CLINICAL PROTOCOL

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

Investigational Product Number:	PF-05208763, SKI-606
Investigational Product Name:	Bosutinib
United States (US) Investigational New Drug (IND) Number:	Not Applicable (N/A)
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	B1871048
Phase:	2b

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale

Amendment 1	30 Mar 2018	• Made changes in study objectives/endpoints and interim analysis.
		  • Added "MMR by 12 months" as a secondary endpoint and "interim look" prior to primary analysis to assess the possibility of early communication with regulatory authorities based on the interim data. This change affected Sections 2, 9.2.2.1 and 9.5.
		  • Added "Time to $MR^{4.0}$ and $MR^{4.5}$" as exploratory objectives and endpoints in Section 2 to be aligned with Section 9.
		  • Split an exploratory objective and endpoint "MMR at 3, 6, 9, 12 (in patients with both Ph+ and Ph negative (-) CP CML) and 18 months" into two separated exploratory endpoints in Section 2 for clarification.
		  • Removed a duplicated exploratory objective and endpoint related to evaluation of BCR-ABL mutations in Section 2.
		• Updated bosutinib information based on the results of Study AV001 and FDA approval for newly diagnosed CML in Section 1.2.4.
		• Incorporated changes of Protocol Administrative Change Letters.
		  • Clarified the required timing of 24-hour urine protein and microscopic assessments in Table 4.
		  • Eliminated the inconsistency in the items of hematology tests (SoA and Section 7.1.1) and the active collection periods of

		AEs and SAEs (SoA and Section 8.1.4). • Clarified the definitions of "loss of MCyR or CCyR" and "loss of CHR" in Sections 6.5 and 9.2.2.4. • Provided examples of the items of laboratory tests for the efficacy assessments in Section 7.1.1. • Added administrative changes, clarification and typographical corrections for clarity and consistency. • Clarified evaluable patients for the analyses of cytogenetic or molecular response in Section 9.2. • Clarified the definitions of "CHR" and "AP/BP CML" for statistical analyses in Sections 9.3.1.3 and 9.3.1.4, and Appendix 2. • Made other minor edits for clarity or consistency where appropriate throughout the document.
Original protocol	31 Jan 2017	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background and Rationale

Bosutinib (Bosulif®) is an orally bioavailable, potent, multi-targeted, dual Src/Abl tyrosine kinase inhibitor (TKI) that has been approved in Japan and multinationally for the treatment of adult patients with Philadelphia chromosome (Ph)-positive(+) chronic phase (CP), accelerated phase (AP), and blast phase (BP) chronic myelogenous leukemia (CML) previously treated with other TKI inhibitor therapy.[1] In December 2017, bosutinib was additionally approved for adult patients with newly diagnosed Ph+ CP CML in the US. This study will investigate the efficacy and safety of bosutinib as a first-line treatment for Japanese adult patients with Ph+ CP CML.

In Japan, patients with newly diagnosed CML are now able to be effectively treated with TKIs, including imatinib, dasatinib, and nilotinib, with their disease controlled for long periods of time. Bosutinib may represent an additional choice for such patients for treatment of their CML in the first-line treatment setting, which could offer these patients a better tolerated and possibly more sustainable treatment option than other available therapies.

Prior clinical studies with bosutinib in CML have used a starting dose of bosutinib of 500 mg once daily (QD). In the previous studies, a substantial number of patients experienced toxicities. The incidence of treatment-emergent adverse events (TEAEs) overall as well as unique TEAEs were lower following dose reduction from 500 mg QD to 400 mg QD, while the efficacy of bosutinib in patients who received dose reductions to 400 mg QD remained favorable. Therefore, it was hypothesized that a starting dose of 400 mg QD in this Phase 2 study in the first-line Japanese CP CML patient treatment setting will result in better tolerability and similar efficacy as a starting dose of 500 mg QD.

Objectives and Endpoints

Primary Objective

- To evaluate major molecular response (MMR) at 12 months (48 weeks) in newly diagnosed Japanese Ph+ CP CML patients harboring b2a2 and/or b3a2 transcripts.

Secondary Objectives

All efficacy analyses for secondary/exploratory objectives will be performed using the same population as primary objective, unless otherwise indicated (detailed in Section 9). For detailed definitions of responses, see Appendix 2.

- To evaluate MMR by 12 and 18 months.

- To estimate the proportion of patients demonstrating complete cytogenetic response (CCyR) by 12 months.

- To evaluate the duration of MMR and CCyR.
- To evaluate event-free survival (EFS).
- To evaluate overall survival (OS).
- To assess the population pharmacokinetics (PK).
- To assess correlations between trough concentrations of bosutinib and key efficacy and safety endpoints.
- To characterize the safety profile of bosutinib in Japanese patients.

Exploratory Objectives

- To evaluate MMR at 3, 6, 9 and 18 months.
- To evaluate MMR at 12 months in patients with both Ph+ and Ph negative (-) CP CML.
- To evaluate molecular response (MR)[1] and MR[2] at 3 months and 6 months, respectively.
- To evaluate $MR^{4.0}$ and $MR^{4.5}$ at 3, 6, 9 and 12 months.
- To evaluate time to MMR, $MR^{4.0}$, $MR^{4.5}$ and CCyR.
- To evaluate the proportion of patients demonstrating a cumulative complete hematologic response (CHR) in patients with Ph+ and both Ph+ and Ph- CP CML.
- To estimate the time to transformation to AP and BP CML on treatment.
- To evaluate the type of BCR-ABL mutations present at treatment completion or discontinuation, or in case of suboptimal response.
- To enable exploratory research through collection of banked biospecimen, unless prohibited by local regulations or ethics committee (EC) decision.

Primary Endpoint

- MMR at 12 months (48 weeks). All Ph+ CP CML patients harboring b2a2 and/or b3a2 transcripts will be assessed and follow-up for MMR as primary endpoint. MMR is defined as ≤0.1% BCR-ABL on the international scale (IS) by quantitative reverse transcriptase polymerase chain reaction (RT-qPCR).

Secondary Endpoints

- MMR by 12 and 18 months.

- CCyR by 12 months.
- Duration of MMR and CCyR.
- EFS
- OS
- Population PK parameters.
- Correlations between trough concentrations of bosutinib and key efficacy and safety endpoints.
- Safety: AEs (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v.4.03); laboratory abnormalities (as graded by NCI CTCAE v.4.03); vital signs (blood pressure, pulse rate); electrocardiograms (ECGs); echocardiogram (ECHO) or multiple gated acquisition (MUGA).

Exploratory Endpoints

- MMR at 3, 6, 9 and 18 months.
- MMR at 12 months in patients with both Ph+ and Ph- CP CML.
- MR^1 and MR^2 at 3 months and 6 months, respectively.
- $MR^{4.0}$ and $MR^{4.5}$ at 3, 6, 9 and 12 months.
- Time to MMR, $MR^{4.0}$, $MR^{4.5}$ and CCyR.
- Cumulative CHR in patients with Ph+ and both Ph+ and Ph- CP CML.
- Time to transformation to AP and BP CML on treatment.
- Type of mutations present at treatment completion/discontinuation or suboptimal response.
- Potential results from exploratory analyses of banked biospecimen (these results may or may not be generated in the context of the present study).

Study Design

Study Overview

This is a Phase 2, open-label, single-arm study designed to evaluate efficacy and safety of bosutinib alone in Japanese adult patients with newly diagnosed CP CML. The primary

endpoint is MMR at 12 months in newly diagnosed Japanese Ph+ CP CML patients harboring b2a2 and/or b3a2 transcripts. Patients will receive bosutinib treatment at a starting dose of 400 mg QD. The dose of bosutinib is allowed to be escalated (up to a maximum of 600 mg QD) for unsatisfactory response or reduced for toxicity.

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

The study will be open for enrollment until approximately 60 Ph+ CML patients harboring b2a2 and/or b3a2 transcripts have been registered. Bone marrow aspirate to assess the Ph status will be obtained at screening, patients with known Ph- prior to registration are not eligible for this study. However, as confirmation of the Ph status prior to registration is not mandatory, Ph- CML patients may also be included. Approximately 3 Ph- CML patients are expected to be registered as approximately 5% of the patients with BCR-ABL-positive CML are diagnosed as Ph- CML.[2,3] All patients will be treated and/or followed up to approximately 3 years (144 weeks) after registration of the last patient, or until study termination, whichever comes first. Patients who permanently discontinue study treatment will be followed for survival, investigator-assessed transformation to AP/BP, duration of response and disease progression, and initiation/response to further anti-cancer therapies, including stem cell transplantation (where applicable).

Study Treatments

All patients will receive bosutinib at a starting dose of 400 mg QD. The dose of bosutinib may 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.

Each patient will receive daily bosutinib for up to approximately 3 years after registration of the last patient (12 months [48 weeks] Core Treatment Phase and the following ≥24 months [96 weeks] Extension Phase) or until the end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first.

Statistical Methods

The primary analysis population for the efficacy evaluation will be the modified as-treated population. The modified as-treated population will consist of all patients with Ph+ CP CML harboring b2a2 and/or b3a2 transcripts who received at least 1 dose of study medication.

The primary efficacy variable is MMR rate at 12 months (48 weeks) which is defined as the proportion of patients achieving MMR at 12 months (48 weeks). MMR is defined as BCR-ABL expression of ≤0.1% of initial BCR-ABL transcript from standardized baseline measured by RT-qPCR.

Sample Size Determination

The primary analysis will use the hypothesis test for a binomial proportion the using normal approximation. The study is powered at greater than 82% to test the null hypothesis that the true MMR rate at 12 months (48 weeks) is 25% versus the alternative hypothesis that the true MMR rate is 40% with one-sided alpha of 5%. A sample size of 60 Ph+ CML patients harboring b2a2 and/or b3a2 transcripts is required for MMR at 12 months (48 weeks). 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), will be considered to be a successful demonstration of efficacy for this study.

As cytogenetic confirmation for Ph chromosome is not required for enrollment and 5% of patients are expected to be Ph- CML, approximately 3 Ph- CML patients may be enrolled, which will not affect the primary analysis.[2,3]

SCHEDULE OF ACTIVITIES

The SCHEDULE OF ACTIVITIES table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SCHEDULE OF ACTIVITIES table in order to conduct evaluations or assessments required to protect the well-being of the patient.

Visit Identifier [a]	**Screening**		**Core Treatment Phase**													**Extension Phase**	**End of Treatment / Withdrawal**
Month	**0**	**0**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**5**	**6**	**9, 12**	**Every 12 weeks up to 2 years, then every 24 weeks thereafter**	**7-28 days after the last dose of study drug**
Week	**0**	**0**	**1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**36, 48**		
Day	**-28 to registration**	**-14 to registration**	**1**	**7**	**14**	**21**	**28**	**42**	**56**	**70**	**84**	**112**	**140**	**168**	**252, 336**		
Visit Time Window				**±4 days**												**±1 week**	
Informed consent	X																
Registration			X														
Inclusion/Exclusion criteria review	X																
Demographic data collection		X															
Sokal score calculation[b]		X															
Medical[c]/Cancer history[d] review		X															
Physical examination[e]		X					X		X		X				X	X	X
Vital signs, weight, and height (screening only)[f]		X	X								X			X	X	X	X
ECOG performance status		X									X					X	X
Extramedullary assessment[g]		X					X		X		X				X	X	
Digital ECG[h]		X	X				X		X		X					As clinically indicated	X
Chest X-ray		X						As clinically indicated									X
Contraception check[i]	X		X				X		X		X	X	X	X	X	X	X
ECHO or MUGA[j]	X							As clinically indicated									X

Visit Identifier [a]	**Screening**		**Core Treatment Phase**													**Extension Phase**	**End of Treatment / Withdrawal**
Month	**0**	**0**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**5**	**6**	**9, 12**	**Every 12 weeks up to 2 years, then every 24 weeks thereafter**	**7-28 days after the last dose of study drug**
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Visit Time Window				**±4 days**												**±1 week**	
Laboratory Tests																	
Hematology including CBC with differential[k]		X		X	X	X	X	X	X	X	X	X	X	X	X	X[y]	X
Chemistry panel with electrolytes and CK[l]		X					X		X		X		X	X	X	X[y]	X
Liver function tests[m]		X					X		X		X		X	X	X	X[y]	X
Estimated glomerular filtration rate		X					X		X		X		X	X	X	X[y]	X
Coagulation panel[n]		X									X					X[y]	X
HBV and HCV test		X															
Dipstick urinalysis (microscopic if abnormalities detected)		X					X				X					X[y]	X
Serum or urine pregnancy test (for women of childbearing potential)	X		X				X		X		X	X	X	X	X	X[y]	X
Study Treatment																	
Study drug administration[o]			Continuous daily from Day 1														
Disease Assessments																	
Bone marrow aspirate[p] for cytogenetics[q] and differential	X[p]										X[q]			X	X[p]	X	X[p]
Peripheral blood for local RT-qPCR for BCR-ABL		X[r]															
Peripheral blood for central RT-qPCR for BCR-ABL[s] and mutation analysis[t]		X									X			X	X	X	X
Other Clinical Assessments																	
Adverse events[u]			X	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Concomitant medications[v]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Other Samplings																	
PK blood sample collection[w]			X				X		X		X						
Banked blood biospecimens[x]		X															

Visit Identifier [a]	Screening		Core Treatment Phase													Extension Phase	End of Treatment / Withdrawal
Month	**0**	**0**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**5**	**6**	**9, 12**	**Every 12 weeks up to 2 years, then every 24 weeks thereafter**	**7-28 days after the last dose of study drug**
Week	**0**	**0**	**1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**36, 48**		
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Visit Time Window				**±4 days**												**±1 week**	
Other																	
Long-term follow-up[z]																X	

Abbreviations: → = ongoing/continuous event; BCR-ABL = Fusion transcript or protein resulting from the 9;22 chromosomal translocation responsible for formation of the Philadelphia Chromosome; CBC = complete blood count; CK = creatine kinase; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; MUGA = multiple gated acquisition; PK = pharmacokinetics; RT-qPCR = Quantitative reverse transcriptase polymerase chain reaction.

a. Day relative to start of study treatment (Day 1).
b. Every effort should be made in order to have Sokal score calculated prior to any anti-CML treatments (ie. at initial diagnosis of patient). Sokal formula is Exp (0.0116 × (age - 43.4) + 0.0345 × (spln - 7.51) + 0.188 × [(plt/700)^2 - 0.563] + 0.0887 × (blasts - 2.1)); Note: Spln=centimeters below costal margin, plt=platelet count, 10^9/L, blasts=% blasts in peripheral blood. If the patient has already received anti-CML treatment prior to screening every effort should be made to obtain test results/data before the start of treatment in order to calculate the Sokal score. If patient did not have prior anti-CML treatment, the Sokal score will be calculated using data obtained at screening.
c. Medical history review includes clinically significant past and current diagnoses (including complete cardiac history) and surgical procedures.
d. Cancer history review includes full history of the course of the patient's cancer including date of diagnosis and any prior treatments, history of blood and platelet transfusions or history of lumbar punctures within 28 days prior to registration.
e. Complete physical examination ensuring examination of liver and spleen will be performed.
f. Vital signs include temperature (axillary), supine blood pressure, and heart rate. Height will be measured at screening only.
g. Extramedullary assessment will include physical examination and based on this assessment and any specific evidence, appropriate imaging testing can be requested by the investigator. The assessment should be done at any time if extramedullary disease is suspected.
h. Digital ECGs to be done in triplicate at each time point and should be performed at the same as PK sampling (if applicable). End of Treatment/Withdrawal visit ECG should be done at least 5 days after the last dose of bosutinib and prior to initiating other anticancer treatment (if possible). ECG should also be performed if clinically significant decrease in ejection fraction is detected by ECHO/MUGA while on treatment, and otherwise as clinically indicated.
i. Male patients who are able to father children and female patients who are of childbearing potential will need to follow the contraception guidelines in Section 4.3.
j. ECHO or MUGA to be performed at screening (within 2 weeks prior to registration) and at End of Treatment/Withdrawal or at Week 96, whichever is earlier. If a patient has undergone ECHO or MUGA as standard of care prior to entering the study, the procedures will not have to be repeated if results are available and the procedures were performed within 28 days prior to registration. To enable meaningful clinical comparison, every effort must be made to ensure that the imaging method used to assess cardiac function remains consistent for each individual patient through the course of the trial.

k. Hematology including automated complete blood count (CBC) (eg, hemoglobin, RBC, WBC, platelets and hematocrit) with differential counts (eg, neutrophils, lymphocytes, monocytes, eosinophils, basophils, metamyelocytes, myelocytes, promyelocytes, myeloblasts, unspecified blast cells and band cells) to be performed locally. Hematology assessments are to be performed at Screening, Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 and then every 12 weeks for the next 72 weeks (ie, until the end of Year 2), then every 24 weeks, and End of Treatment/Withdrawal visit. CHR must be confirmed by 2 assessments at least 4 weeks apart. Hematology to be repeated at least 4 weeks after achieving first CHR.
l. Chemistry panel to be performed locally including: sodium, potassium, chloride, carbon dioxide or bicarbonate (if available), blood urea nitrogen (BUN) or urea, creatinine, glucose, total protein, albumin, calcium, alkaline phosphatase, amylase, lipase, phosphorous or phosphate, and magnesium. Creatine kinase (CK) also to be performed locally. Abnormally high CK values should be confirmed and fractionated (where possible). Uric acid to be obtained until patient achieves a CHR. Supplementation is advised for potassium levels or magnesium levels below the lower limit of normal (LLN), with consideration of the patient's underlying renal function.
m. Liver Function tests to be performed locally including: total bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
n. Coagulation panel to be performed locally including: prothrombin time (PT) expressed as either PT or international normalized ratio (INR) and partial/activated partial thromboplastin time (PTT or aPTT).
o. The first dose of study drug should occur no later than 3 business days after registration of the patient, with the day of first study drug administration = Day 1.
p. Bone marrow obtained as part of standard of care prior to signing informed consent document can be used at screening as long as it was collected within 28 days prior to registration. **Once CCyR or MMR has been achieved, bone marrow aspirates will be performed only if clinically indicated (eg, suboptimal response, suspect disease progression or failed/inadequate Week 48 assessment)**. Patients completing treatment for cytogenetically confirmed treatment failure do not need to repeat bone marrow at treatment completion. Patients ending treatment for reasons other than cytogenetically confirmed treatment failure must undergo treatment completion bone marrow aspirate if previous bone marrow aspirate performed >12 weeks prior. If loss of major molecular response occurs in combination with a 5 × PCR increase for BCR-ABL, a bone marrow aspirate for chromosome banding analysis (CBA) should be obtained.
q. Cytogenetics analysis must be performed so that dose-escalation rules can be appropriately applied (eg, patient should not have 12-week bone marrow aspirate before Day 84 so that at least 12 weeks from first dose is assessed). Cytogenetic assessment of bone marrow aspirate will be performed locally. If cytogenetics is used, it must be performed by CBA of marrow cell metaphases, counting at least 20 metaphases, at 12, 24, 36, and 48 weeks, until CCyR or MMR is achieved, then every 48 weeks.
r. Local PCR result for BCR-ABL confirmation is acceptable prior to informed consent where this has already been conducted as part of initial diagnosis of a patient, provided this molecular diagnosis of CP CML has been made ≤6 months prior to registration. However, central PCR sample must always be conducted after informed consent, as this is a study-specific procedure.
s. RT-qPCR testing for BCR-ABL will be performed at Screening, at 12, 24, 36, and 48 weeks during the Core Treatment Phase and then every 12 weeks until the end of Year 2, then every 24 weeks. If a ≥5-fold increase in BCR-ABL transcripts from the lowest value achieved on study along with loss of MMR is identified and confirmed by duplicate analysis of the same sample, an unscheduled visit sample will be collected within 4-6 weeks to confirm the results. Fifteen (15) mL peripheral blood will be collected at each designated time-point. Additional 5 mL blood will be collected at Week 48; these will serve as back-up samples for the primary endpoint. For patients who achieve undetectable BCR-ABL by RT-qPCR, 20 mL of blood may be collected for PCR analysis. In addition, after the first documented negative BCR-ABL result, 20 mL of blood will be collected for all subsequent sampling time-points until BCR-ABL is no longer negative. 20 mL of blood may be collected as an unscheduled PCR sample from these patients.
t. Mutation analysis will be performed in case of either lack of response, suboptimal response or loss of response defined as: failure to achieve MMR at 12 months; loss of MMR AND rise in BCR-ABL transcript level by ≥5-fold from the lowest value achieved during the study; at the End of Treatment/Withdrawal visit. No mutation analysis will occur at screening. For patients with a positive mutation identified during therapy, follow-up

mutation analyses will be performed in subsequent samples. For a patient with a negative mutation result immediately following relapse, continued mutation analyses may be performed at a frequency of every 6 months (every 24 weeks) as needed.

u. AEs should be documented and recorded at each visit using the NCI CTCAE version 4.03. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If a patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
v. All concomitant medications and non-drug supportive interventions will be recorded in the CRF from 28 days prior to registration and up to 28 days after the last dose of study treatment.
w. The pre-dose PK samples should be collected before (within 3 hrs of) study drug administration on Days 1, 28, 56, and 84. 3 mL of whole blood for plasma drawn into a tube containing potassium ethylenediaminetetraacetic acid (EDTA). See Section 7.3. On PK sampling days, the bosutinib dose should be taken in the hospital under the supervision of the study site personnel. The bosutinib dose should be administered after the PK sample has been collected.
x. Blood sample will be collected for bio-banking if specifically allowed by local Institutional Review Board (IRB) or EC; 1 tube of whole blood (prep D1) will be collected at Screening. If not collected on the designated collection day, collect at the next available time point when bio-specimens are being collected in conjunction with a patient visit.
y. For patients remaining on treatment in the Extension Phase, the investigator should continue to perform biochemistry and hematology testing, per standard of care for CML patients and as clinically indicated in line with local guidelines including cytogenetics when indicated by bone marrow analysis. Patients will have mandatory AE and SAE collection follow-up. These are expected to take place at least every 12 weeks.
z. Long-Term Follow-Up information will be collected via telephone contact up to approximately 3 years after registration of the last patient, or until study termination, whichever comes first, where possible for patients who discontinue the study early. Follow-up calls should be conducted every 12 weeks in the first two years, and then every 24 weeks. The timing of follow-up calls is calculated with Day 1 designated as the starting point.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

This study will investigate the efficacy and safety of bosutinib 400 mg QD as a first-line treatment for Japanese adult patients with Ph+ CP CML.

Bosutinib (Bosulif®) is an orally active Src/Abl kinase inhibitor with potent antiproliferative and proapoptotic activity in CML cells.

1.2. Background and Rationale

1.2.1. CML and the Treatment Options

CML is one of the major types of leukemia. CML is a clonal myeloid neoplasm in which the leukemic cells in over 95% patients have a reciprocal translocation between chromosomes 9 and 22 t(9;22)(q34;q11), the consequence of which is the generation of the Ph. The molecular product of the t(9;22) translocation is the BCR-ABL oncogene, which encodes the constitutively activated BCR-ABL kinase that activates several downstream signaling pathways that mediate myeloproliferation, resistance to apoptosis and genetic instability. More than 95% of CML patients have b2a2 and/or b3a2 coding for BCR-ABL kinase.[4] The transition of patients with CML from CP to BP with an intermediate AP is becoming less common with the chief determinants of survival being disease stage and TKI responsiveness.

Hematopoietic stem cell transplantation (HSCT) is the only curative strategy for CML. Other treatments including chemotherapy, interferon alpha, and TKIs are effective in controlling the disease to varying degrees in all populations. The utility of HSCT is largely limited to pediatric and younger adult patients, especially those with matched donors. In addition to its limited acceptability, HSCT is associated with a substantial morbidity and mortality. The risks accompanying HSCT and the delay in finding or nonavailability of matched donors have necessitated an alternate treatment paradigm wherein agents targeting the BCR-ABL fusion protein, such as TKIs, are considered frontline therapy.

The first such TKI to be used successfully as a therapeutic agent was imatinib. Imatinib was granted approval by the European Commission in November 2001 and by the US Food and Drug Administration (FDA) in December 2002 for the treatment of newly diagnosed patients with CP CML based on results from the IRIS trial. However, despite the overall success of imatinib, some patients fail to achieve the desired response, experience disease progression, or are intolerant to imatinib treatment. After 8 years of follow-up of the IRIS trial, only 55% of the patients originally randomized to the imatinib treatment group remain on study drug. This was primarily due to failure to achieve CCyR (17%), loss of CCyR (15%) and intolerance to imatinib (approximately 5%).[5] While several mechanisms of imatinib resistance have been proposed, the best known and possibly the most clinically prevalent are lack of adherence/compliance (which may reflect AEs in some patients) and/or the development of BCR-ABL mutations, which alter drug sensitivity and can be detected in approximately 40% to 50% of patients with CP CML in which imatinib has failed.[5]

Second-generation TKIs, dasatinib and nilotinib, were initially developed and approved in 2006 and 2007, respectively, for the treatment of patients with resistance or intolerance to

prior therapy, including imatinib. In 2010, both dasatinib and nilotinib were additionally approved for adult patients with newly diagnosed Ph+ CML in CP on the basis of Phase 3 studies that demonstrated favorable results compared with imatinib.[6, 7]

According to the National Comprehensive Cancer Network (NCCN) Version 2, 2014 guidelines[8] and European Leukaemia Net Recommendation,[9] imatinib, dasatinib or nilotinib are considered the standard of care in newly diagnosed patients with Ph+ CML who are not eligible for stem cell transplant. Imatinib has been used as the active comparator in investigations of both dasatinib and nilotinib.

1.2.2. Bosutinib (BOSULIF®, Pfizer)

Bosutinib is an oral, dual Src/Abl TKI with more potent inhibitory activity against BCR-ABL than imatinib in CML cell lines,[10, 11] with minimal inhibitory activity against c-KIT or platelet-derived growth factor receptor.[11, 12] These are 2 nonspecific targets potentially associated with toxicities reported for other second-generation TKIs.

Bosutinib is being developed for the first-line treatment of Ph+ CML and to delay disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD). Human experience with bosutinib is based on preliminary information obtained from patients in clinical studies, including patients with Ph+ leukemias; patients with solid tumors, including advanced or metastatic breast cancer; patients with ADPKD; and healthy subjects. As presented in the May 2016 Bosutinib Investigator's Brochure (IB), approximately 2478 patients, including 2141 patients with cancer, have received at least 1 dose of bosutinib in 24 clinical studies.

Bosutinib has shown an acceptable safety profile in the Phase 1, Phase 2, and Phase 3 studies to date. In general, AEs with bosutinib have included predominantly low-grade gastrointestinal (GI) toxicities and general symptoms such as fatigue and asthenia. Other frequent AEs include rash and increases in plasma levels of hepatic transaminase (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]). Following continuous daily dose administration in cancer patients, most GI AEs resolved with therapy, treatment interruption, and/or dose reduction and less frequently discontinuation of bosutinib in the case of dose-limiting toxicities (DLTs). Serious adverse reactions reported include anaphylactic shock, myelosuppression, GI toxicity (diarrhea), fluid retention, hepatotoxicity, and rash.

The results of the Japan local Phase 1/2 study (Study B1871007) showed consistent with findings in Western populations. The most common AEs reported were diarrhea (95%), nasopharyngitis (57%), rash (57%), lymphopenia (40%), nausea (38%), vomiting (38%), increased ALT (38%), thrombocytopenia (33%), anaemia (30%), and increased AST (30%). The most common grade 3/4 AEs were lymphopenia (25%), neutropenia (21%), thrombocytopenia (21%), increased lipase (19%), and increased ALT (17%).

On 04 September 2012, bosutinib was approved by the FDA for the treatment of adult patients with CP, AP, and BP Ph+ CML with resistance or intolerance to prior therapy. More recently, on 17 January 2013, the Committee for Medicinal Products for Human Use

(CHMP) issued a positive opinion recommending that bosutinib be granted conditional marketing authorization in the European Union (EU), for the treatment of adult patients with CP, AP, and BP Ph+ CML previously treated with one or more TKIs and for whom imatinib, nilotinib, and dasatinib are not considered appropriate treatment options.

Those approvals have been granted mainly based on results obtained from the Phase 1/2 study (Study B1871006) in adult patients with Ph+ leukemias who had failed prior TKI therapy, with the support of the results obtained as part of the Phase 3 study (Study B1871008) comparing bosutinib with imatinib in newly diagnosed Ph+ CP CML patients.

In Japan, on 26 September 2014, bosutinib was approved for the treatment of patients with CML with resistance or intolerance to prior therapy, and this approval has been granted mainly based on results obtained from the Japan local Phase 1/2 study (Study B1871007) in adult patients with Ph+ CML who had failed prior TKI therapy.

1.2.3. Bosutinib as First-Line Treatment for CP CML

In the Phase 3 study (Study B1871008, "Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia" [BELA]), bosutinib (500 mg QD) was compared to imatinib in the first-line treatment of Ph+ CP CML. The primary objective of the study was to compare the complete CCyR at 1 year in CP CML patients receiving bosutinib alone versus patients receiving imatinib alone. The study enrolled 502 patients (250 on bosutinib and 252 on imatinib). No statistically significant difference was observed at 12 months of treatment between the bosutinib and imatinib groups regarding rates of CCyR (70% vs. 68%). Similarly, the cumulative CCyR rates by 24 months were virtually identical at 79% and 81%, respectively. However, in an intent-to treat (ITT) analysis, the MMR rates at 12 months for bosutinib and imatinib were 41% and 27%, and the cumulative MMR rates by 24 months were 61% versus 52%, respectively ($p < 0.05$ for both comparisons). Time to CCyR and MMR was shorter with bosutinib compared to imatinib ($p < 0.001$ for both comparisons). Furthermore, the percentage of patients who experienced treatment failure (4% vs. 13%), progression to AP or BP (2% vs. 5%) or death (3% vs. 5%) was lower among those receiving bosutinib compared to those treated with imatinib. The shorter time to response is important for patients as it means they have a shorter time when they are vulnerable to potential progression to either AP or BP.

Results after a minimum follow-up of 24 months showed that 66% of patients receiving bosutinib and 45% of those treated with imatinib had dose interruptions. Dose reductions were required in 43% and 21% of patients, respectively. The rates of treatment discontinuation were 37% and 29%, respectively. Importantly, treatment discontinuations due to AEs or disease progression in the bosutinib and imatinib groups were 24% versus 4% and 7% versus 13%, respectively.

Compared with imatinib, bosutinib was associated with higher incidences of Grade 3/4 GI toxicities, including diarrhea (12% vs. 1%), vomiting (3% vs. 0%) and abdominal pain (1% vs. <1%), although these AEs were usually transient and manageable. Notably, diarrhea occurred mostly in the first 1-2 months of therapy and improved or subsided spontaneously over time.

Grade 3/4 elevations of ALT (23% vs. 4%), AST (12% vs. 4%) or lipase (11% vs. 6%) were more frequent among patients treated with bosutinib compared to imatinib. Of those patients experiencing Grade 3/4 elevations in transaminase levels in the bosutinib treatment group of this study, 91% were rechallenged. Of these patients, 80% were successfully re-challenged. Overall, 14% of patients were discontinued from bosutinib treatment due to unacceptable transaminase elevations. Grade 3/4 neutropenia, thrombocytopenia and anaemia in the bosutinib and imatinib treatment groups were 10% vs. 24%, 14% vs. 15% and 8% vs. 8%, respectively, indicating that bosutinib is at least as safe as imatinib regarding hematologic toxicity.

In summary, bosutinib was associated with a toxicity profile distinct from that of imatinib. A higher number of patients (n=48, 19%) were discontinued from bosutinib treatment as a result of an AE, including 15 (31%) of 48 patients who discontinued before their first post baseline assessment. One of the goals of this study is to assess safety of bosutinib treatment compared with imatinib treatment. Early discontinuations as a result of toxicity may have contributed to the lower rate of CCyR associated with bosutinib in the ITT population, which included these patients as non-responders.

Although bosutinib therapy was associated with greater rates of diarrhea, vomiting, and aminotransferase elevations compared with imatinib, most instances were transient and, in the case of diarrhea, frequently self-limiting after the first 2 to 3 months of therapy. Fluid retention, which has commonly been observed with dasatinib[13, 14, 15, 16, 17, 18, 19, 20] and imatinib[13, 21, 22] occurred infrequently with bosutinib. Despite the occurrence of liver function test abnormalities with bosutinib treatment, no cases were associated with permanent liver injury or liver failure. Low rates of Grade 3/4 (all causality) anaemia (6%), neutropenia (11%), and thrombocytopenia (14%) were reported with bosutinib. The minimal inhibition of c-KIT by bosutinib may have contributed to the low incidence of myelosuppressive events, particularly Grade 3/4 neutropenia.[23] Overall, there were fewer deaths in the bosutinib treatment group, with no treatment-related deaths and few CML-related deaths in either treatment group. The trends in toxicity profile observed for bosutinib in this study were similar to those previously observed for bosutinib in CP CML after failure of imatinib treatment.[24]

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Bosutinib IB.

1.2.4. Study Rationale

In Japan, patients with newly diagnosed CML are now able to be effectively treated with TKIs, including imatinib, dasatinib, and nilotinib, with their disease controlled for long periods of time. Bosutinib may represent an additional choice for such patients for treatment of their CML in the first-line treatment setting, which could offer these patients a better tolerated and possibly more sustainable treatment option than other available therapies.

In the Phase 3 study (Study B1871008, BELA), which evaluated the effect of treatment in a first-line treatment setting, bosutinib at 500 mg QD did not meet the primary efficacy objective of demonstrating a superior rate of CCyR at 12 months versus imatinib. However,

bosutinib did demonstrate superiority across many other efficacy endpoints including MMR at 12 months, and importantly for patients, the percentage of patients with transformation to AP or BP was lower for bosutinib than imatinib.

In addition, the safety profile of bosutinib was distinct from that of imatinib in terms of increased GI toxicity, especially diarrhea, and increased levels of ALT/AST. However, there were fewer patients with hematological toxicities. Detailed management guidelines for diarrhea have been added to this protocol to help the management of the AE profile of this drug (Appendix 6). In addition, investigators will receive careful training to ensure appropriate understanding of the bosutinib side effect profile.

Prior clinical studies of bosutinib in CML have used a starting dose of bosutinib of 500 mg QD, both in first-line (Study B1871008, BELA) and in later lines of treatment (Studies B1871006 and B1871007). In both studies, a substantial number of patients experienced toxicities. However these were managed in most cases by treatment interruption and/or dose reduction, which allowed the subsequent reintroduction of bosutinib.

In first-line CP CML patients recruited in Study B1871008 (BELA), a total of 92 out 250 patients (37%) treated with bosutinib had a dose reduction from 500 mg QD to 400 mg QD. The median time to first dose reduction to 400 mg QD was 53.5 days with a range from 2 to 612 days.

The incidence of TEAEs overall as well as unique TEAEs were lower following dose reduction from 500 mg QD to 400 mg QD. The overall incidence of Grade 3/4 TEAEs decreased from 88% to 71%. All of the most frequently reported TEAEs (all grades) also decreased: diarrhea (70% to 40%), ALT increased (39% to 30%), nausea (38% to 23%), vomiting (33% to 24%), AST increased (33% to 23%), and thrombocytopenia (30% to 21%). It is notable that the median time on treatment for patients prior to dose reduction was 53.5 days (range: 2-612 days) while the median time on treatment for patients post dose reduction was 449 days (range: 0-1142 days). This suggests that patients on the 400 mg dose are better able to maintain treatment.

The efficacy of bosutinib in patients who received dose reductions to 400 mg QD remained favorable with 46% of patients achieving a CCyR after the dose reduction to 400 mg QD (compared to 58% in the ITT population) and 16% of patients maintaining a previously attained CCyR. In addition, 40% of patients were able to achieve a MMR while on 400 mg QD of bosutinib (compared to 45% in the ITT population). Of those dose reduced to 400 mg QD and who attained a CCyR and MMR, the majority of patients (68% and 71% respectively), were still on treatment and retaining their response at the time of the analyses.

These data from Study B1871008 (BELA) suggest that the use of a starting dose of 400 mg QD in this Phase 2 study in the first-line Japanese CP CML patient treatment setting will result in better tolerability and similar efficacy as a starting dose of 500 mg QD.

Thus, the incidence of TEAEs overall as well as unique TEAEs were lower following dose reduction from 500 mg QD to 400 mg QD, while the efficacy of bosutinib in patients who received dose reductions to 400 mg QD remained favorable. Therefore, it was hypothesized

that a starting dose of 400 mg QD in this Phase 2 study in the first-line Japanese CP CML patient treatment setting will result in better tolerability and similar efficacy as a starting dose of 500 mg QD.

In December 2017, bosutinib was additionally approved for adult patients with newly diagnosed Ph+ CP CML in the US by FDA based on the results of Phase 3 study of bosutinib versus imatinib (Study AV001, BFORE). The MMR rates at 12 months for bosutinib (starting dose of 400 mg QD) and imatinib were 47% and 37% (two-sided p=0.0200), and the CCyR rates by 12 months were 77% and 66% (two-sided p=0.0075) respectively, thus bosutinib showed superior efficacy compared to imatinib.[25] In addition, the most frequently reported treatment-emergent adverse events (TEAEs) (all grades) are diarrhea (70%), nausea (35%), thrombocytopenia (35%), rash (34%), ALT increased (31%), abdominal pain (25%) and AST increased (23%), and this result is consistent with the known safety profile of bosutinib. These results suggest that bosutinib can be an important alternative for patients with newly diagnosed CP CML.

1.3. Banked Biospecimen

Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens section. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) make it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

Banked biospecimens retained in the BBS also can be used in research on CML.

Providing these biospecimens is a required study activity for study sites and patients, unless prohibited by local regulations or by the IRB or EC decision.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	**Primary Endpoint:**
• 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 will be assessed and follow-up for MMR as primary endpoint. MMR is defined as ≤0.1% BCR-ABL on the IS by RT-qPCR.
Secondary Objectives[a,b]:	**Secondary Endpoints:**
• To evaluate MMR by 12 and 18 months. • To estimate the proportion of patients demonstrating CCyR by 12 months. • To evaluate the duration of MMR and CCyR. • To evaluate EFS. • To evaluate overall survival OS. • To assess the population PK. • To assess correlations between trough concentrations of bosutinib and key efficacy and safety endpoints. • To characterize the safety profile of bosutinib in Japanese patients.	• MMR by 12 and 18 months. • CCyR by 12 months. • Duration of MMR and CCyR. • EFS • OS • Population PK parameters. • Correlations between trough concentrations of bosutinib and key efficacy and safety endpoints. • Safety: AEs (as graded by NCI CTCAE v.4.03); laboratory abnormalities (as graded by NCI CTCAE v.4.03); vital signs (blood pressure, pulse rate); ECGs; ECHO or MUGA.
Exploratory Objectives [a,b]:	**Exploratory Endpoints:**
• To evaluate MMR at 3, 6, 9 and 18 months. • To evaluate MMR at 12 months in patients with both Ph+ and Ph- CP CML. • To evaluate MR^{1} and MR^{2} at 3 months and 6 months, respectively. • To evaluate $MR^{4.0}$ and $MR^{4.5}$ at 3, 6, 9 and 12 months.	• MMR at 3, 6, 9 and 18 months. • MMR at 12 months in patients with both Ph+ and Ph- CP CML. • MR^{1} and MR^{2} at 3 months and 6 months, respectively. • $MR^{4.0}$ and $MR^{4.5}$ at 3, 6, 9 and 12 months.

• To evaluate time to MMR, $MR^{4.0}$, $MR^{4.5}$ and CCyR.	• Time to MMR, $MR^{4.0}$, $MR^{4.5}$ and CCyR.
• To evaluate the proportion of patients demonstrating a cumulative complete hematologic response (CHR) in patients with Ph+ and both Ph+ and Ph- CP CML.	• Cumulative CHR in patients with Ph+ and both Ph+ and Ph- CP CML.
• To estimate the time to transformation to AP and BP CML on treatment.	• Time to transformation to AP and BP CML on treatment.
• To evaluate the type of BCR-ABL mutations present at treatment completion or discontinuation, or in case of suboptimal response.	• Type of mutations present at treatment completion/discontinuation or suboptimal response.
• To enable exploratory research through collection of banked biospecimen, unless prohibited by local regulations or ethics committee decision.	• Potential results from exploratory analyses of banked biospecimen (these results may or may not be generated in the context of the present study).

a. All efficacy analyses for secondary/exploratory objectives will be performed using the same population as primary objective, unless otherwise indicated (detailed in Section 9).
b. For detailed definitions of responses, see Appendix 2.

3. STUDY DESIGN

This is a Phase 2, open-label, single-arm study designed to evaluate efficacy and safety of bosutinib alone in Japanese adult patients with newly diagnosed CP CML. The primary endpoint is MMR at 12 months in newly diagnosed Japanese Ph+ CP CML patients harboring b2a2 and/or b3a2 transcripts. Patients will receive bosutinib treatment at a starting dose of 400 mg QD. The dose of bosutinib is 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.

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

The study will be open for enrollment until approximately 60 Ph+ CML patients harboring b2a2 and/or b3a2 transcripts have been registered. Bone marrow aspirate to assess the Ph status will be obtained at screening. Patients with known Ph- prior to registration are not eligible for this study. However, as confirmation of the Ph status prior to registration is not mandatory, Ph- CML patients may also be included. Approximately 3 Ph- CML patients are expected to be registered as approximately 5% of the patients with BCR-ABL-positive CML are diagnosed as
Ph-CML.[2,3] All patients will be treated and/or followed up to approximately 3 years

(144 weeks) after registration of the last patient, or until study termination, whichever comes first. Patients who permanently discontinue study treatment will be followed for survival, investigator-assessed transformation to AP/BP, duration of response and disease progression, and initiation/response to further anti-cancer therapies, including stem cell transplantation (where applicable).

The primary outcome measure, MMR, is appropriate, as achievement and maintenance of MMR is an important endpoint in CML therapy and it appears to predict long-term EFS. The selection of the patient population based on presence of BCR-ABL transcript reflects the current approach to diagnosis of CML, and is in line with the primary endpoint of MMR.

3.1. Study Treatment

All patients will receive bosutinib at a starting dose of 400 mg QD. The dose of bosutinib may 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.

Each patient will receive daily bosutinib for up to approximately 3 years after registration of the last patient (12 months [48 weeks] Core Treatment Phase and the following ≥24 months [96 weeks] Extension Phase) or until the end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent occurs.

Details of the study treatment forms and packaging, and recommendations for dose modifications are included in the Study Treatments Section 5 of the protocol.

4. PATIENT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Diagnosis of CP CML of ≤6 months (from initial diagnosis)

    - Diagnosis of CP CML with molecular confirmation by detection of BCR-ABL rearrangement at screening (cytogenetic assessment for Ph is not required for enrollment; however, patients with known Ph- CML prior to registration are not eligible for this study); diagnosis of CP CML will be defined as all of the following per European LeukemiaNet (ELN) definitions:

a. <15% blasts in peripheral blood and bone marrow;

b. <30% blasts plus promyelocytes in peripheral blood and bone marrow;

c. <20% basophils in peripheral blood;

d. $\geq 100 \times 10^9$/L platelets ($\geq$100,000/mm^3);

e. No evidence of extramedullary disease except hepatosplenomegaly; AND

f. No prior diagnosis of AP or BP-CML.

2. Age ≥20 years.

3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.

4. Adequate Renal Function, including:

   a. Serum creatinine ≤1.5 × upper limit of normal (ULN) or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.

5. Adequate Liver Function, including:

   a. Total serum bilirubin ≤1.5 × ULN unless the patient has documented Gilbert syndrome;

   b. AST and ALT ≤2.5 × ULN; ≤5.0 × ULN if there is liver involvement by leukemia;

6. Able to take oral tablets.

7. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for AEs not constituting a safety risk by investigator judgment.

8. Serum pregnancy test (for females of childbearing potential) negative at screening.

   Female patients of nonchildbearing potential must meet at least 1 of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   c. Have medically confirmed ovarian failure.

All other female patients (including female patients with tubal ligations) are considered to be of childbearing potential.

9. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

10. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Any prior medical treatment for CML, including TKIs, with the exception of hydroxyurea treatment, which is permitted for up to 6 months prior to registration.

2. Any past or current CNS involvement, including leptomeningeal leukemia.

3. Extramedullary disease only.

4. Major surgery or radiotherapy within 14 days prior to registration.

5. History of clinically significant or uncontrolled cardiac disease including:

   - History of, or active, congestive heart failure;
   - Uncontrolled angina or hypertension within 3 months prior to registration;
   - Myocardial infarction within 12 months prior to registration;
   - Clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes);
   - Diagnosed or suspected congenital or acquired prolonged QT interval history or prolonged QTc (QTcF should not exceed 500 msec);
   - Unexplained syncope.

6. Patients with active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

7. Recent or ongoing clinically significant GI disorder (eg, Crohn's disease, ulcerative colitis, or prior total or partial gastrectomy).

8. History of another malignancy within 5 years prior to registration with the exception of basal cell carcinoma or cervical carcinoma in situ or Stage 1 or 2 cancer that is

considered adequately treated and currently in complete remission for at least 12 months.

9. Uncontrolled hypomagnesemia or uncorrected hypokalemia due to potential effects on the QT interval.

10. Known prior or suspected severe hypersensitivity to study drugs or any component in their formulations.

11. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

12. Participation in other studies involving investigational drug(s) within 30 days or 5 half-lives of investigational product, whichever is longer, prior to registration and/or during study participation.

13. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

14. Pregnant female patients; breastfeeding female patients; fertile male and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

4.3. Lifestyle Requirements

In this study, fertile male patients and female patients who are of childbearing potential as applicable to the study will receive bosutinib, which has been associated with suspected teratogenicity/fetotoxicity. Patients who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for at least 28 days after the last dose of bosutinib. The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception for the individual patient and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time points indicated in the schedule of activities table, the investigator or designee will inform the patient of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the patient or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the patient or male patient's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

All sexually active male patients must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study organization.

To facilitate access to an appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, patient study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is bosutinib.

5.1. Allocation to Treatment

Registration will be performed centrally by the sponsor for all patients. Following full assessment and determination that the patient meets all eligibility criteria, the investigator or designee will fax or email a complete Registration Form to the designated sponsor study team member. The sponsor will assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other trial-related documentation or correspondence referencing that patient and fax or email to the site.

No patient shall receive study drug until the investigator or designee has received the following information from the sponsor: confirmation of the patient's enrollment.

5.2. Patient Compliance

For self-administration of bosutinib at home, compliance will be captured and completed by the patient.

A patient diary will be provided to the patients to aid in patient compliance with the dosing instructions. The diary will be maintained by the patient to include missed or changed bosutinib doses. Patients will be required to return all bottles of bosutinib every visit. The number of bosutinib tablets remaining will be documented and recorded at each visit. The patient diary may also be used to support this part of the bosutinib accountability process.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

Bosutinib tablets (100 mg dosage strength) will be supplied by Pfizer in high-density polyethylene (HDPE) bottles. The bosutinib commercial formulation will be supplied in this study. Bosutinib will be labeled according to local regulations.

5.3.2. Preparation and Dispensing

The study treatment should be dispensed at each visit per the schedule of treatment. A qualified staff member will dispense the investigational product in the bottles provided, in quantities appropriate for the study visit schedule. The patient/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing, keep the investigational product away from children, and return the bottle to the site at the next study visit.

5.4. Administration

The starting dose is 400 mg QD, orally, recommended to be taken in the morning with a meal and 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 is imposed on patients' food choices.

Patients will swallow the investigational product whole and will not manipulate or chew the investigational product prior to swallowing. Patients must be instructed that should they miss a dose or vomit any time after taking a dose, they must not "make it up" with an extra dose. Instead, resume the subsequent doses as originally prescribed. Any missed dose may be taken up to 12 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed.

On PK sampling days, the bosutinib dose should be taken in the hospital under the supervision of the study site personnel. The bosutinib dose should be administered after the 0 hour (pre-dose) PK sample has been collected.

Dosing is continuous without planned interruptions; patients who complete 12 months (48 weeks) Core Treatment Phase will continue dosing without interruption into the Extension Phase. Each patient will receive daily bosutinib for up to approximately 3 years after registration of last patient (12 months [48 weeks] Core Treatment Phase and the following ≥24 months [96 weeks] Extension Phase) or until the end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first.

In this study, the dose of bosutinib may be escalated for unsatisfactory response or reduced for toxicity. Dose modifications (as summarized in Table 1) may be performed according to the criteria as summarized in detail in Section 5.4.1 and Section 5.4.2. For dose increases, the investigator must communicate directly with the patient and an additional ad hoc visit should be considered so as not to postpone the start of optimized dosing.

Table 1. Dose Modifications for Bosutinib

Dose Level	Bosutinib (mg)
Second Dose Increase (+2)	600
First Dose Increase (+1)	500
Starting Dose	**400**
First Dose Decrease (-1)	300
Second Dose Decrease (-2)	200*

*subject to sponsor approval

5.4.1. Dose Escalation

Patients should have their dose increased to 500 mg QD and further up to a maximum of 600 mg QD of bosutinib, as tolerated, if all of the following criteria are met:

a. They do not demonstrate an optimal response at Month 3 (ie, BCR-ABL transcripts >10% and/or Ph+ metaphases >35%)

b. They have no Grade 3/4 adverse events at the time of dose escalation, and all prior Grade 3/4 events have resolved to Grade 1/2 as follows:

- All Grade 3/4 hematologic toxicities have resolved to Grade ≤1.
- All Grade 3/4 non-hematological toxicities have resolved to Grade ≤2 and are manageable with supportive therapy. Grade 3/4 non-hematological toxicities resolved to Grade ≤2 which would be acceptable for dose escalation are: vomiting, nausea, abdominal pain, rash, headache, myalgia and fatigue. All other non-hematological toxicities should be Grade ≤1 for dose escalation.
- In addition, for dose escalation to be permitted in a patient who has experienced such toxicities (ie, Grade 3/4 hematologic and non-hematologic), the patient must have been able to be successfully re-challenged (ie, not have experienced recurrence of that toxicity at the Grade 3/4 level) at the lower dose after recovery from the Grade 3/4 toxicity.

AND

c. All Grade 2 non-hematologic toxicities have resolved to Grade ≤1.

All responses will be assessed per protocol at Month 3 for the purpose of dose escalation to support response. If all of the above criteria are met, dose of bosutinib will be increased.

At Month 6, it is recommended that the investigator follow existing CML guidelines (ELN or NCCN, see Appendix 2) to determine if dose escalation is indicated based upon failure to demonstrate an optimal response; however, the protocol does not mandate a dose increase; the decision is left to the clinical judgment of the investigator, taking into account local guidelines. The same safety criteria apply as for the Month 3 dose escalation.

At any time, if the patient loses a complete hematologic or complete cytogenetic response, or has a confirmed loss of MMR and a 5 × PCR increase, then a 1-level dose increase, up to a maximum of 2 dose levels, is suggested, after consultation with the sponsor. In addition, cytogenetic assessment on bone marrow should be reintroduced in the presence of loss of MMR and a 5 × PCR increase and until MMR is achieved again. The same safety criteria apply as for the Month 3 dose escalation.

Lack of response for dose escalation (mandatory at Month 6, and recommended at Month 3) is defined as: BCR-ABL transcripts >10% by qPCR IS and/or Ph+ metaphases >35%.

Additionally, anytime lack of optimal response is demonstrated, a BCR-ABL mutation test must be performed on the same sample if possible.

The BCR-ABL transcript levels (and mutation analyses when appropriate) will be assessed by a central laboratory throughout this study.

5.4.2. Dosing Interruptions and Dose Reductions

The dose of bosutinib may be interrupted and/or reduced for the toxicities described below.

For bosutinib, a dose reduction from 400 mg QD to 300 mg QD is permitted. If a patient requires a second dose reduction from 300 mg QD to 200 mg QD, the investigator should contact the sponsor to determine if the patient may continue on treatment at a lower dose. The second dose reduction must be approved by the sponsor and will only be considered if the patient in question displays optimal response to bosutinib treatment at the time point at which the dose reduction is being considered. Patients should remain on the 200 mg dose for a maximum of 4 weeks or until the toxicity resolves, whichever is sooner, in line with the dose reduction and dose escalation guidelines. The dose may then be re-escalated following the escalation guidelines. Any patient on the 200 mg dose with ongoing toxicity after the 4-week time point will be discontinued from treatment and will continue with Long-Term Follow-Up evaluations. Dose reductions of bosutinib below 200 mg QD will not be permitted.

If the investigator and the sponsor decide that it is not in the best interest of the patient to remain on treatment at a dose lower than 300 mg QD, the patient will be discontinued from treatment and will continue with Long-Term Follow-Up evaluations.

Once the dose has been reduced for a patient, patients should remain on that dose unless the toxicity resolves (Grade ≤1). In that case, the dose may be escalated to the previous starting dose.

Management of Non-Hematologic Treatment-Related Toxicities

The management of non-hematologic treatment-related toxicities is summarized in Table 2.

Patient instructions for the management of diarrhea are presented in Appendix 6.

Table 2. Management of Non-Hematologic Treatment-Related Toxicity

Adverse Event	Action
Elevated liver transaminases	If elevations in ALT, AST >5× institutional ULN occur, bosutinib should be interrupted until recovery to ≤ 2.5×ULN and may be resumed at 400 mg QD thereafter. If recovery takes longer than 4 weeks, discontinuation of bosutinib should be considered. If transaminase elevations ≥3×ULN occur concurrently with bilirubin elevations >2×ULN and alkaline phosphatase <2×ULN, bosutinib should be discontinued.
Diarrhea	For Grade 3/4 diarrhea, bosutinib should be interrupted and may be resumed at 400 mg QD upon recovery to Grade ≤ 1.
Grade 1	Current dose level.
Grade 2	For persistent clinically relevant toxicity[b] not responding to optimal management: Temporarily interrupt treatment, and reintroduce at the same dose or reduce dose by 1 level upon recovery to Grade ≤1 within 4 weeks of stopping test article.
Grade 3[a]	For persistent clinically relevant toxicity[b] not responding to optimal management: Withhold treatment, then dose reduce by 1 level upon recovery to Grade ≤1 within 4 weeks of stopping test article. If recovery takes longer than 4 weeks, the investigator should contact the sponsor to determine if the patient may continue on treatment.
Grade 4[a]	Withhold treatment. Investigator and sponsor to review to determine if patient may continue on treatment with appropriate dose reduction.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; QD = once daily; ULN = upper limit of normal

a. For patients requiring dose reduction due to toxicity, who have been free of the toxicity (Grade ≤1) for at least 1 month and are otherwise tolerating study drug, the investigator may choose to re-escalate dose by 1 dose level back to starting dose.
b. Persistent Clinically Relevant Toxicity is defined as - symptoms of toxicity which, despite optimal medical management, persist for ≥14 days ("persistent") and cause sufficient symptoms or signs of illness in the patient to warrant further intervention, eg, dose adjustment ("clinically relevant").

Patients with Grade 3 non-hematological toxicity which does not respond to optimal management, will be managed by withholding treatment followed by dose reduction by 1 level upon recovery to Grade ≤1. If, upon re-challenge at a reduced dose, the patient remains free of toxicity (Grade ≤1) for at least 1 month, the investigator may choose to re-escalate the dose by 1 level back to the starting dose. If, subsequently, the patient fulfills the criteria for dose escalation due to suboptimal response (detailed in Section 5.4.1), this will be permitted for vomiting, nausea, abdominal pain, rash, headache, myalgia, or fatigue provided that the toxicity is Grade ≤2 is manageable with supportive therapy. All other non-hematological toxicities should be Grade ≤1 for dose escalation.

Patients fulfilling criteria for dose escalation due to suboptimal response, but also exhibiting elevated liver transaminases as described in Table 2, will not be dose escalated at this time, and will be managed according to the instructions in Table 2.

In line with the Summary of Product Characteristics[26] for bosutinib, caution is recommended in patients with previous history of pancreatitis and in patients with increased serum lipase in conjunction with abdominal symptoms. Therefore, for study patients with previous history of pancreatitis, in the event of elevation of lipase level >1.5 × ULN (ie, CTCAE Grade 2 or above), bosutinib treatment should be interrupted immediately, and additional investigations and lipase monitoring should be performed to exclude pancreatitis. In addition, for any study

patient with elevation of lipase level >1.5 × ULN in conjunction with abdominal pain, bosutinib treatment should be interrupted, and similar investigations to exclude pancreatitis performed. Bosutinib treatment may be restarted only once pancreatitis is excluded and lipase levels return to CTCAE Grade ≤1.

Management of Hematologic Treatment-Related Toxicities

Guidelines in Table 3 pertain to patients with normal or higher than normal blood counts or patients who have achieved CHR.

Table 3. Management of Hematologic Treatment-Related Toxicity

Adverse Event	Action
Grade 1	Current dose level
Grade 2	Current dose level
Grade 3[a]	Withhold treatment: If recovered to Grade ≤2 within 2 weeks of treatment hold: re-introduce study drug at same dose. If recovered within 4 weeks of treatment hold: reduce study drug by 1 dose level. At subsequent occurrences of Grade 3 toxicity, dose must be reduced upon recovery to Grade ≤2. If recovery takes longer than 4 weeks, the investigator should contact the sponsor to determine if the patient may continue on treatment.
Grade 4[a]	Withhold treatment. Investigator and sponsor to review to determine if patient may continue on treatment with appropriate dose reduction.

a. For patients requiring dose reduction due to toxicity, who have been free of the toxicity (Grade ≤1) for at least 1 month and are otherwise tolerating study drug, the investigator may choose to re-escalate dose by 1 dose level back to starting dose

Patients fulfilling criteria for dose escalation due to suboptimal response, but also exhibiting Grade 2 hematologic treatment-related toxicity, will be eligible for dose escalation; however, if hematologic toxicity increases to Grade 3/4 after dose escalation, the patient will be managed as per the instructions for Grade 3/4 hematological toxicities in Table 3.

5.5. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for

excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct patients on the proper storage requirements for take home investigational products.

5.6. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

All bottles of study drug must be returned to the investigator by the patient at every visit and at the end of the trial.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Concomitant Treatments

All information on concomitant treatment (medications or procedures) must be recorded on the patient's eCRF (including the name or the medication or procedure and duration of treatment).

If there is a clinical indication for one of these or other medications specifically prohibited during the trial, discontinuation from study therapy or medication may be required. The final decision on any supportive therapy rests with the investigator and/or the patient's primary

physician. However, the decision to continue the patient on study therapy or medication schedule requires the mutual agreement of the investigator, the sponsor, and the patient.

Concomitant treatment considered necessary for the patient's well-being may be given at the discretion of the treating physician.

Concomitant medications and treatments will be recorded from 28 days prior to the registration and up to 28 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis), and the drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, transfusions).

There are no prohibited therapies during the Long-Term Follow-Up Phase.

5.7.1. Prohibited Medications

- Any concurrent chemotherapy, radiotherapy, or anticancer immunotherapy other than as defined in this protocol.
- Any other anti-cancer therapy.
- Any other investigational agents.
- Drugs known to prolong the QT interval or predispose to Torsades de Pointes (see Appendix 4).
- Concurrent anticoagulation therapy with warfarin or related oral anticoagulant therapy. Concurrent therapeutic anticoagulation with low molecular weight heparin will be permitted.
- Prophylactic use of growth factors.

5.7.2. Permitted Medications

- Any medication (other than those prohibited above or per inclusion/exclusion criteria) for a concurrent medical condition is permitted.
- Treatment of diarrhea and other GI symptoms will be optimized.
- Treatment with growth factors, eg, for neutropenia (including granulocyte colony-stimulating factor [G-CSF] according to American Society of Clinical Oncology [ASCO] guidelines).
- Supplementation is advised for potassium levels or magnesium levels below the LLN, with consideration of the patient's underlying renal function.

- Up to 6 months of prior hydroxyurea is permitted prior to signature of informed consent document. Hydroxyurea is also permitted during the first 21 days of study treatment following registration.

- Temporary steroid use will be permitted for treatment of AEs – limited to systemic steroids for no more than 10 days and at doses ≤60 mg prednisone/day or the equivalent. Of note, inhaled and topical steroids are permitted without limitation.

5.7.3. Other Treatment Considerations: Interaction with Other Medical Products and Other Forms of Interaction

The concomitant use of bosutinib with strong or moderate cytochrome P450 (CYP3A) inhibitors (reference Appendix 5) should be avoided, as an increase in bosutinib plasma concentration may occur.

If a strong or moderate CYP3A inhibitor must be administered during bosutinib treatment, an interruption of bosutinib therapy and/or a dose reduction in bosutinib should be considered. Patients should also be strongly encouraged to avoid herbal remedies. Grapefruit and grapefruit juice should also be avoided.

The concomitant use of bosutinib with strong or moderate CYP3A inducers including St. John's Wort should be avoided (Appendix 5); it is not recommended as it will significantly reduce expose to bosutinib.

Bosutinib should be used with caution in patients who have or may develop QT interval prolongation, including those patients taking anti-arrhythmic medicinal products (see Appendix 4).

Inhibitors of platelet aggregation, ie, aspirin, dipyridamole, clopidogrel, and ticlopidine, should be used with caution.

Transfusions for anaemia or thrombocytopenia may only be given in the interest of patient safety. Transfusions will not be permitted in order to allow continued dosing of bosutinib when there is an indication for treatment interruption as outlined in the Dose Adjustment/Treatment Interruption tables (see Table 2 and Table 3).

Caution should be exercised when administering bosutinib concomitantly with proton-pump inhibitors (PPIs). Short-acting antacids should be considered as an alternative to PPIs and administration times of bosutinib and antacids should be separated by at least 2 hours (eg, take bosutinib in the morning and antacids in the evening) whenever possible.

6. STUDY PROCEDURES

As applicable, all visits must occur within the predefined time windows outlined in this protocol.

6.1. Screening

Informed consent must be obtained prior to undergoing any study specific procedures.

For screening procedures, see SCHEDULE OF ACTIVITIES table and ASSESSMENTS section.

6.1.1. Collection of Banked Biospecimen

Collect a genomic banked biospecimen. If missed, collect at the next available time point when biospecimens are being collected in conjunction with a patient visit.

Blood will be collected at screening and retained in a Biobank for exploratory biomarker assessments, unless prohibited by local regulation or by the IRB/EC.

6.2. Core Treatment Phase

For Core Treatment Phase procedures, see SCHEDULE OF ACTIVITIES table and ASSESSMENTS section.

Patients will have visits at the study site on Day 1 and Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24, then every 12 weeks for the first year of treatment in the 12 months (48 weeks Core Treatment Phase). Additional visits may be required for patients requiring dose increases at the Week 12 and Week 24 visits, these will be performed as soon as possible and within 4 weeks of the result requiring dose change being known. Patients not requiring a dose change will be contacted by telephone.

6.3. Extension Phase

For Extension Phase procedures, see SCHEDULE OF ACTIVITIES table and ASSESSMENTS section.

All patients will be treated and/or followed up to approximately 3 years (144 weeks) after registration of the last patient or study termination. Patients who discontinue study therapy early due to disease progression or intolerance to study medication will continue to be followed for survival for up to approximately 3 years (144 weeks) after registration of the last patient or until study termination.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational products, request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient refuses further visits, the patient should continue to be followed for survival. If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.4. End of Treatment/Withdrawal Visit

For End of Treatment/Withdrawal visit procedures, see SCHEDULE OF ACTIVITIES table and ASSESSMENTS section.

Patients who discontinue from study treatment for any reason should complete an End of Treatment/Withdrawal visit between 7 and 28 days after the last dose of study drug, and the patient enters Long-Term Follow-Up.

6.5. Patient Withdrawal

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Section 8.1.3), behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Treatment failure (meeting 1 or more of the following definitions);
  - Transformation to AP or BP at any time (disease progression).
  - After dose escalation (as specified in Section 5.4.1), or documented AEs prohibiting dose escalation and if 1 of the following conditions is met:
    - Failure to achieve a CHR after a minimum of 24 weeks on treatment.
    - Failure to achieve at least a minimal cytogenetic response after a minimum of 24 weeks on treatment.
    - Failure to achieve a major cytogenetic response (MCyR) after a minimum of 48 weeks on treatment.
    - Failure to achieve a CCyR after a minimum of 72 weeks on treatment.
    - Loss of MCyR or CCyR (need at least 30% increase for MCyR or at least one Ph+ metaphase for CCyR confirmed by a follow-up cytogenetic analysis ≥4 weeks later).
    - Loss of CHR. Loss of CHR is 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 count (WBC) that rises to >20.0 × 10^9/L.
      - ✓ Platelet count that rises to ≥600 × 10^9/L.

- ✓ Appearance of palpable spleen or other extramedullary involvement proven by biopsy.
- ✓ Appearance of 5% myelocytes in the peripheral blood.
- ✓ Appearance of blasts or promyelocytes in the peripheral blood.

- 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.

- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
  - Dose is held for longer than 4 weeks for treatment-related toxicity (without consultation with sponsor). Of note, in some instances, if the investigator and sponsor determine it is appropriate, a patient may be allowed to continue on treatment if recovery takes longer than 4 weeks.
  - Need to dose reduce below 300 mg QD. Of note, in some instances, if the investigator and sponsor determine it is appropriate, a patient may be allowed to dose reduce below 300 mg QD.
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment (follow up permitted by patient);
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow up may include:

- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Efficacy Assessment

7.1.1. Efficacy Assessment Methods

Efficacy will be determined by physical examination, analysis of peripheral blood and bone marrow. Automated CBC (eg, hemoglobin, red blood cell (RBC), WBC, platelets, and hematocrit), differential counts (eg, neutrophils, basophils, eosinophils, lymphocytes, metamyelocytes, myelocytes, monocytes, promyelocytes, myeloblasts, unspecified blast cells and band cells), bone marrow differential (eg, plasma cells, promyelocytes, myelocytes, metamyelocytes, eosinophils, lymphocytes, monocytes, myeloblasts, erythroblast, basophil, neutrophils, band neutrophils, unspecified blast cells, megakaryocytes, and erythroid precursors), molecular analysis for BCR-ABL transcripts, cytogenetics, physical examination, and mortality will be used to determine the response to treatment as described in Appendix 2. Molecular and hematologic response rates will be assessed for all patients. Cytogenetic response will be assessed in all Ph+ CML patients. The timing of these assessments is presented in the SCHEDULE OF ACTIVITIES table.

Molecular response monitoring using RT-qPCR for BCR-ABL copy number will be performed on peripheral blood on all patients harboring b2a2 and/or b3a2 transcripts and will be sent to a central vendor for performance and assessment on the IS; sample collection for molecular response monitoring is described in Section 7.1.1.1.

Differential count and cytogenetic assessment on bone marrow aspirate will be performed locally.

Bone marrow obtained as part of standard of care prior to signing the informed consent document may be used at screening as long as it was collected within 28 days prior to registration. Patients completing treatment for cytogenetically confirmed treatment failure do not need to repeat bone marrow at treatment completion. Patients ending treatment for reasons other than cytogenetically confirmed treatment failure must undergo treatment completion bone marrow aspirate if the previous bone marrow aspirate was performed >12 weeks prior to treatment failure. Additional bone marrow aspirations and cytogenetics will be done as indicated (eg, suspect disease progression or failed/inadequate Week 48

[Month 12] assessment). If confirmed loss of MMR occurs in combination with a 5 × PCR increase for BCR-ABL, a bone marrow aspirate for cytogenetics should be obtained.

Standard cytogenetics will be used to determine the presence of the Ph and its percent presence in the bone marrow aspirate. Twenty (20) or more metaphases should be analyzed for this determination, except for the baseline sample. As noted above, cytogenetics will be performed locally. If bone marrow aspirate collected at Week 48 is not adequate for cytogenetic analysis, aspirate should be repeated within 4 weeks. Loss of cytogenetic response must be confirmed by 2 assessments at least 4 weeks apart.

Bone marrow aspirate cell differential will also be used to determine the blast and immature myeloid counts in order to define disease phase.

Mutation testing for BCR-ABL sequencing will also be performed on peripheral blood at study completion, discontinuation or lack of response following dose escalation (Section 5.4.1). Blood will be sent utilizing frozen PAXgene tubes to an approved central vendor for analysis. See lab manual for processing and shipping of samples.

MMR is defined as BCR-ABL ≤0.1% BCR-ABL on the IS by RT-qPCR (Appendix 2) and CCyR is defined as absence of detectable Ph (Appendix 2). Loss of MMR, accompanied by at least 5-fold increase from the smallest recorded BCR-ABL transcripts value, must be confirmed by 2 assessments at least 4 weeks apart.

Complete hematologic response must be of at least 4 weeks in duration and confirmed by 2 assessments at least 4 weeks apart. Complete hematologic response will be evaluated by peripheral blood only utilizing local laboratory results, and clinical exclusion of extramedullary disease. Loss of hematologic response must also be confirmed by 2 assessments at least 4 weeks apart.

Physical examination will be used to assess liver and spleen involvement.

EFS and OS will be obtained from data evaluating the patient's disease status and mortality data.

7.1.1.1. Sample Collection for Molecular Response

In order to monitor molecular response under study treatment, 15 mL of peripheral blood will be collected into 6 PAXgene Blood RNA tubes at each sampling time point. Blood samples for BCR-ABL are to be taken at Screening, Week 12, 24, 36, 48 (with a back-up sample at Week 48), and then every 12 weeks until the end of Year 2, then every 24 weeks.

The samples will be sent to the central RT-qPCR laboratory to evaluate BCR-ABL transcript levels by RT-qPCR. All Month 12 (Week 48) samples will be analyzed in duplicate to confirm the results. When reduction of BCR-ABL to <0.1% of standardized baseline (MMR) or ≥4.0 log, or ≥4.5 log reduction in BCR-ABL transcript levels ($MR^{4.0}$ or $MR^{4.5}$) is achieved, a repeat analysis of the same sample will be performed to confirm the results. If a ≥5-fold increase in BCR-ABL transcripts from the lowest value achieved on study along with loss of

MMR is identified and confirmed by duplicate analysis of the same sample, an unscheduled visit sample will be collected within 4-6 weeks to confirm the results. If the 5 × increase in BCR-ABL is accompanied by loss of MMR, mutation analysis will be performed on the same sample if possible and a bone marrow aspirate sample for cytogenetics will be obtained.

For patients who achieve undetectable BCR-ABL by RT-qPCR, due to variability in sample quality and blood cell counts, a repeat assay using more than 10 mL of blood may be required to determine whether ≥4.0 log or ≥4.5 log reduction in BCR-ABL transcript levels is reached. Therefore, 20 mL of blood may be collected from these patients for PCR analysis. In addition, after the first documented negative BCR-ABL result, 20 mL of blood will be collected for all subsequent sampling time points until BCR-ABL is no longer negative. 20 mL of blood may be collected as an unscheduled PCR sample from these patients.

At each sampling point, 15 mL of peripheral blood will be collected into six (6) 2.5 mL PAXgene Blood RNA tubes included in the sample collection kits. Two (2) additional PAXgene tubes will be collected at Week 48; these will serve as back-up samples for the primary endpoint.

7.1.1.2. Mutation Analysis

Correlation of mutations with treatment response will be studied. The blood samples collected for RT-qPCR will also be used for mutation analysis and will be drawn every 3 months (every 12 weeks) up to years 2 (Core Treatment Phase and Extension Phase) and then every 6 months (every 24 weeks) (Extension Phase). No mutation analysis will occur at Screening. Mutation analysis will be performed in case of either lack of response, suboptimal response or loss of response defined as: failure to achieve MMR at 12 months; loss of MMR AND rise in BCR-ABL transcript level by ≥5-fold from the lowest value achieved during the study; at the End of Treatment/Withdrawal visit. For patients with a positive mutation identified during therapy, follow-up mutation analyses will be performed in subsequent samples. For a patient with a negative mutation result immediately following relapse, continued mutation analyses may be performed at a frequency of every 6 months (every 24 weeks) as needed.

Further mutation analyses will be performed retrospectively as appropriate on patient samples if mutations are identified. Alternative methodologies with improved mutation detection sensitivity may be used for identifying mutations in earlier samples.

7.2. Safety Assessment

Safety assessments will include collection of AEs, SAEs, vital signs and physical examinations, ECG (12-lead), chest X-rays, ECHO/MUGA scans, laboratory assessments, including pregnancy tests and verification of concomitant treatments.

7.2.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed on 2 occasions prior to starting administration of study treatment–once at the start of screening and once at the baseline visit

immediately before starting the study treatment. Following a negative serum pregnancy test result at screening, appropriate contraception must be commenced and another serum or urine negative pregnancy test result will be required at the baseline visit before the patient may receive the study treatment. Urine pregnancy tests will be repeated according to the SCHEDULE OF ACTIVITIES table during the active treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed during the active treatment period or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRBs/ ECs or if required by local regulations.

In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product but may remain in the study.

7.2.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the NCI CTCAE version 4.03) timing, seriousness, and relatedness.

7.2.3. Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the SCHEDULE OF ACTIVITIES table and analyzed at local laboratories.

Table 4. Safety Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis****	Pregnancy Test
Hemoglobin	ALT	PT or INR	Urine dipstick for urine protein: If positive and clinically indicated, collect 24-hr and microscopic (Reflex Testing)	For female patients of childbearing potential, serum or urine
Platelets	AST	PTT or aPTT		
Hematocrit	Alk Phos			
RBC	Sodium			
WBC	Potassium			
Neutrophils	Magnesium			
Lymphocytes	Calcium			
Monocytes	Chloride		Urine dipstick for urine blood: If positive and clinically indicated, collect a microscopic (Reflex Testing)	
Eosinophils	TBili*			
Basophils	BUN or Urea			
Metamyelocytes	Creatinine**			
Myelocytes	Creatine kinase			
Promyelocytes	Fractionated creatine kinase if creatine kinase is abnormally high (if available)			
Myeloblasts				
Unspecified blast cells				
Band Cells	Uric Acid***			
	Glucose (nonfasted)			
	Albumin			
	Phosphorous or Phosphate			
	Total protein			
	Amylase			
	Lipase			
	Carbon dioxide or bicarbonate (if available)			
	Other Tests: HBV and HCV			

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; TBili = total bilirubin; WBC = white blood cell count.
* For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels. ** eGFR will be calculated. *** Uric acid will be obtained until patient achieves a CHR. **** Urinalysis and microscopic (Reflex testing) may include urine protein, urine pH, urine blood/hemoglobin, urine glucose, urine esterase, urine nitrites, urine ketones, urine specific gravity, urine red blood cells, urine white blood cells, urine crystals and urine casts.

7.2.4. Physical Examinations

Patients will undergo physical examinations to include weight, vital signs, assessment of ECOG performance (Appendix 3) status and height; height will be measured at baseline only.

7.2.5. (12-Lead) Electrocardiograms

Triplicate 12-lead (with a 10-second rhythm strip) tracings will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see SCHEDULE OF ACTIVITIES table), 3 consecutive

ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged (>500 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 500 msec. If QTcF interval reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 500 msec the investigational product will be held until the QTcF interval decreases to 500 msec. Patients will then restart the investigational product at the next lowest dose level. If the QTcF interval has still not decreased to 500 msec after 2 weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTcF interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If a patient experiences any cardiac or neurologic AEs (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

7.3. Pharmacokinetics Assessments

Blood samples (3 mL) to provide a minimum of 1.0 mL plasma for PK analysis will be collected into appropriately labeled tubes containing potassium EDTA as outlined in the SCHEDULE OF ACTIVITIES table.

The pre-dose samples may be collected before (within 3 hours) study drug administration. Refer to the SCHEDULE OF ACTIVITIES table for specific timing of the sample collection. Actual date and time of treatment dose and PK sampling should be recorded on the eCRF.

Detailed instructions for PK blood sample collection, processing, storage, and shipment will be provided in a lab manual. PK samples must be processed and shipped as indicated in the lab manual to maintain sample integrity. Any deviations from the processing steps (ie, sample collection and processing, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the PK of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the Clinical Study Report (CSR).

7.4. Banked Biospecimens

Banked biospecimens will be collected from patients for exploratory research relating to the drug response and disease/condition under study. These collections are not typically associated with a planned assessment described in the protocol. They will be handled in a manner that protects each patient's privacy and confidentiality. Banked biospecimens will be assigned the patient's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the patient's ID and the patient's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also postmarketing research. Patients may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses.

Unless prohibited by local regulations or ethics committee decision, a 4-mL blood genomic banked biospecimen **Prep D1 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K_2EDTA] whole-blood collection optimized for DNA analysis)** will be collected at the time specified in the schedule of activities section of the protocol to be retained for potential pharmacogenomic/genomic/biomarker analyses related to drug response and the disease/condition under study. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

The banked biospecimens will be collected from all patients unless prohibited by local regulations or IRB/EC decision.

It is possible that the use of these biospecimens may result in commercially viable products. Patients will be advised in the informed consent document that they will not be compensated in this event.

7.4.1. Additional Research

Unless prohibited by local regulations or IRB/EC decision, patients will be asked to indicate on the consent form whether they will allow banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

Patients need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Banked Biospecimens section will be used. Patients may still participate in the study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event

within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Patient Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a patient withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For patients who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a patient after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

8.1.4.2. Recording Non-Serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the

investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);

- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias (the primary disease under study does not qualify for this) or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Patients who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's Law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's Law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For patients with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's Law case should be reviewed with the sponsor.

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's Law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's Law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's Law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

    - ✓ An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a patient or patient's partner becomes or is found to be pregnant during the patient's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as

SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

- **Analysis Populations**

The as-treated population will consist of all patients who received at least 1 dose of study treatment. However, the primary analysis population for the efficacy evaluation will be the modified as-treated population. The modified as-treated population will consist of all patients with Ph+ CP CML harboring b2a2 and/or b3a2 transcripts who received at least 1 dose of study medication.

All statistical analyses will be performed using the modified as-treated population. The exploratory MMR analyses at 12 months (48 weeks), time to molecular response, OS, and cumulative CHR will also be performed using the as-treated population including the Ph+ and Ph- CML patients. Details about the analysis populations will be provided in the SAP.

The safety population will consist of all patients, regardless of Ph status, who received at least 1 dose of study treatment.

9.1. Sample Size Determination

The primary analysis will be conducted for the modified as-treated population with the hypothesis test of a binomial proportion using the normal approximation. The study is powered at greater than 82.1% to test the null hypothesis that the true MMR rate at 12 months (48 weeks) is 25% versus the alternative hypothesis that the true MMR rate is

40% with one-sided alpha of 5%. The null MMR rate was referred to the historical rates of imatinib.[21,27] The alternative MMR rate was derived from the null MMR rate and the 15% difference of MMR rates to be detected in AV001 study which is the Phase 3 randomized study of bosutinib versus imatinib in newly diagnosed CP CML. For the primary analysis of MMR at 12 months (48 weeks), a sample size of 60 Ph+ CML patients harboring b2a2 and/or b3a2 transcripts is required. As cytogenetic confirmation for Ph is not required for enrollment and 5% of patients are expected to be Ph- CML, approximately 3 Ph- CML patients may be enrolled additionally, which will not affect the primary analysis.

9.2. Efficacy Analysis

In general, efficacy outcomes up to 12 months (48 weeks) will be based on data collected in the Core Treatment Phase of the study (first 12 months [48 weeks] on a per patient basis), with the exception of OS, EFS and duration of responses as measured beyond the first 12 months follow-up. Data from the Core Treatment Phase (first 12 months) will be evaluated and submitted in the Core Treatment Phase study report. Data beyond the first 12 months (48 weeks) from the Extension Phase of the study will also be evaluated and submitted in a final end of study report.

Continuous variables will be summarized by descriptive statistics (sample size [n], mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized in frequency tables (n, frequencies, and percentages). Individual patient data will be presented in listings.

Patients who are Ph- and harbor a BCR-ABL transcript other than b2a2 and/or b3a2 cannot be followed for either molecular (eg, MMR) or cytogenetic (eg, CCyR) response. Patients who are Ph+ and harbor a BCR-ABL transcript other than b2a2 and/or b3a2 are not evaluable for assessment of molecular response, but remain evaluable for CCyR within the Ph+ evaluation for cytogenetic response. All patients who harbor a BCR-ABL transcript other than b2a2 and/or b3a2 are treated as non-responders in the analysis of molecular response. Patients who are Ph- and harbor a b2a2 and/or b3a2 transcript (typical transcript) are evaluable for MMR (not for CCyR) and will be included in the exploratory endpoint of MMR in the Ph unrestricted evaluation for molecular response. All patients will be followed for hematologic response and will remain evaluable for safety endpoints.

9.2.1. Analysis of Primary Endpoint

The primary efficacy variable, MMR rate at 12 months (48 weeks), is defined as the proportion of patients achieving MMR at 12 months (48 weeks). MMR is defined as BCR-ABL expression of ≤0.1% of initial BCR-ABL transcript from standardized baseline measured by RT-qPCR. The analysis of MMR rate will include all patients with Ph+ CML harboring b2a2 and/or b3a2 transcripts. This is anticipated to represent approximately 95% of enrolled patients; 1–2% of patients may harbor other BCR-ABL transcripts not validated for MMR assessment.

The null hypothesis for the primary efficacy analysis will be that the proportion of patients achieving MMR at 12 months (48 weeks) is 25%. The alternative hypothesis will be that the proportion of patients achieving MMR at 12 months (48 weeks) is 40%. 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), will be considered to be a successful demonstration of efficacy for this study. The primary outcome measure will be analyzed using the hypothesis test of a binomial distribution using the normal approximation.

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

The primary analysis will be conducted when all treated patients with Ph+ CML harboring b2a2 and/or b3a2 transcripts have either been followed for at least 12 months (48 weeks), or discontinued from the study prematurely.

The 2-sided 90% confidence interval (CI) of MMR rate at 12 months (48 weeks) will also be calculated. Efficacy outcomes of MMR up to 12 months (48 weeks) will be summarized and submitted in the Core Treatment Phase (when all patients have received 12 months treatment) CSR. Additional analysis of MMR beyond 12 months (48 weeks) will be performed in the Extension Phase of the study.

9.2.2. Analysis of Secondary Endpoints

9.2.2.1. Other Measures of MMR

Evaluations of MMR by 12 and 18 months will be assessed using the frequency tables. The 90% CI will also be calculated.

For the analysis of MMR by 12 and 18 months, a patient is counted as a responder if MMR occurs at or before 12 and 18 months, respectively, even if MMR is subsequently lost at or before the 12- or 18-month time point. A patient never achieving MMR at or before 12 and 18 months will be considered a non-responder, respectively.

9.2.2.2. Cytogenetic Response Assessment

Evaluations of CCyR by 12 months (48 weeks) will be assessed using the frequency tables. The 90% CI will also be calculated.

The CCyR rate by 12 months is defined as the proportion of patients demonstrating CCyR at or before 12 months (48 weeks).

9.2.2.3. Duration of Response

The analysis of secondary endpoints relating to duration of response, such as duration of MMR and CCyR will be based on the estimations of the quartiles of duration and yearly rates using the Kaplan-Meier method. For the analysis of CCyR, the proportion of patients who have confirmed loss of response will also be evaluated.

The duration is measured from the first date of response until the first date of confirmed loss of response, treatment discontinuation due to progressive disease, or death due to disease

progression within 28 days after last dose. An unconfirmed loss followed by treatment discontinuation due to suboptimal response is considered a confirmed loss. Duration of response will be counted while a patient is on treatment and 28 days after last dose. If loss of response has not occurred, the patient will be censored at the last valid assessment.

The duration of MMR will be analyzed for the modified as-treated population and as-treated population separately. The duration of CCyR will be calculated using the modified as-treated population.

9.2.2.4. Event-Free Survival and Overall Survival

The analysis of EFS and OS will be similar to that for duration of response just described.

EFS was defined as the time from first dose to the occurrence of the earliest of the following events while on treatment:

- Death due to any cause.
- Transformation to AP or BP (on treatment).
- Loss of CHR.
    - Loss of CHR is defined as the appearance of any of the following, confirmed by a second determination ≥4 weeks later (unless associated with CML-related treatment discontinuation):
        - ✓ WBC count that rises to >20.0 × 10^9/L.
        - ✓ Platelet count that rises to ≥600 × 10^9/L.
        - ✓ Appearance of palpable spleen or other extramedullary involvement proven by biopsy.
        - ✓ Appearance of 5% myelocytes in the peripheral blood.
        - ✓ Appearance of blasts or promyelocytes in the peripheral blood.
- Loss of CCyR.
    - ✓ Loss of CCyR is defined as at least one Ph+ metaphase confirmed by a second determination ≥4 weeks later (unless associated with CML-related treatment discontinuation).
- 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.

OS is defined as the time from first dose to death due to any cause.

The EFS will be calculated using the modified as-treated population. OS will be analyzed in the modified as-treated population and as-treated population separately.

9.3. Analysis of Other Endpoints

9.3.1. Exploratory Efficacy Endpoints

9.3.1.1. Other Measures of MMR and Reductions in BCR-ABL Transcript

Measures of MMR and reductions in BCR-ABL transcript at different time points will be evaluated by frequency tables. The 90% CI will also be calculated.

The exploratory MMR analysis at 12 months will be analyzed for the as-treated population. The others will be calculated using the modified as-treated population and as-treated population separately.

Subgroup analyses for MMR at 12 months (48 weeks) may be performed and 90% CIs will be presented.

9.3.1.2. Time to Response

The time to response (MMR, CCyR, $MR^{4.0}$, and $MR^{4.5}$) is measured from first dose to the first date of response. In the analysis of cumulative incidence,[28] the competing risk is defined as treatment discontinuation without response. Also, other patients without response will be censored at the last valid assessment for the respective endpoint.

The time to response will be also summarized by descriptive statistics among responding patients.

The time to MMR will be analyzed for the modified as-treated population and as-treated population separately. The time to CCyR will be calculated using the modified as-treated population.

9.3.1.3. Time to Transformation to AP/BP CML

The analysis of the time to transformation to AP/BP CML will be similar to that of the time to response just described.

The time to transformation to AP/BP CML is defined as the time from first dose to the first date of transformation to AP or BP CML. The transformation to AP/BP will be counted while a patient is on treatment up to 28 days after last dose. In the analysis of cumulative incidence,[28] the competing risk is defined as treatment discontinuation without transformation. If transformation has not occurred, the patient will be censored at the last valid hematologic assessment.

Investigators should assess transformation to AP/BP according to the original definition of AP/BP CML (see Table D in Appendix 2). In a statistical analysis, some restrictions (see Table D footnotes in Appendix 2) are adopted in addition to the original definition.

9.3.1.4. Hematologic Response

Evaluations of cumulative CHR will be assessed using the frequency tables. The 90% CI will also be calculated.

The cumulative CHR will be analyzed for the modified as-treated population and as-treated population separately.

Investigators should assess hematologic response according to the original definition of CHR (see Table A in Appendix 2). In a statistical analysis, some restrictions (see Table A footnotes in Appendix 2) are adopted in addition to the original definition.

9.3.2. Mutations

Types of mutations present at treatment completion and when performed during treatment will be summarized.

Summaries of newly observed BCR-ABL mutations in patients post-baseline will be presented by visit.

9.3.3. Population Pharmacokinetic Analysis and Pharmacokinetic/Pharmacodynamic Modeling

PK profiles of bosutinib will be determined using a sparse sampling regimen and population PK analysis approach. A total of 4 PK samples per patient will be drawn. All patients will provide pre-dose blood samples on Day 1, Day 28, Day 56, and Day 84.

PK and pharmacodynamics data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between bosutinib exposure and biomarkers or significant safety and/or efficacy endpoints. The results of these analyses, if performed, may be reported separately.

9.4. Safety Analysis

9.4.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The numbers of events and incidence rates will be tabulated by preferred term and system organ class. AEs will be presented with and without regard to causality. The frequency of overall toxicity, categorized by toxicity Grades 1 through 5, will be described. Additional tables will be provided for AEs that are observed with higher frequency.

TEAEs are defined as AEs that first occurred or worsened in severity after the first administration of the study drug up to 28 days after last dose. AE summaries will include incidence of TEAEs by MedDRA preferred term and system organ class, SAEs including deaths, AEs that led to study drug discontinuation, and AEs by maximum severity and relationship to study drug.

9.4.2. Clinical Laboratory Evaluations

Laboratory assessments will be presented as mean changes from baseline and incidence of abnormal values. Shift tables will be presented for selected parameters.

9.4.3. Vital Signs Measurements, Physical Findings, and Other Safety Evaluations

Other safety outcomes will be presented using descriptive statistics.

9.5. Interim Analysis

A primary analysis will be conducted after Core Treatment Phase of all treated patients and before the final analysis at the end of study.

An interim look will be conducted separately prior to the primary analysis to assess the possibility of early communication with regulatory authorities based on the interim data. This will not be used to judge the early study termination or any changes of study design. This will occur at 3 months after the first dose of the last patient. The following endpoints for patients with sufficient follow-up will be summarized at the interim look:

- Some efficacy endpoints
    - Cumulative incidence of MMR at 12 months using the cumulative incidence function method
    - MMR by 12 months
    - MMR at 3, 6 and 9 months
    - MR[1] at 3 months;
- All safety endpoints;
- All PK endpoints except for primary endpoint related parameters (Exposure-Response relationship will not be included in the interim data)

Analysis of primary endpoint will not be conducted at the interim look. No alpha will be spent at the interim look. Further details are described in the statistical analysis plan.

9.6. Data Monitoring Committee

This study will not use a data monitoring committee. For the purposes of this study, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may

review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

In addition, the study will be conducted in accordance with the protocol, and any applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study patients. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

The informed consent documents and any patient recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the bosutinib, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

End of trial is defined as Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of bosutinib at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 1 month. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for

Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ADPKD	autosomal dominant polycystic kidney disease
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AP	accelerated phase
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BBS	biospecimen banking system
BCR-ABL	Fusion transcript or protein resulting from the 9;22 chromosomal translocation responsible for formation of the Philadelphia Chromosome
BP	blast phase
BUN	blood urea nitrogen
CBA	chromosome banding analysis
CBC	complete blood count
CCyR	complete cytogenetic response
CHMP	committee for medicinal products for human use
CHR	complete hematologic response
CI	confidence interval
CK	creatine kinase
CML	chronic myelogenous leukemia
CP	chronic phase
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EDTA	ethylenediaminetetraacetic acid
EFS	event-free survival
ELN	European LeukemiaNet

Abbreviation	Term
EU	European Union
EudraCT	European Clinical Trials Database
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
Hb	hemoglobin
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug (application)
INR	international normalized ratio
IRB	institutional review board
IS	international scale
IUD	intrauterine device
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
LLN	lower limit of normal
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MMR	major molecular response
MR	molecular response
MUGA	multiple gated acquisition
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OS	overall survival
PCD	primary completion date
PCR	polymerase chain reaction
Ph	philadelphia chromosome
PI	principal investigator
PK	pharmacokinetic
PPI	proton-pump inhibitor
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time

Abbreviation	Term
QD	once daily
RBC	red blood cell
RNA	ribonucleic acid
RT-qPCR	quantitative reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SRSD	single reference safety document
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States
WBC	white blood cell

Appendix 2. Response Definitions

A. Hematologic Responses to Treatment

Hematologic Responses	Definition
Complete Hematologic Response (CHR) had to meet all criteria	• WBC ≤10 × 10^9/L • Basophils <5% in blood • No myelocytes, promyelocytes, myeloblasts in the blood differential • Platelet count <450 × 10^9/L • Spleen non-palpable[a]

a. In a statistical analysis, if spleen disease was not assessed, it is assumed that spleen is non-palpable.

B. Cytogenetic Responses to Treatment

Before Treatment	Cytogenetic Responses (based on analysis of at least 20 metaphases)	% Philadelphia Chromosome Positive Cells
Chronic Phase	None	>95%
	Minimal	66-95%
	Minor	36-65%
	Partial	1-35%
	Complete	0%
	Major	Complete + Partial Rates

C. Molecular Responses to Treatment

Before Treatment	Molecular Response	RT-PCR (BCR-ABL Ratio)
Chronic Phase	Major, or MMR	≤0.1% (corresponding to ≥3 log reduction from baseline*) with a minimum number of ABL transcripts specified by the central laboratory
	MR[1]	A 1 log reduction in BCR-ABL transcript with a minimum number of ABL transcripts specified by the central laboratory
	MR[2]	A 2 log reduction in BCR-ABL transcript with a minimum number of ABL transcripts specified by the central laboratory
	MR[4.0]	Either (i) Detectable disease with ≤0.01% BCR-ABL IS or (ii) Undetectable disease in cDNA with a minimum number of ABL transcripts specified by the central laboratory
	MR[4.5]	Either (i) Detectable disease with ≤0.0032% BCR-ABL IS or (ii) Undetectable disease in cDNA with a minimum number of ABL transcripts specified by the central laboratory in the same volume of cDNA used to test for BCR-ABL

* standardized baseline from central laboratory

D. Definitions of Blast Phase and Accelerated Phase

Patient meeting any of the following criteria:

Blast Phase	≥30% Blasts in blood or bone marrow Extramedullary blast proliferation, other than in spleen
Accelerated Phase	15-29% blasts in blood or marrow, or >30% blasts plus promyelocytes in blood or marrow with blasts <30%; ≥20% basophils in blood Persistent thrombocytopenia (<100×10^9/L) unrelated to therapy[a] Clonal chromosome abnormalities in Ph+ cells (CCA/Ph+), major route, on treatment[b]

a. In a statistical analysis, persistent thrombocytopenia is not considered to define AP progression as the database does not collect data regarding the relationship between the platelet value and therapy.
b. In a statistical analysis, clonal chromosome abnormalities alone are not considered sufficient to define progression to AP unless concurrent presence of another AP criterion.

Appendix 3. Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Grade	Description
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Appendix 4. Summary of Drugs that are Generally Accepted to Have a Risk of Causing QTc Prolongation Potentially Causing Torsades de Pointes

Generic Name
Amiodarone
Arsenic trioxide
Astemizole
Bepridil
Chloroquine
Chlorpromazine
Cisapride
Clarithromycin
Disopyramide
Dofetilide
Domperidone
Droperidol
Erythromycin
Halofantrine
Haloperidol
Ibutilide
Levomethadyl
Mesoridazine
Methadone
Moxifloxacin
Petamidine
Pimozide
Probucol
Procainamide
Quinidine
Sotalol
Sparfloxacin
Terfenadine
Thioridazine
Vandetanib

Adapted from "The University of Arizona Center for Education and Research on Therapeutics"

See the following website for an updated list – Drugs with a Risk of Torsades de Pointes:
https://crediblemeds.org/index.php/drugsearch

Appendix 5. Selected Strong and Moderate CYP3A4 Isoenzyme Inhibitors and Inducers

Inhibitors:

Strong CYP3A Inhibitors	Moderate CYP3A Inhibitors
Lopinavir/ritonavir	Fluconazole
Indinavir	Darunavir/ritonavir
Nelfinavir	Erythromycin
Saquinavir	Diltiazem
Ketoconazole	
Itraconazole	Atazanavir
Voriconazole	Aprepitant
Posaconazole	Amprenavir
Conivaptan	Fosamprenavir
Clarithromycin	Imatinib
Telithromycin	Verapamil
Boceprevir	Tofisopam
Telaprevir	Ciprofloxacin
Mibefradil	
Nefazodone	
Grapefruit products including grapefruit juice	

Inducers:

Strong CYP3A inducers	Moderate CYP3A inducers
Rifampicin	Bosentan
Phenytoin	Nafcillin
Carbamazepine	Efavirenz
St. John's Wort	Modafinil
	Etravirine

Appendix 6. Guidelines for the Management of Diarrhea

Please be sure you understand these instructions BEFORE you leave the office and discuss with your study doctor if you need to obtain antidiarrheal medication before you go home.

Data obtained thus far from patients receiving bosutinib in prior studies performed in patients with CML show that diarrhea is the most common side effect you may have while receiving bosutinib. It has also been observed that diarrhea events, although frequent, are mainly low grade severity, transient, occurring predominantly in the first month of bosutinib treatment and managed by appropriate concomitant medications given for short duration. The purpose of this card is to help ensure appropriate management of diarrhea.

Treating diarrhea as soon as it starts may prevent it from getting worse. Your study doctor may tell you to take antidiarrheal medication(s) with the first loose stool or diarrhea. Please contact your study doctor as soon as possible if you have an episode of diarrhea. If you are dizzy or weak because of diarrhea, come to the office or go to the hospital immediately.

When calling the study doctor to report an event of diarrhea you should provide as much of the information below as possible, in order to help your study doctor to assess your diarrhea and decide on the best treatment:

- Number of stools per day as compared to your normal bowel habits;
- Presence of diarrhea during the night;
- Presence of fever, dizziness, abdominal pain/cramping or weakness;
- What the stool looks like, that is, watery, bloody or mucusy;
- When you took your last dose of study drug;
- Any other information that could explain your diarrhea (change in diet/food, recent travel, contact with other people experiencing vomiting and/or diarrhea).

Recommendations

1. Dietary Changes

If you have diarrhea:

- Stop all lactose-containing products (eg, milk, yogurt, cheese);
- Drink 8 to 10 large glasses of clear liquids per day;
- Eat frequent small meals;
- Eat low fat foods including bananas, rice, applesauce and/or toast;

Your study doctor may have other suggestions.

2. Medications

Your study doctor may prescribe a medication to treat diarrhea. Take the medications as directed by your study doctor. In case of more severe diarrhea and any diarrhea associated with fever, pain, infection, or dehydration, you may receive IV fluids, antibiotics and/or other medications.

3. Study Medication Adjustments

Your study doctor may instruct you to change the dose of your study medication, depending on how severe the diarrhea is and how you respond to treatment(s) for the diarrhea.