AN OPEN-LABEL BOSUTINIB TREATMENT EXTENSION STUDY FOR SUBJECTS WITH CHRONIC MYELOID LEUKEMIA (CML) WHO HAVE PREVIOUSLY PARTICIPATED IN BOSUTINIB STUDIES B1871006 OR B1871008

Compound:	PF-05208763
Compound Name:	Bosutinib
United States (US) IND Number:	68,268
European Clinical Trial Database (EudraCT) Number:	2013-000691-15
Protocol Number:	B1871040
Phase:	NA

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 2	7 November 2016	Patients being studied in China are to be excluded from the pharmacokinetic (PK) analysis and the centralized testing at end-of-treatment mutational analysis of the BCR-ABL kinase domain meant to explore mechanisms of underlying resistance to treatment. This decision by the Sponsor is made due to the lack of local laboratory resources in China, weighed against impact of <10 % of overall patients enrolled in China. PK data and genetic sequencing analysis will be collected from all the other patients and countries participating in this study. Schedule of Activities as well as Assessment (Section 7) are updated to reflect this decision. Lifestyle guidelines and requirements for contraception are updated throughout the protocol for consistency with updated Pfizer SOPs; all sections updated to reflect requirement that patients of childbearing potential must agree to use 2 highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment. Inclusion and exclusion criteria, section 4.1 and 4.2 are now updated for consistency, as well as Lifestyle Guidelines, section 4.3. Compliance 5.4.3 and Appendix 3. Instructions are updated for use of (missed or changed) dose diary. The protocol is updated to specify that the dose diary is to be given to each patient at each visit and is no longer an optional tool. A new dose diary is to be provided for each patient by the responsible site staff at each drug dispensation visit. The dose diary is to be updated by the patient if the bosutinib dose is changed or if any bosutinib doses are missed. The dose diary is to be reviewed by responsible site staff at each patient visit including phone contacts.

		Correction of spelling throughout protocol of Creatine Kinase Section 8 Adverse Event Reporting updated per Pfizer SOPs Section 15 Reporting requirements updated per Pfizer SOPs
Amendment 1	10 August 2016	Section 1: Introduction section updated to reflect current information on bosutinib and current leukemia guidelines for standard of care; including protocol summary, CML treatment options, and background information on bosutinib. Section 2: Study Objectives updated to fulfill a European Medicines Agency (EMA) post-approval requirement for the collection and analysis of the pharmacokinetics (PK) of bosutinib to assess correlations between trough concentrations of bosutinib and key efficacy and safety parameters. Section 3: Study Design updated to allow for: Extension of bosutinib dosing of all eligible patients to be studied for at least 10 years. Visit window allowance widened from ±4 days to ±14 days (2 weeks between 6- and 12-months and for telephone contacts (every 3 months). Schedule of Activities (SOA) Table 1 updated to reflect wider visit window allowance, the inclusion of PK sample collection, and assurance of contraceptive check per current SOPs. Collection of data on any subsequent TKI therapy or other anti-cancer treatment administered following discontinuation of bosutinib and the response to other treatments (if applicable). Section 4.3 Lifestyle Guidelines; updated

		Contraception Language per current SOPs. Section 4.4 Sponsor Medically Qualified Individual Section updated per current Protocol SOPs. Section 5 updated to allow more frequent dose dispensation per site policy or specific patient needs, and IP return practice updated to allow IP destruction per site policy or local regulation. Updates also made to reflect current protocol SOPs. Sections 5.4 and 5.4.1 Investigational Product (IP) and information updated per current protocol requirements and to allow for possibility of local sourcing of bosutinib drug supplies. Section 5.6.3 Other Concomitant Treatment Considerations updated with current information on bosutinib. Section 6 (and Section 7.1): Study Procedures Updated: Sections 6.2 and 7.1 Study procedures and efficacy assessment sections updated for consistency and allowance for local practice of molecular response in Chronic Myeloid Leukemia (CML) disease assessment using reverse transcriptase polymerase chain reaction (RT-PCR) to assess BCR-ABL fusion transcript levels). This update to protocol reflects current treatment guidelines. These assessments will be performed at each investigative site's investigative site's local laboratory. Section 7 Assessments Updated Section 7.1, Updated study conduct plans requiring standardization of mutational analysis of the BCR-ABL kinase domain to explore mechanisms of underlying resistance to treatment. This analysis is now to be performed by a central laboratory as arranged

		by Pfizer. Section 7 Pharmacokinetics requirements for each patient added to protocol amendment. Section 8 Adverse Event and Exposure definitions updated per new protocol SOPs. Section 9 Update made to Data Analysis and Statistical Methods sections to define diarrhea and PK analyses. Section 9.8 Data Monitoring Committee section updated per current protocol SOPs. Section 12 Patients informed consent section updated to reflect current protocol SOPs. Section 15 Communication of study results updated to reflect current protocol SOPs.
Original protocol	25 February 2013	Not applicable

PROTOCOL SUMMARY

Background and Rationale:

Bosutinib (Bosulif®) is an orally bioavailable, potent, selective, dual Src-Abl tyrosine kinase inhibitor (TKI) that has been developed as a tablet formulation for the treatment of adult patients with Philadelphia positive (Ph+) chronic phase chronic myelogenous leukemia (CML) previously treated with other tyrosine kinase therapy.

CML is the fourth most commonly occurring adult leukemia and accounts for nearly 5,000 new cases annually in the United States.[1] CML classically follows a tri-phasic course with most patients being diagnosed in an initial, chronic phase (CP) which eventually progresses into a more advanced accelerated phase (AP) and culminates in a blast phase (BP), a highly treatment-refractory form of acute leukemia that shows either a myeloid or a lymphoid phenotype.

The transformation of CML from a fatal disease to a chronic illness that took place over the last decade has been due to the development of TKIs, small-molecule inhibitors of the kinase activity of BCR-ABL1.[2]

Bosutinib is being developed for the treatment of Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (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 subjects in clinical studies, including subjects with Ph+ leukemias; subjects with solid tumors, including advanced or metastatic breast cancer; subjects with autosomal dominant polycystic kidney disease; and healthy subjects. As presented in the May 2016 Bosutinib Investigator Brochure, 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 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 subjects, 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).

On 04 September 2012 bosutinib was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with chronic, accelerated, or blast-phase Ph+ CML with resistance or intolerance to prior therapy. More recently, on 17 January 2013, the 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 tyrosine kinase inhibitor(s) 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 (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 (B1871008) comparing bosutinib with imatinib in newly diagnosed chronic phase Ph+ CML patients.

This study is a treatment-extension protocol aimed to allow long-term bosutinib treatment in patients with chronic or advanced phases Ph+ CML who received bosutinib in a previous Pfizer sponsored CML study (ie, Studies B1871006 and B1871008) and who are thought to have the potential, as judged by the investigator, to derive clinical benefit from continued treatment with bosutinib. It will also enable the collection of subsequent TKI therapy and long-term survival data for these patients, including those who have already discontinued treatment and are in the long-term follow-up phase or who have completed the parent study. Finally, this study will fulfill the European Medicines Agency (EMA) post approval requirement for the collection and analysis of safety data about diarrhea incidence after switch from clinical study to commercial bosutinib formulation. Every effort should be made to enroll qualified patients into this extension study. The patients enrolled in China, due to a lack of local resources, are excluded from the requirements for pharmacokinetic (PK) and mutational analyses of the BCR-ABL kinase domain testing.

Objectives:

- To allow long-term bosutinib treatment in patients with chronic or advanced phases of Ph+ CML who received bosutinib in a previous Pfizer-sponsored CML study (ie, Studies B1871006 and B1871008) and who have the potential, as judged by the investigator, to derive clinical benefit from continued treatment with bosutinib;
- To collect long-term safety and efficacy data for bosutinib;
- To assess the duration of clinical benefit for Ph+ CML patients treated with bosutinib;
- To fulfill the EMA post-approval requirement for the collection and analysis of safety data about diarrhea incidence after switch from clinical study to commercial bosutinib formulation.

Endpoints:

The objective of the study is to provide long-term access to bosutinib treatment and assess long-term safety, tolerability and duration of clinical benefit, without any formal hypothesis testing; therefore, there is no formal primary endpoint. In addition, data to be collected are planned to be different in the first line CP patients relative to the later line and advanced patients. For all patients regardless of the line of treatment:

For all patients:

- Long-term safety of bosutinib, including type, incidence, severity, timing, seriousness and relatedness of adverse events (AEs) and laboratory abnormalities as well as reason of treatment discontinuation. A special focus will be made on diarrhea in order to satisfy the EMA post-commitment request;

- BCR -ABL mutations present at the time patients discontinue Bosutinib. (Samples collected for all patients except those enrolled at sites in China)

- Overall survival (OS);

- Fulfill the EMA post-approval requirement to compare the pharmacokinetic analysis of C_{trough} of bosutinib in this study to C_{trough} of previous studies. (Samples collected for all patients except those enrolled at sites in China)

For 2nd or later line patients coming from study B1871006 who are still on treatment with bosutinib, the following efficacy endpoints will be assessed (Appendix 1):

- Duration of hematologic and cytogenetic responses;

- Progression-free survival;

- Time to transformation to accelerated or blast phase.

Study Design:

This is an open-label bosutinib treatment extension protocol. This protocol will be offered to those bosutinib patients who were previously enrolled in one of the two parent CML bosutinib studies (B1871006 or B1871008).

Patients to be enrolled will include those who, at the time of this protocol amendment, approval, are still receiving bosutinib in either one of the parent studies and are benefiting from bosutinib treatment as judged by the investigator, as well as those patients who have already discontinued bosutinib as part of the parent studies and are in follow-up for survival. The former group will continue to receive bosutinib as part of the extension study; the latter group will only enter into the long-term survival follow-up part of the extension study.

In order to have the most accurate and unbiased statistical analysis of long-term survival, the maximum number of patients who have received bosutinib should be enrolled in the extension study including those who have completed the 2 years of follow-up as planned in Study B1871006 and then discontinued the study. For this purpose every effort should be made to re-contact the patients who have completed the parent Study B1871006 and offer them the opportunity to participate in the extension study.

Each patient will remain in the extension study, either on bosutinib treatment or in long-term survival follow-up phase, until the last patient has reached 10 years of follow-up, as calculated from the date of his/her first dose of bosutinib administered in the parent study. When this milestone is reached, the present study will be closed. At that time, patients still benefiting from bosutinib will switch to the most appropriate therapy available at that time.

Study Treatment:

In this extension study, patients who are still on treatment will receive open-label bosutinib. The commercial formulation of bosutinib will be used in this study. Dosing will be continuous and at the dose currently administered in the respective parent study. Each patient will receive daily bosutinib until such time as the last patient reaches 10 years of follow-up, unless disease progression, unacceptable toxicity, death, withdrawal of consent or Sponsor study discontinuation occurs.

Statistical Method:

All bosutinib patients from the parent Studies B1871006 and B1871008 that are still on treatment, in survival follow-up or who have completed the parent study will be offered enrollment in this extension study.

Data from the two parent studies will be combined with data from this study for the analysis of efficacy. All bosutinib patients randomized in parent Study B1871008 or dosed in parent Study B1871006 will be included in the efficacy analyses. Analyses will be presented by disease stage (ie, CP, AP, BP) and by line of therapy.

Descriptive summaries and confidence intervals (if applicable) will be provided; no inferential analyses are planned for this study.

The time-to-event endpoints of overall survival, time to transformation, progression-free survival, and duration of response will be summarized via the Kaplan-Meier method or cumulative incidence, whichever is more appropriate, depending on the competing risks.

All patients dosed in the two parent studies will be included in the safety analyses. Data from the two parent studies will be combined with data from this study for the analysis of safety.

Table 1. SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS for detailed information on each procedure and assessment required for compliance with the protocol.
The investigator may schedule unplanned visits in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

A. Schedule of Activities for CML 1st-line patients coming from Study B1871008

Study Visit	Initial[a]	On Treatment			End of Treatment	Long-Term Follow-up
Schedule	≤28 days from last dose on parent study	Site visit		Phone call[c]	≤28 days after last dose of bosutinib	Every 3 months[a]
		At Month 3	Every 12 months[b]	Every 3 months[c]		
Visit Window[a]	±4 days	±4 days	±14 days	±14 days	±14 days	±14 days
ICD signature	X					
Eligibility criteria review	X					
Bosutinib Administration	Continuous Daily Dosing					
Physical Examination	X[d]				X	
Vital Signs	X[d]				X	
ECOG	X[d]				X	
Chest X-Ray	X[d]	As clinically indicated			X	
ECHO or MUGA	X[d]	As clinically indicated			X	
ECG	X[d]	As clinically indicated			X	
Hematology[e]	X[d]		X		X	
Biochemistry[f]	X[d]		X		X	
Liver function tests[g]	X[d]		X		X	
Coagulation Panel[h]	X[d]				X	
Serum pregnancy test	X[d]	As clinically indicated			X	
Dipstick Urinalysis[i]	X[d]				X	
AEs and concomitant medications[j]	X	X	X	X	X	
Collection of diarrhea information	X	X[k]				
Survival follow-up						X[l]
PK sample collection[m]		Refer to footnote m				
Contraception check[n]	X[d]	X	X	X	X	
IP dispensation, dosing check[o]		X	X	X	X	
(Data collection of any) Bone Marrow Aspirate or Peripheral Blood for Cytogenetics (Karyotyping or FISH) or Molecular Analysis per local practice standards)[p]			X		X	
BCR-ABL Mutation analysis[q]					X	

a. 1 month is defined as a 4-week or 28-day period. Study visit can be performed with a ±2 week (14 day) window.
b. For patients who have already discontinued bosutinib in the parent study and directly enter in the long-term follow-up phase of this extension study, the procedures will include ICD signature; data collection of any subsequent TKI therapy or anti-cancer treatment and response following discontinuation of bosutinib; and survival data.
c. Phone call every 3 months will be performed between study visits to collect safety information, including dosing administration information.
d. All end of treatment procedures performed as part of the parent study may serve as the initial/baseline assessment for this study as long as they are performed within 28 days prior to starting treatment on this study. If the necessary assessments were not performed within the 28 days, these assessments should be performed as part of this study at baseline.
e. Hematology panel including: complete blood counts (CBC) with 5-part differential, platelet count, absolute neutrophil count (ANC), red blood cell count (RBC), and hemoglobin (Hgb). Hematology to be repeated within 4 weeks if loss of CHR is seen (as applicable).
f. Biochemistry panel 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, and magnesium. Creatine kinase also to be performed. Abnormally high creatine kinase values should be confirmed and fractionated (where possible). Supplementation is advised for potassium levels or magnesium levels below the lower limit of normal, with consideration of the patient's underlying renal function.
g. Liver Function tests including: total bilirubin, AST and ALT.
h. Coagulation panel including: prothrombin time expressed as either prothrombin time (PT) or international normalized ratio (INR); and partial thromboplastin time (PTT or APTT).
i. Microscopic exam should be done if abnormalities detected.
j. This will include reporting of adverse events, any medication and non-pharmacological treatments.
k. Diarrhea information will be recorded by the patient in the patient diarrhea card provided at the baseline visit. Completed cards will be collected after the first 3 months of treatment in this extension protocol.
l. Follow-up will be conducted every 3 months from last dose of bosutinib. Long-term follow-up information will be collected via visit or telephone contact until the last patient reaches 10 years 524 weeks of follow-up, with one month of treatment=28 days for study purposes) from first dose of bosutinib (including the time on parent study). Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.
m. Pharmacokinetic Data: One pre-dose PK sample per patient (except those at Chinese sites) will be drawn, to be collected at first possible occasion after at least 2 weeks of uninterrupted dosing at steady state dose level.
n. Contraceptive Check: patients of child-bearing potential will be required to verbally affirm the use of 2 highly effective methods of contraception until at least 28 days after the last dose of bosutinib. This conversation will be documented in the patient's source document.
o. Dispensing or prescribing of bosutinib at least every 6 months, or more frequently as indicated.
p. Data collection of either cytogenetic or residual molecular response testing. (Molecular response monitoring using reverse transcriptase polymerase chain reaction (RT-PCR) measurement of BCR-ABL fusion transcript levels in on peripheral blood may be performed in lieu of monitoring via cytogenetics, once molecular response is achieved, and according to standard of care and current treatment guidelines at investigative site).
q. Mutation analysis of the BCR-ABLl transcript will be performed using a peripheral blood sample collected at the end-of-treatment visit in order to identify mutations acquired upon treatment with bosutinib. Mutations will be identified by direct sequencing of the BCR-ABL transcript performed at a Central Laboratory as arranged by the Sponsor. Peripheral blood from all eligible patients (except from patients enrolled at sites in China) will be collected and shipped frozen to a central vendor for analysis. Specific instructions for handling and shipment of these samples can be found in Study Reference Manual.

B. Schedule of Activities for CML 2nd line or patients coming from Study B1871006

Study Visit	Initial[a]	On Treatment			End of Treatment	Long-Term Follow-Up LTFU
Schedule	≤28 days from last dose on parent study	Site visit At Month 3	Site visit Every 6 months[b]	Phone call Every 3 months[c]	≤28 days after last dose of bosutinib	Every 3 months[b]
ICD signature	X					
Eligibility criteria review	X					
Bosutinib Administration	Continuous Daily Dosing					
Physical Examination	X[d]				X	
Vital Signs	X[d]				X	
ECOG	X[d]				X	
Extramedullary Assessment	X[d]		X		X	
Chest X-Ray	X[d]	As clinically indicated			X	
ECHO or MUGA	X[d]	As clinically indicated			X	
ECG	X[d]	As clinically indicated			X	
Hematology[e]	X[d]		X		X	
Biochemistry[f]	X[d]		X		X	
Liver function tests[g]	X[d]		X		X	
Coagulation Panel[h]	X[d]				X	
Serum pregnancy test	X[d]	As clinically indicated			X	
Dipstick Urinalysis[i]	X[d]				X	
Bone Marrow Aspirate or Peripheral Blood for Cytogenetics (Karyotyping or FISH) or Molecular Analysis per local practice standards)[j]	X[k]		X		X	
AEs and concomitant medications[k]	X	X	X	X	X	
Collection of diarrhea information[l]	X	X				
Survival follow-up						X[m]
PK sample collection[n]		Refer to footnote n	Refer to footnote n		Refer to footnote n	
Contraception Check[o]	X	X	X	X	X	
IP dispensation, dosing check[p]		X	X	X	X	
Bcr-Abl Mutation analysis[q]					X	

a. For patients who have already discontinued bosutinib in the parent study and directly enter in the long-term follow-up phase of this extension study, the procedures will include ICD signature; collection of data on any subsequent TKI therapy or other anti-cancer treatment and response to other treatment (if applicable) following discontinuation of bosutinib, and survival data.

b. 1 month is defined as a 4-week or 28-day period. Study visit can be performed with a ±2 week (14-day) window.

c. Phone call every 3 months will be performed between study visits to collect safety information, including dosing administration information.

d. All end of treatment procedures performed as part of the parent study may serve as the initial/baseline assessments for this study as long as they are performed within 28 days prior to starting treatment on this study. If the necessary

assessments were not performed within the 28 days, these assessments should be performed as part of this study at baseline.

e. Hematology panel including: complete blood counts (CBC) with 5-part differential, platelet count, absolute neutrophil count (ANC), red blood cell count (RBC), and hemoglobin (Hgb). Hematology to be repeated within 4 weeks if loss of CHR is seen (as applicable).

f. Biochemistry panel 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, and magnesium. Creatine kinase also to be performed. Abnormally high creatine kinase values should be confirmed and fractionated (where possible). Supplementation is advised for potassium levels or magnesium levels below the lower limit of normal, with consideration of the patient's underlying renal function.

g. Liver Function tests including: total bilirubin, AST and ALT.

h. Coagulation panel including: prothrombin time expressed as either prothrombin time (PT) or international normalized ratio (INR); and partial thromboplastin time (PTT or APTT).

i. Microscopic exam should be done if abnormalities detected.

j. Bone Marrow Aspirate or Peripheral blood for Cytogenetics using Karyotyping or FISH (Florescence In Situ Hybridization) will be conducted locally per SOC and site practice. Molecular response monitoring using reverse transcriptase polymerase chain reaction (RT-PCR) measuring BCR-ABL fusion transcript levels may be performed on peripheral blood. in lieu of monitoring via cytogenetics, once molecular response is achieved and according to standard of care and current treatment guidelines at investigative site, and if performed data will be collected in the eCRF.

k. Diarrhea information will be recorded by the patient in the patient diarrhea card provided at the baseline visit. Completed cards will be collected after the first 3 months of treatment in this extension protocol.

l. This will include reporting of adverse events, and medications and non-pharmacological treatments.

m. Follow-up will be conducted every 3 months from last dose of bosutinib. Long-term follow-up information will be collected via visit or telephone contact until the last patient reaches 10 years (524 weeks of follow-up, with 1 month of treatment=28 days for study purposes) from first dose of bosutinib (including the time on parent study). Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

n. Pharmacokinetic Data One pre-dose PK sample per eligible patient (except for those from sites in China) will be drawn, to be collected at first occasion after at least 2 weeks of uninterrupted dosing with bosutinib at steady state dose level.

o. Contraceptive Check: patients of child-bearing potential will be required to verbally affirm their use of 2 highly effective methods of contraception until at least 28 days after their last dose of bosutinib. This conversation which will be documented in the patient's source document.

p. Dispensing or prescribing of bosutinib at least every 6 months, or more frequently as indicated.

q. Mutation analysis of the BCR-ABLl transcript will be performed using a peripheral blood sample collected at the end-of-treatment visit for all eligible patients (except from patients enrolled at sites in China) in order to identify mutations acquired upon treatment with bosutinib. Mutations will be identified by direct sequencing of the BCR-ABL transcript performed at a Central Laboratory as arranged by the Sponsor. Peripheral blood for all eligible patients will be collected and shipped frozen to a central vendor for analysis. Specific instructions for handling and shipment of these samples can be found in Study Reference Manual.

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

1. INTRODUCTION

1.1. Indication

Bosutinib is an orally bioavailable, potent, selective, dual Src-Abl TKI that has been developed as a tablet formulation for the treatment of adult patients with Philadelphia positive (Ph+) chronic phase CML) previously treated with other tyrosine kinase therapy.

1.2. Background and Rationale

1.2.1. Chronic Myeloid Leukemia

Chronic myelogenous leukemia (CML) is the fourth most commonly occurring adult leukemia and accounts for nearly 5,000 new cases annually in the United States.[1] CML is a clonal myeloid neoplasm that originates from the translocation t(9;22) (q34;q11), the consequence of which is the generation of the Philadelphia (Ph) chromosome.[16] The molecular substrate of the t(9;22) translocation is the transcription of the hybrid *BCR-ABL1* oncogene, which encodes the constitutively activated BCR-ABL1 protein that activates several downstream signaling pathways that mediate myeloproliferation, resistance to apoptosis and genetic instability.[16] CML classically follows a tri-phasic course with most patients being diagnosed in an initial chronic phase (CP) which eventually progress into a more advanced accelerated phase (AP) and culminates into a blast phase (BP), a highly treatment-refractory form of acute leukemia that adopts either a myeloid or a lymphoid phenotype.

The transformation of CML from a fatal disease to a chronic illness that took place over the last decade is due to the development of tyrosine kinase inhibitors (TKIs), small-molecule inhibitors of the kinase activity of BCR-ABL1.[2]

Bosutinib is being developed for the treatment of Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (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 subjects in clinical studies, including subjects with Ph+ leukemias; subjects with solid tumors, including advanced or metastatic breast cancer; subjects with autosomal dominant polycystic kidney disease; and healthy subjects. As presented in the May 2016 Bosutinib Investigator Brochure, 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 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 subjects, 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).

On 04 September2012 bosutinib was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with chronic, accelerated, or blast-phase Ph+ CML with resistance or intolerance to prior therapy. More recently, on 17 January 2013, the 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 tyrosine kinase inhibitor(s) 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 (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 (B1871008) comparing bosutinib with imatinib in newly diagnosed chronic phase Ph+ CML patients.

1.2.2. Bosutinib (Bosulif®) as Therapeutic Option for CML

As of 03 September 2015, approximately 2478 patients, including 2141 patients with cancer, have received at least 1 dose of bosutinib in 24 clinical studies. On 4 September 2012 Bosulif® was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with CP, AP or BP Ph+ CML with resistance or intolerance to prior therapy. More recently, on 27 March 2013, the EMA 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 tyrosine kinase inhibitor(s), and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

Both approvals were granted based on the results obtained from the Phase 1/2 study single arm study (3160A4-200-WW, "B1871006 or Study 200") in adult patients with Ph+ leukemias whose disease had failed prior TKI therapy, supported by the safety results obtained as part of the Phase 3 study (3160A4-3000-WW) comparing Bosulif® with imatinib in newly diagnosed CP Ph+ CML patients. In addition, the EMA was provided descriptive narrative information from the bosutinib compassionate use program in patients with Ph+ CML who had received at least one prior TKI treatment and progressed or were intolerant, and otherwise not considered suitable for other TKI therapy and analyses from a subset of B1871006 (Study 200) patients whose disease had failed prior imatinib and/or nilotinib or dasatinib and were contraindicated for treatment with dasatinib or nilotinib, and 4th line patients.

Efficacy and safety data from the Phase 1/2 study, B1871006, and the Phase 3 study, B1871008 (Study 3000), are presented below according to phase of disease and line of therapy, as of 28 March 2011 and 15 February 2012 (B1871006) and as of 26 September 2011 (B1871008). Pooled safety data from B1871006, B1871008, and the Phase 1/2 Japanese study, B1871007 (Study 2203), are presented below as of 15 November 2010. The most current efficacy and safety data are contained in the Investigator's Brochure.

Second-Line CP CML

A total of 288 CP CML patients were enrolled and treated in the second-line setting in B1871006. The primary population for the efficacy response analyses was the evaluable population for imatinib-resistant patients, which included all treated patients with an adequate baseline assessment for the respective endpoint. The major cytogenetic response (MCyR) rate at Week 24 in the primary cohort (imatinib-resistant second-line CP CML) for the evaluable population (n=186) was 35.5%, with 24.2% attaining complete cytogenetic response (CCyR). Cumulative MCyR (defined as any on-treatment MCyR response during that period) was achieved in 55.4% of patients, with 43.0% attaining a CCyR. Cumulative MCyR and CCyR were newly achieved or maintained from baseline in 58% and 46% of patients, respectively. For patients with imatinib-intolerant CP CML, the MCyR rate at Week 24 in the evaluable population (n=80) was 30.0%, with a 25% CCyR rate at Week 24. Cumulative MCyR was achieved in 48.8% of patients, with 42.5% attaining a CCyR. Cumulative MCyR and CCyR were newly achieved or maintained from baseline in 61% and 54% of patients, respectively. In the evaluable population of second-line CP CML (n=287), 85.0% achieved cumulative Complete Hematologic Response (CHR), a secondary endpoint defined as a confirmed CHR or maintenance of baseline CHR during treatment with bosutinib. Of the 141 patients who did not have a CHR at baseline, 77.3% achieved a confirmed CHR. The Kaplan-Meier (K-M) estimates of Progression-Free Survival (PFS) for the CP CML second-line all-treated population (n=288) were 91.3% and 80.6% at Year 1 and Year 2, respectively; the K-M median PFS has not been reached. The K-M estimates of overall survival (OS) were 96.8% and 90.6% at Years 1 and 2, respectively; the K-M median OS has yet to be reached.

Third-Line CP CML

A total of 115 CP CML patients who received imatinib followed by dasatinib or nilotinib (ie, third line) and 3 CP CML patients who received imatinib followed by dasatinib and nilotinib (ie, fourth line) were enrolled and treated in B1871006. These 3 patients are included in all efficacy analyses presented for the third-line CP CML population. The primary population for the efficacy responses analyses was the evaluable population, which included all patients with an adequate baseline assessment for the respective endpoint. In the third-line CP CML evaluable population (n=108), 26.9% achieved MCyR by Week 24, with 13.9% attaining CCyR. The cumulative MCyR was 32.4%, with 24.1% attaining CCyR. Cumulative MCyR and CCyR were newly achieved or maintained from baseline in 39% and 31% of patients, respectively.

In the dasatinib-resistant cohort (n=35), 25.7% of patients had MCyR by Week 24, with 8.6% attaining CCyR. In the dasatinib-intolerant cohort (n=43), 25.6% had MCyR by Week 24, with 18.6% attaining CCyR. In the nilotinib resistant cohort (n=26), 26.9% had MCyR by Week 24, with a CCyR rate of 11.5%.

In the evaluable population of third-line CP CML (n=116), 73.3% of patients achieved a confirmed CHR or maintained a baseline CHR during treatment with bosutinib. Of the 68 patients who did not have a CHR at baseline, 64.7% achieved a confirmed CHR. The

K-M estimates of PFS for the all-treated population were 76.6% and 73.2% at Years 1 and 2, respectively; the K-M median PFS has not been reached. The K-M estimates of OS for the all-treated population were 91.2% and 82.9% at Years 1 and 2, respectively; the K-M median OS has not been reached.

Three (3) patients were enrolled who were resistant or intolerant to all currently approved TKIs for CML (imatinib, dasatinib, and nilotinib). One (1) patient who was intolerant to imatinib, dasatinib, and nilotinib due to Grade 3 skin toxicity entered the study with a partial cytogenetic response (PCyR) and subsequently achieved CCyR and complete molecular response (CMR) within 24 weeks of starting bosutinib. The patient has remained on bosutinib for over 33 months and has maintained a CCyR and CMR as of the last analysis at the time of the database snapshot, which is also clinically relevant, given that the patient previously only tolerated dasatinib for a total of 39 days and nilotinib for a total of 24 days.

Advanced Leukemias

A total of 164 patients with advanced Ph+ leukemia were enrolled and treated in B1871006. The primary population for the efficacy response analyses was the evaluable population, which included all patients with an adequate baseline assessment for the respective endpoint. In AP CML patients in the evaluable population (n=69), the confirmed overall hematologic response (OHR) rate by Week 48 was 55.1%. In BP CML patients in the evaluable population (n=60), the confirmed OHR rate by Week 48 was 28.3%.

Summary safety data across all patient cohorts in B1871006 showed most patients (560, 98%) reported at least 1 drug-related treatment-emergent adverse event (TEAE). Treatment-related TEAEs reported in ≥10% of patients were diarrhea in 454 (80%) patients, nausea in 238 (42%) patients, vomiting in 195 (34%) patients, thrombocytopenia in 167 (29%) patients, rash in 157 (28%) patients, abdominal pain in 97 (17%) patients, alanine aminotransferase (ALT) increased in 91 (16%) patients, anemia, fatigue, and neutropenia in 81 (14%) patients each, abdominal pain upper in 76 (13%) patients, and aspartate aminotransferase (AST) increased in 71 (12%) patients.

Treatment-related TEAEs of Grade 3 or higher included thrombocytopenia in 117 (21%) patients, neutropenia in 58 (10%) patients, diarrhea in 44 (8%) patients, ALT increased in 36 (6%) patients, and rash in 32 (6%) patients.

As of February 15, 2012, 134 (23.5%) patients have permanently discontinued bosutinib treatment because of AEs. The most frequent AEs that led to discontinuation were thrombocytopenia (26 patients, 4.6%), ALT increased (11 patients, 1.9%), neutropenia (8 patients, 1.4%), diarrhea and vomiting (7 patients, 1.2% each).

First-Line CP CML

In the Phase 3 study 3160A4-3000-WW (B1871008), bosutinib was compared to imatinib in the frontline treatment of CP Ph+ CML. The primary objective of the study was to compare the complete cytogenetic response (CCyR) at one year in CP patients receiving bosutinib alone versus patients receiving imatinib alone. The study enrolled 502 pts (250 on bosutinib

and 252 on imatinib). Results after a minimum follow-up of 24 months showed that 66% of patients receiving bosutinib and 45% of those treated with imatinib had dosing 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 adverse events or disease progression in the bosutinib and imatinib arms were 24% versus 4% and 7% versus 13%, respectively. No statistically significant difference was observed after 12 months of treatment between the bosutinib and imatinib arms regarding rates of CCyR (70% vs. 68%). Similarly, the cumulative CCyR rates by 24 months were virtually identical at 79% and 81%, respectively. However, on an intention-to-treat analysis, the MMR (major molecular response) rates at 12 months 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.

Compared with imatinib, bosutinib was associated with higher incidences of Grade 3-4 gastrointestinal toxicities, including diarrhea (12% vs. 1%), vomiting (3% vs. 0%) and abdominal pain (1% vs. <1%), although these adverse events were usually transient and manageable. Notably, diarrhea occurred mostly in the first 1-2 months of therapy and improved or subsided spontaneously over time. The rates of Grade 3-4 non-hematologic toxicities were ≤1% in both arms of the study. Grade 3-4 elevations of alanine aminotransferase (23% vs. 4%), aspartate aminotransferase (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 arm of this study, 91% were rechallenged. Of these patients, 80% did not experience subsequent elevations in transaminase levels that merited treatment discontinuation. Overall, 14% of patients were discontinued from bosutinib treatment due to unacceptable transaminase elevations. Grade 3-4 neutropenia, thrombocytopenia and anemia in the bosutinib and imatinib arms 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.

Ph+ Leukemia

Pooled safety data are reflected below (with a cutoff date of 15 November 2010). A total of 870 Ph+ leukemia patients across multiple, global Pfizer-sponsored clinical trials received at least 1 dose of single-agent bosutinib. These patients were either newly diagnosed Ph+ chronic phase CML, or were patients with resistant or intolerant Ph+ chronic, accelerated, or blast phase CML or Ph+ acute lymphoblastic leukemia (ALL). Of these patients**,** 248 are from the Phase 3 study in previously untreated CML patients, 570 and 52 are from two Phase 1/2 studies in previously treated Ph+ leukemias. The median duration of therapy was 16.6 months (range: 0.03 to 30.4 months) in the Phase 3 study, 11 months (range: 0.03 to 55.1 months), and 5.5 months (range: 0.3 to 30.4 months), in the Phase 1/2 studies respectively.

At least 1 adverse reaction of any toxicity grade was reported for 848 (97.5%) patients. The treatment-related adverse reactions reported for ≥20% of patients were diarrhea (78.5%), nausea (42.1%), thrombocytopenia (38.5%), vomiting (37.1%), abdominal pain (33.4%), rash (32.4%), anaemia (27.4%), pyrexia (23.4%), and alanine aminotransferase increased (22.3%). At least 1 Grade 3 or Grade 4 adverse reaction was reported for 531 (61.0%) patients. The Grade 3 or Grade 4 adverse reactions reported for ≥5% of patients were thrombocytopenia (25.4%), anaemia (12.3%), neutropenia (11.5%), alanine aminotransferase increased (10.2%), diarrhea (9.1%), rash (6.1%), lipase increased (5.2%) and aspartate aminotransferase increased (5.0%).

Complete information for bosutinib may be found in the Single Reference Safety Document (SRSD), which for this study is the Bosutinib Investigator's Brochure. (IB).

1.2.3. Study Rationale

This study is a treatment extension protocol to allow the opportunity of long-term treatment with bosutinib for patients who received bosutinib in previous Pfizer sponsored CML studies B1871006 and B1871008 and who are thought to have the potential, as judged by the investigator, to derive clinical benefit from continued treatment with bosutinib.

In addition this study:

- Will allow collection of subsequent TKI therapy and long-term survival data for all bosutinib patients who have discontinued bosutinib treatment in parent studies B1871006 and B1871008 but are known to be alive as of their last long-term follow-up visit;

- Will provide the opportunity to gather additional long-term safety and selected efficacy data for bosutinib in all CML patients, including 1st-line patients in chronic phase, as well as second-, third- and even fourth-line patients in chronic, accelerated and blast CML phases;

- Will satisfy the EMA post-approval commitment to provide safety data about diarrhea incidence after the patients switch from clinical study to commercial bosutinib formulation;

- Will fulfill the EMA post-approval requirement for the collection and analysis of the pharmacokinetics (PK) of bosutinib administered once daily.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

- To allow long-term bosutinib treatment in patients with chronic or advanced phases Ph+ CML who received bosutinib in a previous Pfizer sponsored CML study (ie, studies B1871006 and B1871008) and who have the potential, as judged by the investigator, to derive clinical benefit from continued treatment with bosutinib;

- To collect long-term safety and efficacy data for bosutinib;
- To assess the duration of clinical benefit for Ph+ CML patients treated with bosutinib;
- To fulfill the EMA post approval requirement for the collection and analysis of safety data about diarrhea incidence after switch from clinical study to commercial bosutinib formulation;
- To fulfill the EMA post-approval requirement for the analysis of the PK of bosutinib administered once daily.

2.2. Endpoints

The objective of the study is to provide long-term access to bosutinib treatment and assess long-term safety, tolerability and duration of clinical benefit, without any formal hypothesis testing; therefore, there is no formal primary endpoint.

In addition, data to be collected are planned to be different in the first line CP patients relative to the later line and advanced patients.

For all patients regardless of the line of treatment:

- Long-term safety of bosutinib, including type, incidence, severity, timing, seriousness and relatedness of AEs and laboratory abnormalities as well as reason of treatment discontinuation. A special focus will be made on diarrhea in order to satisfy the EMA post-commitment request;
- BCR -ABL mutations present at the time patients discontinue Bosutinib.
(For all patients except those enrolled at sites in China)
- Overall survival (OS);
- Fulfill the EMA post-approval requirement to compare the pharmacokinetic analysis of C_{trough} of bosutinib in this study to C_{trough} of previous studies.

For 2nd or later line patients coming from study who are still on treatment with **bosutinib**, the following efficacy endpoints will be assessed (Appendix 1):

- Duration of hematologic and cytogenetic responses;
- Progression free survival;
- Time to transformation to accelerated or blast phase.

Refer to Section 7.1.1 for more details on endpoint definitions.

3. STUDY DESIGN

This is an open-label bosutinib treatment extension protocol. This protocol will be offered to those bosutinib patients who were previously enrolled in one of the two parent CML bosutinib studies (B1871006 or B1871008).

Patients to be enrolled will include those who – at the time of this protocol approval - are still receiving bosutinib in either one of the parent studies and are benefiting from bosutinib treatment as judged by the investigator, as well as those patients who have already discontinued bosutinib as part of the parent studies and are in long-term follow-up (LTFU) for survival. The former group will continue to receive bosutinib as part of the extension study; the latter group will only enter into the long-term survival follow-up part of the extension study. Data on any subsequent therapy with TKIs or other anti-cancer therapy and response following bosutinib will be collected on LTFU patients, if available study.

Each patient will remain in the extension study, either on bosutinib treatment or in long-term survival follow-up phase, until the last patient has reached 10 years of follow-up, as calculated from the date of his/her first dose of bosutinib administered in the parent study. When this milestone is reached, the present study will be closed. At that time patients still benefiting from bosutinib will switch to the most appropriate therapy available at that time.

4. PATIENT SELECTION

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

4.1. Inclusion Criteria

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

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

1. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study.

2. Previous enrollment in the bosutinib arm of one of the two Pfizer parent Studies B1871006 or B1871008. This includes:

    a. Patients still receiving bosutinib in either StudyB1871006 or Study B1871008;

    b. Patients who have discontinued bosutinib but are still in the long-term follow-up phase of the Study B1871006 or B1871008;

    c. Patients from Study B1871006 who have discontinued bosutinib and have already completed the long-term follow-up period.

3. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4. Male and female patients of childbearing potential must agree to use 2 highly effective methods of contraception throughout the study and for at least 28 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

In order to be considered a female of non-childbearing potential the patient 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 or 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 and documented ovarian failure.

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

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Participation in other studies involving investigational drug(s) (Phases 1-4) while patient in the active treatment phase of the current study.

2. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are Pfizer employees directly involved in the conduct of the trial.

3. Other severe 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.

4. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects 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 Guidelines

In this study, fertile male subjects and female subjects who are of childbearing potential will receive bosutinib. Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy 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 subject, will confirm and document that the subject has selected 2 appropriate methods of contraception for the individual subject from the list of permitted contraception methods (see below) and will confirm and document that the subject has been instructed in their consistent and correct use. At time points indicated in the Schedule Of Activities, the investigator or designee will inform the subject of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or designee will instruct the subject to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the subject 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 (ie, oral, inserted, injected, implanted, transdermal) provided the subject or male subject'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 spermicide (ie, foam, gel, film, cream, 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 post-vasectomy 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).

   NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the Study Reference Manual.

To facilitate access to appropriately qualify 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 compound identifiers, patient study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the patient directly and if a patient calls that number they will be directed back to the investigational site.

During LTFU, patients will be assessed for survival status, as well as details of any subsequent TKI or other anti-cancer therapy.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

For those patients continuing on bosutinib treatment, bosutinib will be administered continuously on a daily basis as in parent Studies B1871006 and B1871008. Patients will receive the same bosutinib dose administered at the time of completion of the parent study.

In this extension study, patients who are still on treatment will receive open-label bosutinib. The commercial formulation of bosutinib will be used in this study. Dosing will be continuous and at the dose currently administered in the respective parent study unless disease progressions, unacceptable toxicity, death, withdrawal of consent, or Sponsor study discontinuation occurs.

Each patient will receive daily bosutinib until such time as the last patient enrolled in one of the parent studies reaches 10 years of dosing follow up.

Every effort should be made to continue bosutinib without interruptions while transitioning the patient from the parent to the present extension study. However, if needed, allowance for dosing interruptions can be made for a maximum of 28 days during the transition for logistic reasons.

If the patient completed the parent study while bosutinib was on hold due to toxicity, the patient must have recovered from toxicity before resuming treatment with bosutinib in the extension study. Please refer to the dosing guidelines for bosutinib reintroduction (Section 5.2).

5.2. Bosutinib Dose Modifications

The starting bosutinib dose is 500 mg once daily, however the dose can vary from 300 mg to 600 mg as described in the table below:

Table 2. Available Dose Levels

Dose Level	Daily Bosutinib Dose
+1	600 mg[a]
0 (Optimal bosutinib dose)	**500 mg**
-1	400 mg[b]
-2	300 mg[b,c]

a. The maximum dose escalation on study is 600 mg/day. Dose escalation to a dose greater than 600 mg is prohibited.

b. Once the dose has been reduced for a patient, the patient should remain on that dose unless an additional dose reduction is required or the dose is escalated as defined in the dose management instructions in case of toxicity (see Table 3 and Table 4 and relevant footnotes).

c. If a patient requires a dose reduction below 300 mg, the investigator should contact the sponsor to determine if the patient may continue on treatment at a lower dose. However, no dose reductions below 200 mg/day will 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/day, the patient will be discontinued from treatment and will only be followed up for survival.

5.2.1. Bosutinib Dose Escalation

As in the parent studies, patients will be allowed to dose escalate to 600 mg as long as no grade 3/4 or persistent grade 2 adverse drug reactions are observed, and at least one of the following lack of efficacy criteria is met:

- For 1st line patients: loss of complete cytogenetic response. Cytogenetic assessment done as part of standard of care practice will be used to determine the cytogenetic response, including loss of response.
- For 2nd or 3rd line patients in chronic phase: loss of major cytogenetic response.
- For all patients: loss of hematologic response defined as CHR for patients in chronic phase and OHR for advanced Ph+ CML patients.

In addition, if it is determined via RT-PCR (conducted by local lab) that a patient who had achieved a previous MMR now has a rising level of Bcr-Abl transcript (1 log increase), the investigator should contact the sponsor to determine if the patient's dose should be escalated to improve response.

5.2.2. Bosutinib Dose Reduction and Dosing Interruptions

As in the parent studies, the bosutinib dose can be reduced and/or dosing interrupted in case of treatment-related toxicity according to the guidelines described in the following tables.

Table 3. Non Hematologic Treatment Related Toxicity

Adverse Event	Action
Grade 1	Remain on current dose level
Grade 2	For persistent, clinically relevant toxicity not responding to optimal management: Interrupt bosutinib, then reintroduce at the same dose or reduce dose by one level upon recovery to Grade ≤1 within 4 weeks of stopping treatment.
Grade 3[a]	For persistent, clinically relevant toxicity not responding to optimal management: Interrupt bosutinib, then dose reduce by 1 level upon recovery to Grade ≤1 within 4 weeks of stopping treatment. If recovery takes longer than 4 weeks, the investigator should contact the sponsor to determine if the patient may continue on bosutinib.
Grade 4[a]	Interrupt bosutinib. Investigator and sponsor to determine if patient may continue on bosutinib with appropriate dose reduction.

a. For patients who have required a dose reduction due to toxicity, but then have been free of the specific toxicity (Grade ≤1) for at least 1 month and are otherwise tolerating bosutinib well, the investigator may choose to re-escalate the dose by one dose level each month (ie, increase the daily dose by 100 mg/month) until the patient is back to the starting or previous dose (whichever is higher). See Table 2 for available dose levels.

Table 4. Hematologic Treatment Related Toxicity

Adverse Event	Action
Grade 1	Remain on current dose level
Grade 2	Remain on current dose level
Grade 3[a]	First episode: Interrupt bosutinib until recovery to Grade ≤2. If patient recovers within 2 weeks of treatment hold: re-introduce bosutinib at same dose. If patient recovers within 4 weeks of treatment hold: reduce bosutinib by one dose level. Additional episodes: Interrupt bosutinib until recovery to Grade ≤2 and then reduce bosutinib by one dose level. In both cases, if recovery takes longer than 4 weeks, the investigator should contact the sponsor to determine if the patient may continue bosutinib.
Grade 4[a]	Withhold bosutinib. Investigator and sponsor to determine if patient may continue bosutinib 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 bosutinib, the investigator may choose to re-escalate the dose by

One dose level each month (ie, increase the daily dose by 100 mg/month) until the patient is back to the starting or previous dose (whichever is higher) per dosing tables – see Table 2). See Table 2 for available dose levels.

5.3. Bosutinib Treatment Discontinuation

Patients meeting any of the following criteria should discontinue bosutinib:

1. Disease progression, including:

    - Evolution from chronic phase (or from return to chronic phase for advanced patients) to accelerated phase or blast crisis (on two consecutive assessments at least a week apart).

    - Evolution from accelerated phase to blast crisis (on two consecutive assessments at least a week apart).

    - One of the following conditions occurring after dose escalation (as specified in Section 5.2.1, Dose Escalation) or presence of adverse events prohibiting dose escalation:

        - For 1st line patients, loss of complete or major cytogenetic response (need at least 30% increase confirmed by a follow-up cytogenetic analysis >1 month later). Cytogenetic assessment done as part of standard of care practice will be used to determine the cytogenetic response status.

        - For 2nd or later line patients, loss of major cytogenetic response (need at least 30% increase).

        - For all lines of treatment, loss of complete hematologic response confirmed by 2 assessments at least 2 weeks apart.

        - For all lines of treatment, increasing WBC defined as doubling of WBC, occurring over a period of ≥1 month, with the second WBC >20 x 10^9/L and confirmed at least 1 week later.

2. Bosutinib treatment interruption for longer than 4 weeks due to treatment-related toxicity, unless decided (and documented) otherwise by the investigator and Sponsor (see Table 3 and Table 4).

3. Bosutinib dose reduction below 300 mg/day. Except if after documented discussion with the investigator and Sponsor, it has been determined as appropriate for the patient to continue on bosutinib dose below 300 mg/day. No dose reductions below 200 mg/day will be permitted.

4. Withdrawal of consent.

5. Sponsor decision.

6. Pregnancy.

7. Death.

Survival follow-up information will be obtained for all patients who discontinue bosutinib treatment. See Treatment Completion and Follow-up section for detailed procedures to be performed upon treatment completion and for LTFU.

5.4. Investigational Product Supplies

Formulation and Packaging

Bosutinib is commercially available in 100 mg and 500 mg tablets and central supply or locally obtained commercial supplies of Bosutinib will be used for this study.

For specific countries in which approval has been granted and if not a financial hardship to the patient, a prescription may be provided to the Ph+ CML patients to source bosutinib for the study as directed by local regulations.

Bosutinib will be labeled in accordance with local regulations.

5.4.1. Preparation and Dispensing

The study site will dispense bosutinib or provide a prescription to the patient at least every six months, if deemed appropriate by the Investigator, to allow for per specific patient or Site requirements.

The investigator must ensure that the patient has an adequate supply of bosutinib to last until the next visit.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

5.4.2. Administration

Bosutinib will be self-administered by the patient, once daily, orally, with food, preferably in the morning. Preliminary data suggests that both tolerance and absorption may be improved with food, including adequate dietary fats; no restriction is imposed on patient's food choice. Tablets should not be crushed, split, or dissolved and patients should be instructed to swallow the study medication whole without manipulation or chewing of the medication prior to swallowing. If a patient vomits any time after taking a dose, they are instructed not to take another dose and to resume subsequent doses the next day as prescribed.

Medication errors may result, in this study, from the consumption of the drug by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the electronic case report form (eCRFs) and on the Serious Adverse Event (SAE) form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- 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.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE eCRF page.

5.4.3. Compliance

Compliance will be reviewed by the sponsor's site monitor utilizing source documents, Dispensing and Inventory Records (DIRs) or Investigational Product Accountability Log (IPAL), and bosutinib electronic case report forms (eCRFs). Site personnel will monitor each patient for dosing compliance and document it appropriately in the eCRF. Dose diarieswill be provided to patients as a tool for the recording of bosutinib dose information in cases of missed or changed dose. (see Appendix 3).

5.5. Investigational Product Storage and Accountability

Bosutinib should be stored at controlled room temperature (between 15-25°C/59-77°F or FOR JAPAN ONLY between 1-30°C/34-86°F as per the Japanese pharmacopoeia) in a locked storage area. Freezing is not permitted.

Storage conditions stated in the Single Reference Safety Document (SRSD) will be superseded by the label storage.

Investigators and site staff are reminded to check temperatures daily (ie, manually or by using alarm systems to alert of any excursions) and ensure that temperature monitoring device(s) is (are) working correctly as required for proper storage of investigational products. Any temperature excursions should be reported to the sponsor.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of the temperature range described in the labeling are not considered excursions.

Regulatory agencies require accounting for the disposition of all investigational drugs received by each clinical site. The investigator is responsible for maintaining information related to drug disposition which at minimum consists of the date received, date dispensed, quantity dispensed and the patient to whom the drug was dispensed.

The investigator is also responsible for the accounting of all unused investigational product (IP) and used investigational product (IP) containers.

IP storage and accountability will be reviewed by the monitor during routine monitoring visits.

Patients will be required to return all unused investigational product (IP) at the time new investigational product (IP) bottles are dispensed and at the end of treatment. Returned medication must not be re-dispensed. All bottles must be returned to the investigator by the patient, and the investigator will return the bottles to Pfizer. Local IP destruction or destruction via vendor is allowed, per Site or local policy or laws.

5.6. Concomitant Medication(s)

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

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral) removal, does not need to be recorded. Anesthetics used for any surgical procedures performed while the patient is enrolled in the study can be recorded as "unspecified anesthesia" on the concomitant treatment records; it is not necessary to list the specific anesthetics. Non-pharmacological treatment and/or procedures (ie, physical therapy, etc.) will be collected only if related to an adverse event.

Palliative and supportive care for cancer-related symptoms will be offered to all patients in this study.

5.6.1. Prohibited

All concomitant medications restrictions apply only **while the patient is on the active treatment phase of the study** (ie, receiving bosutinib), and include:

- Any anti-leukemia treatment other than the regimen defined in this protocol, including donor lymphocyte infusions;
- Any other investigational agents while the patient is receiving bosutinib.

5.6.2. Permitted

- Any medication (other than those prohibited above) for a concurrent medical condition is permitted;
- Treatment of diarrhea and other gastrointestinal symptoms will be optimized ie, that diarrhea will be monitored and managed using standards of care, including antidiarrheals, antiemetics, and/or fluid replacement;

- Palliative and supportive care for disease-related symptoms or toxicity due to study treatment;

- Treatment with growth factors (including G-CSF and/or M-CSF in Japan) (according to ASCO guidelines). No prophylactic use of growth factors will be allowed;

- Supplementation is advised for potassium levels or magnesium levels below the lower limit of normal, with consideration of the patient's underlying renal function.

5.6.3. Other Concomitant Treatment Considerations: Interaction with other Medicinal Products and Other Forms of Interaction

CYP3A inhibitors

The concomitant use of bosutinib with strong or moderate CYP3A inhibitors should be avoided, as an increase in bosutinib plasma concentration may occur (reference Appendix 6).

Caution should be exercised if mild CYP3A inhibitors are used concomitantly with bosutinib. Selection of an alternate concomitant medicinal product with no or minimal CYP3A enzyme inhibition potential, if possible, is recommended.

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, including St. John's Wort. Grapefruit should also be avoided.

The concomitant use of bosutinib with strong or moderate CYP3A inducers should be avoided; 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 6).

- For advanced leukemia patients requiring –azoles and for whom the antifungal therapies cannot be discontinued, careful monitoring of adverse events, including QTc prolongation via ECG testing, is important.

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

- Transfusions for anemia 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.

Proton-pump inhibitors (PPIs)

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

Please refer to the Schedule Of Activities for a complete list of procedures to be performed and associated time points.

Note that all study procedures listed below will apply only to patients participating in the active treatment phase of this extension study. For patients who have already discontinued bosutinib in one of the parent studies but are now included in the long-term follow-up phase of this extension study, the procedures will include ICD signature and data collection of any subsequent therapy with TKIs or other anti-cancer therapy and response following bosutinib discontinuation, as well as long-term survival data.

All tests described below will be performed locally and all the results obtained will be captured in the electronic case report form (eCRF).

6.1. Initial Visit

There is no screening period for this protocol. All required initial procedures should be performed between the EOT study visit of the parent study (B1871006 or B1871008) and Day 1 (baseline) of this extension study (Maximum time window = 28 days).

All end of treatment procedures performed as part of the parent study may serve as the initial or baseline assessments for this study. If the necessary assessments were not performed within the 28 days before Day 1, these assessments should be performed as part of the baseline visit of the extension study.

Every effort should be made to conduct the EOT visit of the parent study and the Day 1 baseline visit of the extension study on the same day in order to allow uninterrupted bosutinib dosing. However, if needed, a 28-day period is allowed between the last dose of bosutinib on the previous parent study and the first dose of bosutinib on this extension study.

The following procedures should be conducted as part of the baseline visit:

- Signature of the ICD;
- Review of patient's eligibility (ie, inclusion/exclusion criteria);
- Complete physical examination to include vital signs (temperature, sitting or supine blood pressure, heart rate and weight). ECOG performance status should also be assessed (see Appendix 4). Extramedullary disease assessment will also be performed;

- Electrocardiogram (ECG);
- Echocardiogram (ECHO) or multiple gated acquisition scan (MUGA);
- Chest X-ray;
- Hematology panel with complete blood counts (CBC) including:
    - White blood cell count (WBC), with 5-part differential (with manual confirmation of abnormalities);
    - Platelet count;
    - Absolute neutrophil count (ANC);
    - Red blood cell count (RBC);
    - Hemoglobin (Hgb).
- Chemistry panel 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 and magnesium. Creatine kinase (CK) should also be performed. Abnormally high CK should be confirmed and fractionated creatine kinase performed (if available). Uric acid to be obtained until the patient achieves a CHR;
- Liver Function Tests (LFTs) including: total bilirubin, AST and ALT;
- Coagulation tests including: prothrombin time expressed as either prothrombin time (PT) or international normalized ratio (INR); and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT);
- Dipstick urinalysis (microscopic if abnormal);
- Serum pregnancy test (for women of childbearing potential);
- Review of and implementation of the patient diarrhea card;
- Review of adverse events and concomitant medications;
- Contraception check.

  For all patients **except 1st line patients enrolled from B1871008:** an additional blood sample to perform cytogenetic assessment by FISH, except if conventional cytogenetics has been performed and adequate results obtained as part of the end of treatment visit of the parent study.

- According to standard of care and current treatment guidelines, bone marrow or blood sample will be collected for CML disease assessment via cytogenetic assessment by karyotype or by FISH. If appropriate, in lieu of cytogenetic assessment molecular response monitoring using reverse transcriptase polymerase chain reaction (RT-PCR) for molecular assessment (of BCR-ABL fusion transcript levels in peripheral blood may be performed. These assessments will be performed at a laboratory local to Investigational Site and data for B1871006 and B1871008 patients will be collected in the eCRF if available.

Note that all abnormalities revealed by baseline testing will be managed as an adverse event and should follow the guidelines defined in Section 5.2 and 5.3 if needed.

6.2. Study Period

Visit schedules and study procedures will be different based on the line of treatment of the patients (ie, if enrolled from B1871006 vs. B1871008). Study visit can be performed with a ±14-day (2-week) window (1 month is defined as a 4-week or 28-day period).

- 1st line chronic phase patients enrolled from study B1871008 will be followed up only to collect safety, survival and BCR-ABL mutational status data (the latter does not apply to patients enrolled at China Sites).. Study visits will occur every 12 months (once a year), and a phone call will be implemented every 3 months between study visits at the site in order to collect an update on the patient's current safety status and dosing and to remind the patient about use of the dosing diary and importance of contraception compliance. All information collected during the phone calls will be immediately recorded in the eCRF.

  One additional study visit will be arranged after the first 3 months ±4 days of treatment in order to collect all diarrhea information reported on the patient diarrhea card provided at the baseline visit.

  Patients who are continuing bosutinib therapy should have their disease status assessed according to the local standard of care.

- For 2nd and later line patients enrolled from study B1871006, study visits will occur every 6 months (twice a year) and a phone call will be implemented every 3 months, between scheduled visits in order to get an update on current patient's status, assessment of any adverse events, and dosing compliance, and a contraceptive check.

  Procedures performed as part of the study visits may include:

  - Extramedullary disease assessment;

  - According to standard of care and current treatment guidelines, bone marrow or blood sample will be collected for CML disease assessment via cytogenetic assessment by karyotype or by FISH. If appropriate, in lieu of cytogenetic assessment molecular response monitoring using reverse transcriptase polymerase

chain reaction (RT-PCR) for molecular assessment (of BCR-ABL fusion transcript levels in peripheral blood may be performed. These assessments will be performed at a laboratory local to Investigational Site and data will be collected if available.

- Hematology panel with complete blood counts (CBC) (see Section 6.1 for details);
- Chemistry panel (see Section 6.1 for details);
- Liver Function Tests (LFTs) (see Section 6.1 for details);
- Bone Marrow Aspirate for differential ONLY for patients in advanced phase;
- Review of adverse events and concomitant medications.

One additional study visit will be arranged after the first 3 months on treatment in order to collect all diarrhea information reported on the patient diarrhea card provided at the baseline visit.

6.3. Treatment Completion Visit

The End of Treatment (EOT) visit should be performed for all patients once they have permanently discontinued bosutinib as described in Section 5.3. The visit should occur within 28 days after the last dose of bosutinib. The following procedures are required:

- Complete physical examination including vital signs, ECOG performance status and extramedullary disease assessment;
- Electrocardiogram (ECG);
- Chest X-ray;
- Mutation analysis of the BCR-ABLl transcript will be performed using a peripheral blood sample collected at the end-of-treatment visit in order to identify mutations acquired upon treatment with bosutinib. Mutations will be identified by direct sequencing of the BCR-ABL transcript performed at a Central Laboratory as arranged by the Sponsor. Peripheral blood for all eligible patients (except from patients enrolled at sites in China) will be collected and shipped frozen to a central vendor for analysis. Specific instructions for handling and shipment of these samples can be found in Study Reference Manual;
- Cytogenetic or residual molecular response testing. Molecular response monitoring using reverse transcriptase polymerase chain reaction (RT-PCR) measurement of BCR-ABL fusion transcript levels in peripheral blood may be performed in lieu of monitoring via cytogenetics, once molecular response is achieved, and according to standard of care and current treatment guidelines at investigative site;

- Hematology panel with complete blood counts (CBC) (see Section 6.1 for details);
- Chemistry panel(see Section 6.1 for details);
- Liver Function Tests (LFTs) (see Section 6.1 for details);
- Coagulation tests (see Section 6.1 for details);
- Dipstick urinalysis (microscopic if abnormal);
- Serum pregnancy test (for women of childbearing potential);
- Contraceptive check;
- Dosing compliance check;
- Review of adverse events and concomitant medications.

6.4. Long-Term Follow-up Visit

Patients who discontinue treatment with bosutinib prior to the end of the study will enter into the Long-Term Follow-Up period. Patients will be followed for the duration of study in order to assess the survival status of the patient. Details of any subsequent therapy with TKIs or other anti-cancer therapy and response following bosutinib discontinuation will be collected on LTFU patients if available.

Follow-up will be conducted every 3 months from the last dose of bosutinib. Information will be collected via clinical visit or telephone contact

6.5. Patient Withdrawal

Patients may withdraw from the study 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 or 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 why a patient may discontinue or be withdrawn from the study include, but are not limited to, adverse event patient request, protocol violation, patient noncompliance, and study termination by the sponsor. When a patient discontinues or is withdrawn, the investigator will notify the sponsor.

The treatment completion visit must be performed for all patients who discontinue from receiving further bosutinib administration. Furthermore, follow-up should be performed unless the patient died, voluntarily withdrew consent, or the sponsor terminated the study. All information should be recorded on the appropriate eCRF.

If a 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.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient to return all unused investigational product(s), request the patient to return for a final visit, and follow-up with the patient regarding any unresolved adverse events (AEs).

If a patient is lost to follow-up, or is voluntarily withdrawn from any study participation, every effort must be made to obtain any pertinent follow-up information and/or perform a treatment completion visit.

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, which 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 which he/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 fashion.

7.1. Efficacy Assessments

7.1.1. Efficacy Assessment Methods

Efficacy will be determined by analysis of peripheral blood and physical examination for all patients except those in advanced phase of the disease for whom a bone marrow differential count will be needed. Refer to the Schedule Of Activities for time points. Assessments will continue per Schedule Of Activities until treatment completion.

Automated complete blood counts and differential counts (with manual confirmation of abnormalities), physical examination and cytogenetics by FISH will be used to determine response to treatment as outlined in Appendix 1.

Number of Ph+ cells will be assessed by fluorescence in situ hybridization (FISH) from peripheral blood (PB) sample. To ensure reliable estimation of cytogenetic response, the cytogenetic assessment must be performed on at least 200 nuclei. PB FISH is not only more sensitive but also less invasive for the patient than conventional bone marrow (BM) cytogenetics.[29] Studies have demonstrated the strong correlation between BM and PB FISH as well as BM conventional cytogenetics.[30-37]

However, conventional cytogenetics on BM, requiring at least 20 metaphases, may be performed when loss of cytogenetic response is suspected by PB FISH or at the end of therapy. Loss of cytogenetic response must be confirmed by 2 assessments at least 4 weeks apart.

Hematologic responses must be of at least 4 weeks in duration confirmed by 2 assessments at least 4 weeks apart. Hematologic response will be evaluated by peripheral blood only for patients in chronic phase and by both peripheral blood and bone marrow for patients in advanced phase. Loss of hematologic response must also be confirmed by 2 assessments at least 2 weeks apart.

Molecular response monitoring using reverse transcriptase polymerase chain reaction (RT-PCR) measurement of BCR-ABL fusion transcript levels may be performed on peripheral blood in lieu of monitoring the patient via cytogenetics, once molecular response is achieved, and according to standard of care and current treatment guidelines at Site. This data will be collected in the eCRF.

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

All tests described above will be performed locally.

7.2. Safety Assessments

Refer to the Schedule Of Activities for time points.

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0. Patients are to be followed for adverse events for 28 days after last dose of bosutinib, regardless of causality. Furthermore, all treatment-related adverse events will be followed until Grade ≤1, return to baseline, or in the case of impairment, until the condition stabilizes.

7.2.1. Safety Assessment Methods

Safety will be assessed by physical examination (including vital signs) and laboratory tests (see Appendix 5), including chest X-ray and ECHO/MUGA scans.

All safety assessments are outlined in the schedule of activity and include adverse event and concomitant medication review, assessment of disease status, PK collection for all eligible patients (except from patients enrolled at sites in China), and ECG monitoring.

7.2.2. Special Recording of Diarrhea Events

EMA has required that ad hoc analyses are conducted in order to evaluate the incidence of diarrhea after study patient's transition to the bosutinib commercial formulation. To satisfy this request, a diarrhea card will be provided to the patients to collect the details of diarrhea events during the first three months on study treatment (see Appendix 2).

Diarrhea cards will be provided to all patients at the baseline visit. The cards will be collected at the Month 3 study visit; data reported by the patient will be reviewed by the investigator and recorded in the eCRF.

7.2.3. Safety Laboratory Determinations

The investigator will review laboratory test results to determine the occurrence of clinically important abnormalities (ie, AEs). If laboratory values do not return to normal or baseline within a reasonable period, the etiology should be identified and documented appropriately. Only laboratories associated with the investigative site should be used by the investigator for all determinations, unless a special test is required. Every effort should be made by each investigator to designate one primary laboratory for all determinations unless a special test is required. It is the responsibility of site staff to collect valid laboratory certifications and normal ranges for all local laboratories used during the course of the study.

7.2.4. Contraceptive Check

Patients of child-bearing potential will be required to verbally affirm their use of 2 highly effective methods of contraception until at least 28 days after their last dose of bosutinib. This conversation which will be documented in the patient's source records.

7.3. Pharmacokinetics

Steady-state trough concentrations (C_{trough}) of bosutinib will be determined. A total of 1 PK sample per subject will be drawn. All eligible patients (except from patients enrolled at sites in China) will provide a pre-dose blood sample following at least 2 weeks of uninterrupted dosing with bosutinib at the same dose level. This sample will be collected at their first scheduled visit following all appropriate approvals and implementation of protocol amendment # 1. Biological specimen samples for pharmacokinetic analysis must be identified with labels provided by the sponsor.Concentrations of bosutinib will be determined in plasma using a Pfizer -approved and validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay.

The objective of the pharmacokinetic analysis is to compare the C_{trough} of bosutinib in this study to C_{trough} of previous studies.

7.3.1. Blood Collections for Plasma PK and BCR-ABL Mutation Analysis

Blood samples (3 mL) to provide approximately 1.0 mL plasma for PK analysis will be collected into appropriately labeled tubes at times specified in the Schedule Of Activities.

One pre dose PK sample per eligible patient will be drawn, to be collected at first occasion after at least 2 weeks of uninterrupted dosing at the same dose level. 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 study drug, samples may be used for further characterization and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report.

BCR-ABL **Mutation Analysis**

Analysis of the BCR-ABL transcript will be performed using a peripheral blood sample collected at the end-of-treatment visit from each eligible patient in order to identify mutations acquired upon treatment with bosutinib. Mutations will be identified by direct sequencing of the BCR-ABL transcript performed at a Central Laboratory as arranged by the Sponsor. Peripheral blood will be collected and shipped frozen to a central vendor for analysis. Specific instructions for handling and shipment of these samples can be found in Study Reference Manual.

7.3.2. Pregnancy Testing

For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed within 28 days of the first dose of bosutinib at the baseline visit and at the end of treatment visit. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), repeated at the end of the study to confirm the patient has not become pregnant during the study. In the case of a positive hCG test, the patient will be withdrawn from study medication but may remain in the study. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

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] group or 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 when the investigator becomes awareof the event **All events are to be reported to Pfizer, regardless as to causation**. 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 and document the time of his/her first awareness of the event.In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately upon discovery, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded reports.

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 subject 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 subject/[parent(s)/legal guardian/legally acceptable representative]. In addition, each study subject/[parent(s)/legal guardian/legally acceptable representative] 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 Subject 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 subject 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 subject begins from the time the subject provides informed consent, which is obtained before the subject'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; except as indicated below] after the last administration of the investigational product.

For subjects 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 subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject 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 subject 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;
- Progression/worsening of underlying disease
- 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 subject 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 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, subject 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 subject;
- 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

For oncology studies, investigators report AEs using concise medical terminology (verbatim) as well as collect on the *CRF* the appropriate Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03, Publish Date: 14 June 2010, http://ctep.cancer.gov/reporting/ctc.html) listed in the Cancer Therapy Evaluation Program.

The investigator will use the following definitions of severity in accordance with the current CTCAE version to describe the maximum intensity of the adverse event.

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

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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects 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 subject's individual baseline values and underlying conditions. Subjects 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:

- Subjects 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 subjects 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 subject 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.

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 subject or subject's partner becomes or is found to be pregnant during the subject'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 subject 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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject 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 subject 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 and Lack of Efficacy

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

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

*For lack of efficacy (particularly for studies conducted with vaccines, contraceptives, and products used in the treatment of life-threatening diseases or conditions [eg, anti-infectives]), see the Lack of Efficacy section below.

8.4.4.1. Medication Errors

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

Medication errors include:

- Medication errors involving subject 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 subject.

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**.

8.4.4.2. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the endpoint definition and/or its analysis will also be reflected in the clinical study report.

9.1. Sample Size Determination

This study does not include any formal sample size determination. All bosutinib patients from the two parent studies B1871006 and B871008 who are still on-treatment at the initiation of this study, or known to be alive as of their last LTFU visit, or who have completed the parent study will be offered enrollment in this extension study.

9.2. Analysis of Efficacy

Data from the two parent studies will be combined with the data from this study for the analysis of efficacy. All bosutinib patients randomized in parent Study B1871008 or dosed in parent Study B1871006 will be included in the efficacy analyses. Analyses will be presented by disease stage (ie, CP, AP, BP) and by line of therapy.

Descriptive summaries and confidence intervals (if applicable) will be provided; no inferential analyses are planned for this study.

The time-to-event endpoints of overall survival, time to transformation, progression-free survival, and duration of response will be summarized via the Kaplan-Meier method or cumulative incidence,[2] whichever is more appropriate, depending on the presence of competing risk.

9.3. Overall Survival

Overall survival (OS) or survival time is defined as the interval from the date of randomization (first line patients enrolled from B1871008) or first dosing (second or later line patients enrolled from B1871006) in the parent study to the date of death due to any cause. Patients not known to have died are censored at the last known alive date. OS will be calculated for all patients enrolled in the parent study B1871008 and dosed in the parent study B1871006.

9.4. Time to Transformation to AP/BP

Time to transformation is defined as the time from the date of first dose in the parent study to the first date of confirmed transformation to AP or BP. For patients without transformation, censorship is at the last evaluation date.

Time to transformation will be calculated only for patients in 2nd or plus line setting while on treatment.

9.5. Progression-Free Survival

Progression-free survival (PFS) is the interval from the date of first dose of bosutinib in the parent study until the earlier date of progression or death from any cause. Patients without events are censored at the last evaluation date.

PFS will be calculated only for patients in 2nd or above line setting.

9.6. Duration of Response

Duration of response (MCyR, CHR, OHR) is measured from the date of the earliest demonstration of a response, until the earliest date of confirmed loss of that response. For patients without loss of response, censorship is at the last evaluation date. Duration of response will be calculated only for patients in 2nd or plus line setting who respond to treatment.

9.7. Safety Analysis

Treatment-emergent AE (defined as any event increasing in severity from parent study baseline, or any new event starting during bosutinib therapy or within 30 days of the last bosutinib dose) incidence rates will be described both with and without regard to causality. The frequency of occurrence of overall toxicity, categorized by toxicity grades, will be described. Listings of laboratory test results collected at baseline and during the study will be generated and descriptive statistics summarizing changes in laboratory tests over time will be presented.

The incidence of diarrhea from the 2 parent studies and the incidence of diarrhea from extension study will be tabulated in order to compare the clinical and commercial formulations of bosutinib.

The pharmacokinetic analysis (collected for all patients except those from sites in China) will compare the C_{trough} of bosutinib in this study to C_{trough} of previous studies.

All patients dosed in the parent Studies B1871006 and B1871008 will be included in the safety analyses. Data from the two parent studies will be combined with the data from this study for the analysis of safety.

9.8. Data Monitoring Committee

This study will not use a Data Monitoring Committee. The Sponsor's procedures for ongoing periodic safety reviews will be applied by an internal safety review team with medical and statistical expertise to review individual and summary data collected in the safety and clinical databases.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits 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 is 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.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), 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.

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 is true. Any corrections to entries made in the CRFs, 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's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, ie, 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 (ie, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), 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 (ie, 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 to 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 (IRB)/Independent Ethics Committee (IEC)

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and 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 on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial patient. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

Whenever consent is obtained from a patient’s legally acceptable representative or legal guardian, the patient’s assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the

investigator determines that a patient's decisional capacity is so limited, he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (ie, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (ie, parent, spouse) and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator must ensure that each study patient, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legal representative 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 Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, 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 in all participating countries is defined as Last Patient Last Visit, which will occur when the last patient would have spent approximately 10 years (either on treatment or in long-term follow-up from the first dose of bosutinib in the parent study (B1871006 or B1871008). When this milestone is reached, the present study will be closed. At that time, the patients still benefiting from bosutinib will switch to the most appropriate therapy available at that time.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug 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 or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within one week of notification. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

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 subject 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.

15.1. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigators, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigators will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigators will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigators agree to delay the disclosure for a period not to exceed an additional 60 days.

Investigators will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigators agree that the first publication is to be a joint publication covering all centers. 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, Investigators are free to publish separately, patient to the other requirements of this Section.

For all publications relating to the Study, 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 Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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APPENDICES

Appendix 1. Tables Defining Responses to Treatment

A Hematologic Responses Definition

Hematologic Responses	Definition
Return to Chronic Phase (RCP) (or CP for subjects with CP)/ **Minor Hematologic Response (MiHR)** (for Ph+ ALL subjects) Subjects had to meet all criteria	Disappearance of features defining accelerated and blast phases, but still in chronic phase as noted by: • <15% Blasts in both blood and marrow • <30% Blasts + promyelocytes in both blood and marrow • <20% Basophils in both blood and marrow (marrow not applicable for Ph+ ALL) • No extramedullary involvement other than liver/spleen
Accelerated Phase had to meet at least 1 criterion	• 15-29% Blasts in blood or marrow • ≥30% Blasts + promyelocytes in blood or marrow • ≥20% Basophils in blood or marrow <u>only applicable to advanced phase</u> • Platelets <100x109/L (not related to therapy)
Blast Phase had to meet at least 1 criterion	• ≥30% blasts in blood or bone marrow • Extramedullary involvement other than liver/spleen
No Evidence of Leukemia (NEL) had to meet all criteria	• WBC ≤ institutional ULN • 450 x109/L > Platelets ≥20x109 /L • ANC ≥0.5x109/L • <20% basophils in blood • No blasts or promyelocytes in blood • Myelocytes + metamyelocytes <5% in blood • No extramedullary involvement (incl. hepato- or splenomegaly)
Complete Hematologic Response (CHR) had to meet all criteria	<u>only applicable for advanced phase</u> • ≤5% bone marrow blasts • WBC ≤ institutional ULN • Platelets <450 × 109/L • <20% basophils in blood • No blasts or promyelocytes in blood • Myelocytes + metamyelocytes <5% in blood • No extramedullary involvement (incl. hepato- or splenomegaly) <u>only applicable to advanced phase</u> • ≤5% bone marrow blasts • ANC ≥1.0 × 109/L • Platelets ≥100 × 109/L
Overall Hematologic Response (OHR) had to meet at least 1 criterion	CHR +NEL +RCP + MiHR (if applicable)
Major Hematologic Response (MHR) (had to meet at least 1 criterion)	CHR +NEL

Abbreviations: ANC=absolute neutrophil count, ULN=upper limit of normal range, WBC=white blood cell

B. Cytogenetic Responses to Treatment

Cytogenetic Responses*	% Philadelphia chromosome positive cells
None	>95%
Minimal	66-95%
Minor	36-65%
Partial	1-35%
Complete	0% from conventional cytogenetics or <1% from FISH
Major	Complete + Partial Rates

* Based on analysis of 200 nuclei if done from blood sample or based on analysis of 20 metaphases if done from bone marrow sample.

C. Minimal Residual Disease Assessment (Quantitative PCR performed locally)

Response by Type	Definitions
Molecular Deep Molecular Response (MR4, MR4.5, MR5)	MR4= either (i) detectable disease with ≤0.01% BCR-ABL1 ^{IS} or (ii) undetectable disease in cDNA with a minimum number of ABL1 transcripts specified by the local laboratory in the same volume of cDNA used to test for BCR-ABL1. MR4.5 =either (i) detectable disease with ≤0.0032% BCR-ABL1 ^{IS} or (ii) undetectable disease in cDNA with a minimum number of ABL1 transcripts specified by the local laboratory in the same volume of cDNA used to test for BCR-ABL1. MR5 =either (i) detectable disease with ≤0.001% BCR-ABL1 ^{IS} or (ii) undetectable disease in cDNA with a minimum number of ABL1 transcripts specified by the local laboratory in the same volume of cDNA used to test for BCR-ABL1.
Major (MMR)	Ratio of $BCR\text{-}ABL^{IS}$ ≤0.1% with a minimum number of ABL1 transcripts specified by the local laboratory.
MR2	Ratio of $BCR\text{-}ABL^{IS}$ ≤1% with a minimum number of ABL1 transcripts specified by the local laboratory.
MR1	Ratio of $BCR\text{-}ABL^{IS}$ ≤10% with a minimum number of ABL1 transcripts specified by the local laboratory.

Appendix 2. Patient Diarrhea Card

Guidelines for the Management of Diarrhea for Participants in the bosutinib Extension Study

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 including your own experience from your participation in study B1871006 or B1871008 show that diarrhea is the most common side effect you may have while receiving bosutinib. It has also been showed that diarrhea events, although frequent, are mainly low grade in severity, don't last long, occur predominantly in the first month of bosutinib treatment, and managed by appropriate concomitant medications given for short duration.

We do not anticipate any specific change in gastrointestinal disorders including diarrhea, however we are interested in additional characterization of diarrhea after extended treatment and helping to ensure appropriate management of any new episode 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.

Information to provide

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).

We will also provide you with a specific card which will help you to capture any relevant information occurring at the time of a diarrhea event.

Recommendations

1. Changes to your diet

If you have diarrhea:

- Stop all lactose-containing products (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.

Patient Diarrhea Card 1/2

Patient Number: _ _ _ _ _ _ _ _ _ _ _

Project: Bosutinib Extension study – Protocol B1871040

This form will help you to collect any relevant information associated with diarrhea episode during the first 3 months on bosutinib in the extension study

Date mmm/dd/yy	Number of loose stools per day	Associated Symptoms / Comments	Did you take any anti-diarrheal medication? Which dose?	Current dose of bosutinib	Have you modified/stopped your dose of bosutinib?	Re-viewer initials

Patient Diarrhea Card 2/2

Patient Number: _ _ _ _ _ _ _ _ _ _ _ _

Project: Bosutinib Extension study – Protocol B1871040

This form will help you to collect any relevant information associated with diarrhea episode during the first 3 months on bosutinib in the extension study

Compared with your previous experience in the B1781006 (3160A4-200) or B1871008 (3160A4-3000) study how would you rate your current status with regards to diarrhea side effects?

much better	better	similar	worse	much worse

Date: _ _ _ _ / _ _ _ _ / _ _ _ _ (mmm/dd/yy)
Additional Comments:

Appendix 3. Dose Diary –

Protocol ID: B1871040	**Subject ID:__________________**

BOSUTINIB DOSE DIARY
INSTRUCTIONS TO THE PATIENT

(DOSE ONLY TO BE CHANGED WHEN INSTRUCTED BY STUDY DOCTOR)

Date Diary Issued : _ _/__ __ __/_ _ _ _ (DD/MMM/YYYY)
Total Bosutinib Dose: _____ mg Once Daily This dose is to be made by taking the following combination of tablets : **Take _____ 100 mg tablets once daily**
Date New Dose Began : _ _/__ __ __/_ _ _ _ (DD/MMM/YYYY)
Total Bosutinib Dose: _____ mg Once Daily This dose is to be made by taking the following combination of tablets : **Take _____ 100 mg tablets once daily**
Date New Dose Began : _ _/__ __ __/_ _ _ _ (DD/MMM/YYYY)
Total Bosutinib Dose: _____ mg Once Daily This dose is to be made by taking the following combination of tablets : **Take _____ 100 mg tablets once daily**
Date New Dose Began : _ _/__ __ __/_ _ _ _ (DD/MMM/YYYY)
Total Bosutinib Dose: _____ mg Once Daily This dose is to be made by taking the following combination of tablets : **Take _____ 100 mg tablets once daily**

DOSING for Bosutinib:

Take your study drug as prescribed below:

- Take orally, once daily, at approximately the same time every day.
- Take with a meal and water, preferably in the morning.
- Tablets should be swallowed whole. Do not chew, crush, split, or dissolve the tablets.
- Do not take the tablets if broken, cracked, or otherwise not intact.
- If you vomit any time after taking a dose, do not take another dose the same day. Restart dosing the next day as prescribed

Talk to your study doctor prior to starting any prescription or over the counter medications while participating in this study.

MISSED DOSES:

- If you miss a dose by more than 12 hours do not make up the missed dose. Just wait until the next time you are supposed to take it.

STUDY VISITS:

- **Do not take your study drug on days of your study clinic visits; bring your study drug with you to the clinic. You will take the study drug at the clinic when instructed by the study nurse, after your blood work or other tests are done.**
- You must return all study drug bottles/containers, along with any unused study drug, at each study visit, as instructed by your study doctor and his/her study staff.

DRUG STORAGE:

- Keep your drug in the bottles provided by your study doctor and do not transfer them to any other container.
- Store your study drug at room temperature (between 15 and 25 degrees C or 59 to 77 degrees F).
- Store out of the reach of children or pets.

DOSE DIARY INSTRUCTIONS

1. If you have any questions about how or when to take your study drug, please call your study doctor or his/her study staff.
2. If you miss a dose (s) Record the date, the number of tablets you missed
3. Please record any information, such as "forgot to take dose" in the Dosing Notes/Comments column, as needed.
4. If you miss an entire dose at any time, or are instructed by your study doctor to withhold a dose, please mark an "X" on that dose time.
5. Please return these forms and the study medication bottles with left over tablets to your study doctor, when you go for your next appointment.

Date	Time Dose Taken	Number of 100 mg Tablets Taken	Dosing Notes/Comments

Appendix 4. Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Grade	Description	*Karnofsky Score**
0	Fully active, able to carry on all pre-disease activities without restriction.	*100*
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).	*80 or 90*
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.	*60 or 70*
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	*40 or 50*
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	*20 or 30*

* Karnoksy score is provided for comparison purposes only. Please record ECOG grade only.

Appendix 5. Laboratory Tests to be performed

Hematology panel with complete blood count (CBC) which includes:

- White blood cell count, with 5-part differential (with manual confirmation of abnormalities)
- Platelet count
- Absolute neutrophil count (ANC)
- Red blood cell count (RBC)
- Hemoglobin (HgB)

Chemistry panel with electrolytes which includes:

- Sodium
- Potassium
- Chloride
- Creatinine
- Glucose
- Total protein
- Albumin
- Calcium
- Alkaline phosphatase
- Amylase
- Lipase
- Phosphorous
- Magnesium
- Creatine kinase
- Uric acid until patient achieves CHR

- Carbon dioxide or bicarbonate (if available)
- Blood urea nitrogen (BUN) or urea
- Fractionated creatine kinase if creatine kinase is abnormally high (if available)

Liver Function Tests which includes:

- Total Bilirubin
- AST
- ALT

Coagulation Tests which includes:

- Prothrombin Time (PT in seconds) or INR
- Partial Thromboplastin Time (PTT or APTT)

Dipstick urinalysis (microscopic if abnormal)

Serum Pregnancy Test (for women of childbearing potential)

Appendix 6. 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