CHR, loss of CCyR or loss of CHR) and 19 patients (31.7%) had competing risk events (treatment discontinuation without an EFS event). The cumulative incidence of EFS events at Week 48 was 1.7% (90% CI: 0.2, 6.4) in the modified as-treated population.

Overall Survival:

Data for OS was not mature at the data cut-off date; at this time-point 1 patient had died during the study. The Kaplan-Meier estimate of OS at Week 48 was 100.0% (90% CI: 100.0, 100.0) in the modified as-treated population.

Pharmacokinetic Results:

A summary of trough bosutinib plasma concentrations over time is provided in Table 7. The mean bosutinib concentration averaged over Days 28, 56, and 84 was 82.75 ng/mL (standard deviation: 47.956 ng/mL) (range: 7.59 to 260 ng/mL). Trough concentrations were stable over time (Figure 1).

Additional population PK or PK/pharmacodynamic modeling analyses will be conducted and summarized in a separate population modeling analysis report.

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Table 7. Summary of Trough Bosutinib Plasma Levels (ng/mL) - PK Analysis Set

Visit	Statistic	Total (N=60)
Day 1	n	60
	Mean (SD)	0.000 (0.0000)
	95% CI	0.0, 0.0
	Median	0.000
	Min, Max	0.00, 0.00
Day 28	n	34
	Mean (SD)	83.564 (64.1056)
	95% CI	61.2, 105.9
	Median	66.500
	Min, Max	1.38, 363.00
Day 56	n	41
	Mean (SD)	85.963 (46.4095)
	95% CI	71.3, 100.6
	Median	82.600
	Min, Max	3.28, 216.00
Day 84	n	44
	Mean (SD)	79.659 (41.5369)
	95% CI	67.0, 92.3
	Median	69.100
	Min, Max	19.10, 199.00
Average Concentration	n	51
	Mean (SD)	82.748 (47.9555)
	95% CI	69.3, 96.2
	Median	71.200
	Min, Max	7.59, 260.00

Cutoff Date: 12Mar2019
[1] BLQ - Below Limit of Quantification. Concentrations that are BLQ and reported as less than the Lower Limit of Quantification (BLQ < LLOQ) will be replaced with zero for Day 1. For Days 28, 56 and 84 values of BLQ (< LLOQ) will be replaced with LLOQ/2.
[2] Average concentration = mean of Day 28, 56 and 84 trough concentrations
CCI [redacted]

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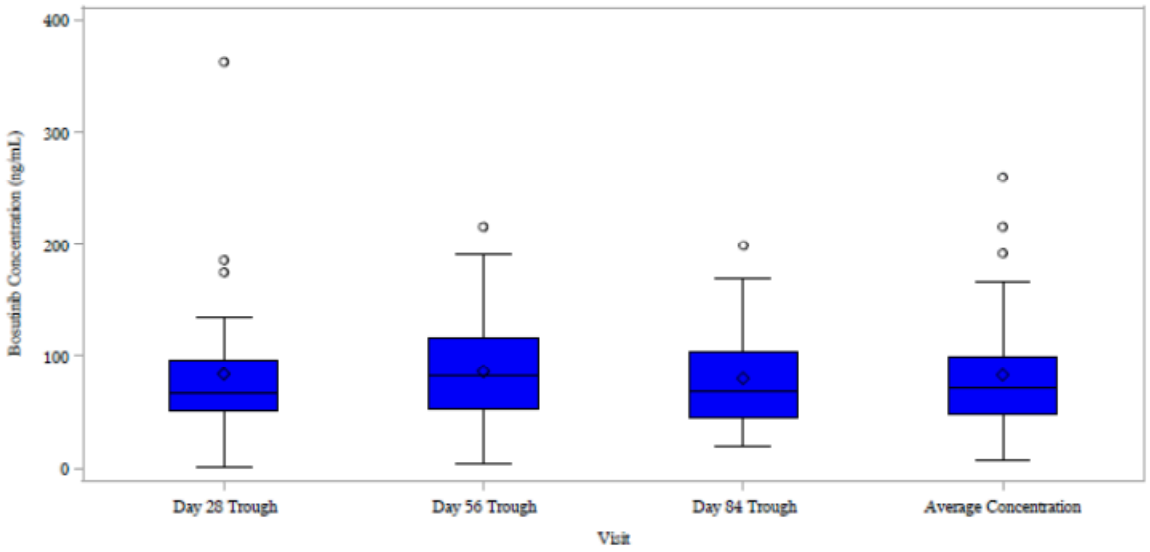
Figure 1. Box Plot of Trough Bosutinib Plasma Concentrations (ng/mL) - Pharmacokinetic Analysis Set



Concentrations that were BLQ and reported as less than the LLOQ (BLQ <LLOQ) for Days 28, 56, and 84 were replaced with LLOQ/2.
Box plot provides median (horizontal line), mean (diamond), outliers (circles) and 25%/75% quartiles with whiskers to the last points within 1.5 times the interquartile range.
Abbreviations: BLQ=below limit of quantification; LLOQ=lower limit of quantification.

Safety Results:

Study Drug Dosing and Duration:

The summary of exposure to the study drug in as-treated population is provided in Table 8, and duration of treatment and duration of study is provided in Table 9.

Patients received a median of 419.0 doses (range: 9 to 615 doses) of the study drug; the median actual dose intensity was 354.73 mg/day (95.3 to 494.1 mg/day). Patients had a median of 21.0 missed doses (range: 0 to 136). The median dose intensity was lower than starting dose (400 mg/day) because many patients needed temporary discontinuation and/or dose reduction of study drug for the management of AE.

The median duration of study treatment was 15.31 months (range: 0.30 to 21.85 months) and the median duration on study was 16.56 months (range: 11.07 to 21.85 months).

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Table 8. Summary of Exposure to Study Drug - As-Treated Population

	Bosutinib (N=60)
Cumulative Actual Total Dose (mg)	
n	60
Mean (SD)	135876.7 (85103.63)
Median	148550.0
Min, Max	3600, 310300
Number of Doses	
n	60
Mean (SD)	356.5 (208.73)
Median	419.0
Min, Max	9, 615
Missed Doses	
n	60
Mean (SD)	34.2 (33.33)
Median	21.0
Min, Max	0, 136
Actual dose intensity (mg/day) [a]	
n	60
Mean (SD)	305.36 (107.037)
Median	354.73
Min, Max	95.3, 494.1
Relative dose intensity (%) [b]	
n	60
Mean (SD)	76.34 (26.759)
Median	88.68
Min, Max	23.8, 123.5

Cutoff Date: 12Mar2019
aCD: Actual cumulative dose in mg,
LDD: Last dose date of zero or non-zero dose of the study drug, DF: Date of the first non-zero dose of the study drug.
a. Actual dose intensity (mg/day)=aCD/(LDD - DF + 1).
b. Relative dose intensity (%)=100 × (actual dose intensity)/(theoretical dose intensity).
CCI [redacted]

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Table 9. Summary of Treatment Duration and Study Duration - As-Treated Population

	Bosutinib (N=60)
Duration of Treatment (Days) [a]	
n	60
Mean (SD)	387.6 (200.03)
Median	466.0
Min, Max	9, 665
Duration of Treatment (Months) [a]	
n	60
Mean (SD)	12.734 (6.5713)
Median	15.309
Min, Max	0.30, 21.85
Duration of Study (Days) [b]	
n	60
Mean (SD)	499.0 (90.24)
Median	504.0
Min, Max	337, 665
Duration of Study (Months) [b]	
n	60
Mean (SD)	16.392 (2.9646)
Median	16.557
Min, Max	11.07, 21.85

Cutoff Date: 12Mar2019
Months was calculated as Days/30.44.
a. Duration of therapy was the time from treatment start to last dose of treatment.
b. Duration of study was from the date of first dose of study drug to last known alive date or withdrawn date.
CCI [redacted]

CLINICAL STUDY REPORT SYNOPSIS

Treatment-Emergent Adverse Events:

A summary of all-causality and treatment-related AEs is presented in Table 10. A total of 60 patients (100.0%) reported at least 1 TEAEs, and 14 patients (23.3%) reported treatment-emergent SAEs. A total of 568 AEs were reported of which 428 were treatment-related.

No deaths during bosutinib treatment were reported in the study. A total of 45 patients (75.0%) had Grade 3 or Grade 4 AEs. Thirty-three (33) patients (55.0%) had a dose reduction, and 42 patients (70.0%) had a temporary discontinuation associated with AEs. A total of 18 patients (30.0%) discontinued the study drug due to AEs.

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Table 10. Summary of Treatment-Emergent Adverse Events (All-Causalities and Treatment-Related) - As-Treated Population

Number (%) of Subjects:	Bosutinib (N=60) All-Causality n (%)	Bosutinib (N=60) Treatment-Related n (%)
Subjects evaluable for adverse events	60	60
Number of adverse events	568	428
Subjects with adverse events	60 (100.0)	59 (98.3)
Subjects with medication error events	0	0
Subjects with serious adverse events	14 (23.3)	12 (20.0)
Subjects with maximum Grade 3 or 4 adverse events	45 (75.0)	45 (75.0)
Subjects with maximum Grade 5 adverse events	0	0
Subjects with Grade 3 and higher adverse events	45 (75.0)	45 (75.0)
Subjects with adverse events leading to discontinuation of study drug	18 (30.0)	18 (30.0)
Subjects with adverse events leading to dose reduction of study drug	33 (55.0)	32 (53.3)
Subjects with adverse events leading to temporary discontinuation of study drug	42 (70.0)	41 (68.3)

Cutoff Date: 12Mar2019
Includes data up to 28 days after the last dose of study drug.
Except for the number of AEs, subjects were counted only once in each row.
Serious AEs - according to the Investigator's assessment.
CTCAE v4.03 applied.
CCI [redacted]

The all-causality TEAEs that occurred in ≥10% of patients are presented by SOC and preferred term in Table 11. The most common TEAEs (≥20%) experienced by patients receiving bosutinib were diarrhea (86.7%), alanine aminotransferase (ALT) increased (55.0%), aspartate aminotransferase (AST) increased (46.7%), nausea (28.3%), nasopharyngitis (28.3%), blood alkaline phosphatase increased (26.7%), rash (26.7%), lipase increased (26.7%), vomiting (25.0%), pyrexia (23.3%) and platelet count decreased (21.7%). There were gastrointestinal events and liver function related events reported with high frequency, which were consistent with known bosutinib safety profile.

Treatment-related TEAEs were experienced by 59 patients (98.3%).

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The most common treatment-related TEAEs (≥20%) experienced by patients receiving bosutinib were diarrhea (86.7%), ALT increased (55.0%), AST increased (46.7%), nausea (26.7%), blood alkaline phosphatase increased (26.7%), lipase increased (25.0%) and rash, vomiting, and platelet count decreased (all reported in 21.7% patients).

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Table 11. Summary of Treatment-Emergent Adverse Events in at Least 10% of Subjects by MedDRA System Organ Class and Preferred Term in Decreasing Frequency Order (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)	
	All-Causality	Treatment-Related
Number (%) of Subjects: by System Organ Class and Preferred Term	n (%)	n (%)
With Any Adverse Event	60 (100.0)	59 (98.3)
GASTROINTESTINAL DISORDERS	52 (86.7)	52 (86.7)
Diarrhoea	52 (86.7)	52 (86.7)
Nausea	17 (28.3)	16 (26.7)
Vomiting	15 (25.0)	13 (21.7)
Constipation	7 (11.7)	5 (8.3)
Abdominal pain upper	6 (10.0)	5 (8.3)
INVESTIGATIONS	51 (85.0)	49 (81.7)
Alanine aminotransferase increased	33 (55.0)	33 (55.0)
Aspartate aminotransferase increased	28 (46.7)	28 (46.7)
Blood alkaline phosphatase increased	16 (26.7)	16 (26.7)
Lipase increased	16 (26.7)	15 (25.0)
Platelet count decreased	13 (21.7)	13 (21.7)
Gamma-glutamyltransferase increased	11 (18.3)	11 (18.3)
Amylase increased	9 (15.0)	9 (15.0)
Lymphocyte count decreased	7 (11.7)	7 (11.7)
Neutrophil count decreased	7 (11.7)	7 (11.7)

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Table 11. Summary of Treatment-Emergent Adverse Events in at Least 10% of Subjects by MedDRA System Organ Class and Preferred Term in Decreasing Frequency Order (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)	
	All-Causality	Treatment-Related
Number (%) of Subjects: by System Organ Class and Preferred Term	n (%)	n (%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	42 (70.0)	39 (65.0)
Rash	16 (26.7)	13 (21.7)
Rash maculo-papular	8 (13.3)	8 (13.3)
INFECTIONS AND INFESTATIONS	39 (65.0)	8 (13.3)
Nasopharyngitis	17 (28.3)	2 (3.3)
Upper respiratory tract infection	6 (10.0)	1 (1.7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	19 (31.7)	19 (31.7)
Anaemia	10 (16.7)	10 (16.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	17 (28.3)	11 (18.3)
Pyrexia	14 (23.3)	8 (13.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	15 (25.0)	9 (15.0)
Back pain	7 (11.7)	1 (1.7)
HEPATOBILIARY DISORDERS	12 (20.0)	11 (18.3)
Liver disorder	7 (11.7)	6 (10.0)
NERVOUS SYSTEM DISORDERS	7 (11.7)	5 (8.3)
Headache	7 (11.7)	5 (8.3)

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Table 11. Summary of Treatment-Emergent Adverse Events in at Least 10% of Subjects by MedDRA System Organ Class and Preferred Term in Decreasing Frequency Order (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)	
	All-Causality	Treatment-Related
Number (%) of Subjects: by System Organ Class and Preferred Term	**n (%)**	**n (%)**

Cutoff Date: 12Mar2019
Includes data up to 28 days after the last dose of study drug.
Subjects were counted only once per event.
MedDRA v21.1 coding dictionary applied.
CCI [redacted]

CLINICAL STUDY REPORT SYNOPSIS

Grade 3 and Higher Treatment-Emergent Adverse Events:

A summary of incidence of all-causality and treatment-related Grade ≥3 TEAEs in at least 5% of patients is provided in Table 12.

There were no Grade 5 TEAEs reported in the study. Grade ≥3 TEAEs were experienced by 45 patients (75.0%) in the study, of which Grade 3 events were reported in 34 patients (56.7%) and Grade 4 events were reported in 11 patients (18.3%).

The most common Grade ≥3 TEAEs (≥10%) experienced by patients receiving bosutinib were ALT increased (33.3%), AST increased (18.3%), diarrhea (15.0%) and lipase increased (15.0%). Out of the reported Grade ≥3 TEAEs, the majority of the TEAEs were considered to be treatment-related.

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Table 12. Summary of Treatment-Emergent Adverse Events of Grade 3 and Higher in at Least 5% of Subjects by MedDRA System Organ Class and Preferred Term in Decreasing Frequency Order (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)	
	All-Causality	Treatment-Related
Number (%) of Subjects: by System Organ Class and Preferred Term	n (%)	n (%)
With Any Adverse Event	45 (75.0)	45 (75.0)
INVESTIGATIONS	35 (58.3)	33 (55.0)
Alanine aminotransferase increased	20 (33.3)	20 (33.3)
Aspartate aminotransferase increased	11 (18.3)	11 (18.3)
Lipase increased	9 (15.0)	8 (13.3)
Neutrophil count decreased	5 (8.3)	5 (8.3)
Lymphocyte count decreased	4 (6.7)	4 (6.7)
Gamma-glutamyltransferase increased	3 (5.0)	3 (5.0)
Platelet count decreased	3 (5.0)	3 (5.0)
GASTROINTESTINAL DISORDERS	9 (15.0)	9 (15.0)
Diarrhoea	9 (15.0)	9 (15.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	7 (11.7)	7 (11.7)
Lymphopenia	4 (6.7)	4 (6.7)
HEPATOBILIARY DISORDERS	7 (11.7)	7 (11.7)
Liver disorder	5 (8.3)	5 (8.3)

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Table 12. Summary of Treatment-Emergent Adverse Events of Grade 3 and Higher in at Least 5% of Subjects by MedDRA System Organ Class and Preferred Term in Decreasing Frequency Order (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)	
	All-Causality	Treatment-Related
Number (%) of Subjects: by System Organ Class and Preferred Term	**n (%)**	**n (%)**

Cutoff Date: 12Mar2019
Includes data up to 28 days after the last dose of study drug.
Subjects were only counted once per event.
MedDRA v21.1 coding dictionary and CTCAE version 4.03 applied.
CCI [redacted]

CLINICAL STUDY REPORT SYNOPSIS

Permanent Discontinuations due to Adverse Events:

The details of AEs leading to study drug discontinuations are provided in Table 13. A total of 18 patients (30.0%) experienced AEs leading to discontinuation of study drug. The most common AEs leading to discontinuation of study drug (≥5% of patients) were ALT increased (10.0%) and AST increased (8.3%). All the events leading to permanent discontinuation were considered to be treatment-related.

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Table 13. Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuations (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)	
	All-Causality	Treatment-Related
Number (%) of Subjects: by System Organ Class and Preferred Term	n (%)	n (%)
With Any Adverse Event	18 (30.0)	18 (30.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (1.7)	1 (1.7)
Thrombocytopenia	1 (1.7)	1 (1.7)
HEPATOBILIARY DISORDERS	2 (3.3)	2 (3.3)
Drug-induced liver injury	1 (1.7)	1 (1.7)
Liver disorder	1 (1.7)	1 (1.7)
INFECTIONS AND INFESTATIONS	1 (1.7)	1 (1.7)
Pneumonia	1 (1.7)	1 (1.7)
INVESTIGATIONS	10 (16.7)	10 (16.7)
Alanine aminotransferase increased	6 (10.0)	6 (10.0)
Aspartate aminotransferase increased	5 (8.3)	5 (8.3)
Lipase increased	2 (3.3)	2 (3.3)
Hepatic enzyme increased	1 (1.7)	1 (1.7)
Neutrophil count decreased	1 (1.7)	1 (1.7)
Pancreatic enzymes increased	1 (1.7)	1 (1.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (1.7)	1 (1.7)
Pleural effusion	1 (1.7)	1 (1.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (6.7)	4 (6.7)

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Table 13. Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuations (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)	
	All-Causality	Treatment-Related
Number (%) of Subjects: by System Organ Class and Preferred Term	n (%)	n (%)
Drug eruption	2 (3.3)	2 (3.3)
Erythema multiforme	2 (3.3)	2 (3.3)

Cutoff Date: 12Mar2019
Includes data up to 28 days after the last dose of study drug.
Subjects were counted only once per event.
MedDRA v21.1 coding dictionary applied.
CCI [redacted]

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Dose Reductions or Temporary Discontinuations due to Adverse Events:

A total of 42 patients (70.0%) temporarily discontinued the study drug due to AEs. The most common AEs leading to temporary discontinuation of study drug (≥5% of patients) were ALT increased (28.3%), AST increased (16.7%), liver disorder (10.0%), diarrhea (10.0%), lymphocyte count decreased (5.0%), and neutrophil count decreased (5.0%).

A total of 33 patients (55.0%) had their dose reduced due to AEs. The most common AEs leading to dose reduction of the study drug (≥5% of patients) were ALT increased (21.7%), AST increased (13.3%), lipase increased (8.3%), and neutrophil count decreased (5.0%).

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events:

Deaths:

There was 1 death reported after the SAE reporting period (ie, after the last dose of study drug + 28 days) among patients who participated in this study. The reason of the death was disease progression, and was not related to the study drug.

Other Serious Adverse Events:

A summary of the incidence of all-causality and treatment-related SAEs by SOC, preferred term and maximum Common Terminology Criteria for Adverse Events are provided in Table 14.

The incidence of SAEs was reported in 14 patients (23.3%), of which SAEs reported in 12 patients (20.0%) were considered to be treatment-related. The SAE of diabetic retinopathy reported in 1 patient and the SAEs of wound infection and ankle fracture reported in another patient were not considered to be treatment-related.

The most frequently reported treatment-emergent SAEs (≥2 patients) were diarrhea, liver disorder and dehydration (all reported as 3.3%).

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Table 14. Summary of Serious Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum CTCAE Grade (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)			
CTCAE Grade	All-Causality		Treatment-Related	
Number (%) of Subjects: by System Organ Class and Preferred Term	All Grades n (%)	Grade≥ 3 n (%)	All Grades n (%)	Grade≥ 3 n (%)
With Any Adverse Event	14 (23.3)	14 (23.3)	12 (20.0)	12 (20.0)
EYE DISORDERS	1 (1.7)	1 (1.7)	0	0
Diabetic retinopathy	1 (1.7)	1 (1.7)	0	0
GASTROINTESTINAL DISORDERS	2 (3.3)	2 (3.3)	2 (3.3)	2 (3.3)
Diarrhoea	2 (3.3)	2 (3.3)	2 (3.3)	2 (3.3)
Vomiting	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Pyrexia	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
HEPATOBILIARY DISORDERS	3 (5.0)	3 (5.0)	3 (5.0)	3 (5.0)
Liver disorder	2 (3.3)	2 (3.3)	2 (3.3)	2 (3.3)
Drug-induced liver injury	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
INFECTIONS AND INFESTATIONS	4 (6.7)	3 (5.0)	3 (5.0)	3 (5.0)
Gastroenteritis	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Pneumonia	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Pyelonephritis	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Sepsis	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Wound infection	1 (1.7)	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (1.7)	1 (1.7)	0	0

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Table 14. Summary of Serious Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum CTCAE Grade (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)			
CTCAE Grade	All-Causality		Treatment-Related	
Number (%) of Subjects: by System Organ Class and Preferred Term	All Grades n (%)	Grade≥ 3 n (%)	All Grades n (%)	Grade≥ 3 n (%)
Ankle fracture	1 (1.7)	1 (1.7)	0	0
INVESTIGATIONS	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Alanine aminotransferase increased	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Aspartate aminotransferase increased	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
METABOLISM AND NUTRITION DISORDERS	2 (3.3)	2 (3.3)	2 (3.3)	2 (3.3)
Dehydration	2 (3.3)	2 (3.3)	2 (3.3)	2 (3.3)
RENAL AND URINARY DISORDERS	1 (1.7)	0	1 (1.7)	0
Acute kidney injury	1 (1.7)	0	1 (1.7)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Pleural effusion	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (3.3)	2 (3.3)	2 (3.3)	2 (3.3)
Drug eruption	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Erythema multiforme	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)

Cutoff Date: 12Mar2019
Includes data up to 28 days after the last dose of study drug.
Subjects were counted only once per event.
MedDRA v21.1 coding dictionary and CTCAE v4.03 applied.
CCI [redacted]

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Other Significant Adverse Events:

The summary of all treatment-emergent adverse event of special interest (AESI) categories, all-causalities and treatment-related are provided in Table 15. These events included cardiac, edema, effusion, gastrointestinal, hemorrhage, hypertension, infection, myelosuppression, liver-related, rash, vascular, and renal AEs. No hypersensitivity AESIs were reported in the study.

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Table 15. Summary of Treatment-Emergent Adverse Events of Special Interest Categories (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)			
CTCAE Grade	All-Causality		Treatment-Related	
Number (%) of Subjects: by AESIs Categories and Preferred Term	All Grades n (%)	Grade≥ 3 n (%)	All Grades n (%)	Grade≥ 3 n (%)
With Any Adverse Event	60 (100.0)	41 (68.3)	59 (98.3)	41 (68.3)
CARDIAC	3 (5.0)	0	3 (5.0)	0
Pericardial effusion	3 (5.0)	0	3 (5.0)	0
EDEMA	3 (5.0)	0	2 (3.3)	0
Face oedema	1 (1.7)	0	1 (1.7)	0
Oedema	1 (1.7)	0	1 (1.7)	0
Weight increased	1 (1.7)	0	0	0
EFFUSION	5 (8.3)	1 (1.7)	5 (8.3)	1 (1.7)
Pleural effusion	4 (6.7)	1 (1.7)	4 (6.7)	1 (1.7)
Pericardial effusion	3 (5.0)	0	3 (5.0)	0
GASTROINTESTINAL	52 (86.7)	9 (15.0)	52 (86.7)	9 (15.0)
Diarrhoea	52 (86.7)	9 (15.0)	52 (86.7)	9 (15.0)
Nausea	17 (28.3)	0	16 (26.7)	0
Vomiting	15 (25.0)	1 (1.7)	13 (21.7)	1 (1.7)
HEMORRHAGE	5 (8.3)	0	1 (1.7)	0
Contusion	1 (1.7)	0	0	0
Epistaxis	1 (1.7)	0	1 (1.7)	0
Haemorrhoidal haemorrhage	1 (1.7)	0	0	0

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Table 15. Summary of Treatment-Emergent Adverse Events of Special Interest Categories (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)			
CTCAE Grade	All-Causality		Treatment-Related	
Number (%) of Subjects: by AESIs Categories and Preferred Term	All Grades n (%)	Grade≥ 3 n (%)	All Grades n (%)	Grade≥ 3 n (%)
Metrorrhagia	1 (1.7)	0	0	0
Petechiae	1 (1.7)	0	1 (1.7)	0
Retinal haemorrhage	1 (1.7)	0	0	0
HYPERTENSION	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Hypertension	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
INFECTION	39 (65.0)	4 (6.7)	8 (13.3)	4 (6.7)
Nasopharyngitis	17 (28.3)	0	2 (3.3)	0
Upper respiratory tract infection	6 (10.0)	0	1 (1.7)	0
Influenza	5 (8.3)	0	0	0
Gastroenteritis	4 (6.7)	1 (1.7)	1 (1.7)	1 (1.7)
Cystitis	3 (5.0)	0	1 (1.7)	0
Bronchitis	2 (3.3)	0	1 (1.7)	0
Tinea pedis	2 (3.3)	0	1 (1.7)	0
Angular cheilitis	1 (1.7)	0	0	0
Conjunctivitis	1 (1.7)	0	0	0
Eye infection	1 (1.7)	0	0	0
Herpes simplex	1 (1.7)	0	0	0
Infectious colitis	1 (1.7)	0	0	0
Lung infection	1 (1.7)	0	1 (1.7)	0
Onychomycosis	1 (1.7)	0	0	0

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Table 15. Summary of Treatment-Emergent Adverse Events of Special Interest Categories (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)			
CTCAE Grade	All-Causality		Treatment-Related	
Number (%) of Subjects: by AESIs Categories and Preferred Term	All Grades n (%)	Grade≥ 3 n (%)	All Grades n (%)	Grade≥ 3 n (%)
Otitis externa	1 (1.7)	0	0	0
Paronychia	1 (1.7)	0	0	0
Pneumonia	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Pyelonephritis	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Rhinolaryngitis	1 (1.7)	0	0	0
Sepsis	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Sinusitis	1 (1.7)	0	0	0
Urethritis	1 (1.7)	0	0	0
Urinary tract infection	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Wound infection	1 (1.7)	0	0	0
LIVER-RELATED	48 (80.0)	29 (48.3)	47 (78.3)	29 (48.3)
Alanine aminotransferase increased	33 (55.0)	20 (33.3)	33 (55.0)	20 (33.3)
Aspartate aminotransferase increased	28 (46.7)	11 (18.3)	28 (46.7)	11 (18.3)
Blood alkaline phosphatase increased	16 (26.7)	0	16 (26.7)	0
Liver disorder	7 (11.7)	5 (8.3)	6 (10.0)	5 (8.3)
Ascites	2 (3.3)	0	2 (3.3)	0
Blood bilirubin increased	2 (3.3)	1 (1.7)	2 (3.3)	1 (1.7)
Hepatic function abnormal	2 (3.3)	0	2 (3.3)	0
Transaminases increased	2 (3.3)	1 (1.7)	2 (3.3)	1 (1.7)
Bilirubin conjugated increased	1 (1.7)	0	1 (1.7)	0

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Table 15. Summary of Treatment-Emergent Adverse Events of Special Interest Categories (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)			
CTCAE Grade	All-Causality		Treatment-Related	
Number (%) of Subjects: by AESIs Categories and Preferred Term	All Grades n (%)	Grade≥ 3 n (%)	All Grades n (%)	Grade≥ 3 n (%)
Drug-induced liver injury	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Hepatic enzyme increased	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Hepatobiliary disease	1 (1.7)	0	1 (1.7)	0
Liver function test abnormal	1 (1.7)	0	1 (1.7)	0
Liver injury	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
MYELOSUPPRESSION	27 (45.0)	16 (26.7)	27 (45.0)	16 (26.7)
Platelet count decreased	13 (21.7)	3 (5.0)	13 (21.7)	3 (5.0)
Anaemia	10 (16.7)	0	10 (16.7)	0
Lymphocyte count decreased	7 (11.7)	4 (6.7)	7 (11.7)	4 (6.7)
Neutrophil count decreased	7 (11.7)	5 (8.3)	7 (11.7)	5 (8.3)
Thrombocytopenia	5 (8.3)	2 (3.3)	5 (8.3)	2 (3.3)
White blood cell count decreased	5 (8.3)	1 (1.7)	5 (8.3)	1 (1.7)
Lymphopenia	4 (6.7)	4 (6.7)	4 (6.7)	4 (6.7)
Neutropenia	3 (5.0)	2 (3.3)	3 (5.0)	2 (3.3)
Leukopenia	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
RASH	33 (55.0)	3 (5.0)	29 (48.3)	3 (5.0)
Rash	16 (26.7)	1 (1.7)	13 (21.7)	1 (1.7)
Rash maculo-papular	8 (13.3)	1 (1.7)	8 (13.3)	1 (1.7)
Dermatitis acneiform	4 (6.7)	0	4 (6.7)	0
Eczema asteatotic	4 (6.7)	0	1 (1.7)	0

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Table 15. Summary of Treatment-Emergent Adverse Events of Special Interest Categories (All-Causalities and Treatment-Related) - As-Treated Population

Number of Subjects Evaluable for AEs	Bosutinib (N=60)			
CTCAE Grade	All-Causality		Treatment-Related	
Number (%) of Subjects: by AESIs Categories and Preferred Term	All Grades n (%)	Grade≥ 3 n (%)	All Grades n (%)	Grade≥ 3 n (%)
Eczema	3 (5.0)	0	2 (3.3)	0
Rash generalised	2 (3.3)	0	2 (3.3)	0
Rash papular	2 (3.3)	0	2 (3.3)	0
Dermatitis contact	1 (1.7)	0	0	0
Erythema	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
RENAL	4 (6.7)	0	4 (6.7)	0
Acute kidney injury	2 (3.3)	0	2 (3.3)	0
Blood creatinine increased	1 (1.7)	0	1 (1.7)	0
Renal impairment	1 (1.7)	0	1 (1.7)	0
VASCULAR	1 (1.7)	0	0	0
Peripheral coldness	1 (1.7)	0	0	0

Cutoff Date: 12Mar2019
Includes data up to 28 days after the last dose of study drug.
MedDRA v21.1 coding dictionary and CTCAE v4.03 applied.
CCI [redacted]

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An analysis of AESI did not identify any new safety signals. Within the categories of AESIs (cardiac, edema, effusion, gastrointestinal, hemorrhage, hypertension, infection, liver-related, myelosuppression, rash, renal, and vascular), the most frequent Grade ≥3 events were liver-related, myelosuppression, gastrointestinal, infection and rash AESIs, which was consistent with the known safety profile of bosutinib. The overall incidence of cardiac, hemorrhage, effusion, vascular, hypertension, and renal AESIs was low (<9%).

For the gastrointestinal AESIs, including the most frequently reported event of diarrhea (86.7%), the median time to first event was 1.0 days (range: 1 to 271 days), and there were no patients who permanently discontinued due to the gastrointestinal AESIs. For the liver-related AESIs, the most common AESIs were ALT increased (33 patients [55.0%]), AST increased (28 patients [46.7%]), blood alkaline phosphatase increased (16 patients [26.7%]) and liver disorder (7 patients [11.7%]). The median time to first event was 15.0 days (range: 1 to 169 days). A total of 10 patients (16.7%) were permanently discontinued due to liver-related AESIs. Among those patients with liver-related AESIs, 58.3% of patients had their study drug dose temporarily stopped in response to liver-related AESIs; of which most patients were successfully rechallenged with study drug and there were no cases of Hy's law or permanent liver injury observed in the study. Vascular and cardiac AEs were reported infrequently (1.7% and 5.0%, respectively). Vascular event search criteria included coronary artery disorders, arteriosclerosis, stenosis, vascular insufficiency and necrosis, embolism and thrombosis. The only reported vascular AE was peripheral coldness. Cardiac event search criteria included cardiac arrhythmias, heart failures, pericardial disorders, and QT prolongation. The only reported cardiac AE was pericardial effusion.

Renal AESIs were reported in 6.7% of patients and all the events were considered to be treatment-related. The renal AESIs were resolved in 3 out of 4 patients and no permanent discontinuation was reported due to renal AESIs. Effusion AESIs (pleural effusion and pericardial effusion) were reported in 8.3% of patients. Edema AESIs were reported in 5.0% of patients. There was 1 AESI of hypertension (Grade 3) that was reported in the study and no events of hypersensitivity AESIs were reported.

The most frequently reported blood chemistry related laboratory abnormalities were ALT increased, AST increased, alkaline phosphatase increased, creatinine increased, and hypoalbuminemia and hypocalcemia. The most frequently reported hematological laboratory abnormalities were lymphocyte count decreased, hemoglobin decreased (anemia) and platelet count decreased.

Overall, there were no clinically significant findings in ECGs/vital signs and left ventricular ejection fraction.

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Conclusions:

In Japanese patients with newly diagnosed Ph+ CP CML, bosutinib showed favorable efficacy similar to Study AV001, which demonstrated the superior efficacy of bosutinib 400 mg QD to imatinib 400 mg QD, one of the standard therapies, therefore it is suggested that bosutinib offers clinically meaningful benefit for Japanese patients with newly diagnosed Ph+ CP CML.

Bosutinib had a generally acceptable profile in Japanese patients with newly diagnosed Ph+ CP CML. The safety profile of bosutinib was consistent with the known safety profile of bosutinib and no new safety signals were identified.

In conclusion, the benefit-risk balance of bosutinib at a starting dose of 400 mg QD in Japanese patients with newly diagnosed Ph+ CP CML is considered favorable. Bosutinib can be an important effective treatment option for Japanese patients with newly diagnosed Ph+ CP CML.