A PHASE 4 SAFETY AND EFFICACY STUDY OF BOSUTINIB (BOSULIF®) IN PATIENTS WITH PHILADELPHIA CHROMOSOME POSITIVE CHRONIC MYELOID LEUKEMIA PREVIOUSLY TREATED WITH ONE OR MORE TYROSINE KINASE INHIBITORS

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Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	21 January 2014	Not applicable (N/A)
Amendment 1	07 September 2017	Protocol Summary, Table 1: Updated for consistency to reflect the revisions in the protocol body; Protocol Summary & Section 1.2.3: Added decision to decrease the number of patients in the 4th-/later-line cohort from the initial target of 75 to at least 45 patients. Protocol Summary & Section 2: Added biobanked biospecimens as an exploratory objective as per new protocol template and a result of the Biospecimen Work Group initiative; Protocol Summary, Table 1, and Section 7. Clarified if bone marrow or peripheral blood sample is required for mutation analysis of the tyrosine kinase domain, when the assessment will be performed, and that the same sample will be used to perform qRT-PCR and mutation analysis; Protocol Summary, Table 1, Sections 2.2 3, 6, 7.1.1.1, and 9.2.1: Removed the requirement of karyotype imaging submissionfor independent central review; Protocol Summary Updated to provide scientific rationale regarding the inclusion of the Ph- CML patients in this study; Protocol Summary, Added a definition of “Full Analysis Set” (FAS); Protocol Summary, Table 1, Section 7: Clarified contraceptive check requirements; Protocol Summary, Table 1, Section 6 & 7: hepatitis B serology testing added to screening tests; Protocol Summary Table 1: Updated to add footnotes regarding contraception checks and coagulation tests

		(footnotes); Protocol Summary Updated to provide further clarifications to footnotes; Protocol Summary, Table 1, Sections 6 and 7, and Appendices 5 and 11: Made changes reflective of the latest version of European LeukemiaNet (ELN) recommendations for the management of chronic myelogenous leukemia (CML) (published in 2013); Protocol Summary, Sections 2.1, 2.2.1.2, and 9.2.2: Updated to add new secondary endpoints composed of duration of CCyR duration of MMR and clarifications regarding the analysis of the primary endpoint; Section 1.2.1: Updated to add information about ponatinib (Iclusig®), a third-generation TKI; Section 1.2.2: Updated the number of patients treated with bosutinib in clinical studies as of 01 September 2016. Section 1.2.2 & section 2: Incorporated updates to the Biospecimens language text on biobanked biospecimens as per new protocol template; Section 2: Combined the Obectives and endpoints section into a table format according to new protocol template To clearly show the relationship between each objective and its associated endpoint; Section 2: Added biobanked biospecimens as an exploratory objective as per new protocol template and a result of the Biospecimen Work Group initiative; Sections 3:Updated to include timeframe for complete blood count, cytogenetic and molecular assessments; Section 4.1: Inclusion criterion clarification: “All patients must have screening bone marrow (BM) cytogenetic analysis with conventional banding performed within 30 days prior to study entry”; Section 4.1: Inclusion criterion clarification regarding chronic hemolysis for the total bilirubin assessment;

		Section 4.2: New exclusion criterion added for hydroxyurea or anagrelide during screening for their use within 72 hours preceding CML disease assessment; Section 4.3: Clarified special warnings related to QTc prolongation based upon recent pharmacological study results; Section 4.3: Removed the sentence, "Patients on medications that are substrates of P-glycoprotein who cannot be switched to alternative medications that are not substrates of P-glycoprotein" as a recent pharmacological study did not show interaction between bosutinib and substrates of P-glycoprotein; Section 4.3: Updated information regarding the concomitant use of CYP3A inhibitors and inducers based on recent pharmacological studies results; Section 4.3 and 5.2.2: Updated information regarding renal impairment during bosutinib treatment based on clinical study results. Updated recommended dose modification in the non-hematological toxicity table if renal impairment to align with the product label; Section 4.4 Lifestydle guidelines: Contraception language was updated for clarity based on stakeholder feedback in new protocol template; Section 5: Added definition of investigational product as per new protocol template to help distinguish between investigational products and non-investigational products used in a study; Section 5.1: New section added to define instructions on allocation to treatment process description; Section 5.2: Dose modification guidelines updated to align with clinical practice; Section 5.3: Disease progression criteria updated according to the CML disease phase; Section 5.4.3: Added language regarding vomited dose instructions;

		Section 5.4.1: Clarified local drug supply prescription requirement specifically for Ph+ CML patients, per local regulations in certain countries; Section 5.4.3: Added language regarding vomited dose instructions; Section 5.4.3: Medication error definition updated per new protocol template and moved to section 8.4.4; Section 5.5: Updated section on IP storage and temperature excursion as per new protocol template; Section 5.5.1: Added section on destruction of investigational product as per new protocol template; Section 5.6.2: Clarified the use of blood cell transfusions and growth factors regarding CBC assessment for data analysis due to impact on assessment for response; also clarified the use of hydroxyurea or anagrelide during bosutinib treatment; and use of corticosteroids during bosutinib treatment; Section 5.7.3: Clarified header and reference to Appendix 3 regarding full list of drugs that could lead to QTc prolongation; Section 6: Clarified when disease assessment should be performed; Section 6.1: Clarified previous treatments data collection, as only previous therapies for CML should be recorded in the CRF; Section 6.1: Reference to appendix 1 removed; Section 6.1: Clarified acceptable documentation of CML diagnosis; Section 6.1: Added collection of medical history, smoking status at screening visit; Section 6.1: Added screening window extension for chest X-ray, ECHO, and MUGA scan to allow for flexibility; Section 6.1: Bone marrow aspirate not needed when

		disease status is proven to be MMR by qRT-PCR; Section 6.1 & 6.2: Clarified whether blood or bone marrow sample will be used for molecular response and mutational analysis; Section 6.1 & 6.2: Added Hepatitis serology at screening; Section 6.1: Added serum pregnancy test as acceptable and contraceptive check; Section 6.2: Clarified additional tests required if clinically indicated (HbA1C, cholesterol, HDLc, LDLc, Hepatisi B; Section 6.2: Added contraceptive checks and pregnancy tests, coagulation tests; Section 6.2 & 6.3: Added collection of current smoking status; Section 6.2: Clarified that the degree of CyR is assessed from bone marrow exclusively until achievement of CCyR. Then the use of FISH until MMR is reached is possible. Added guidance in case of loss of CCyR; Section 6.2: Added guidance when progression and/or failure is suspected; Section 6.2: Added guidance on molecular response assessment; Section 6.2: Added guidance on blood and plasma for biobanking collection at the time of first response; Section 6.3: Added FACT-leu administration at EOT; Section 6.4: Clarified bone marrow transplantation treatment data collection during follow-up phase; Updated requirements for long-term follow-up phase: new TKI treatment, time to disease progression, or Section 7.1.1.1: Clarified Cytogenic response assessment; Section 7.1.1.2: Clarified CHR criteria used for

		Accelerated Phase (AP) and Blast Phase (BP) CML; Section 7.1.1.4: Clarified Molecular Response assessment; Section 7.2: Clarified that patient diary card and Fact leu should be verified for potential AEs, as advised by PRC; Section 8: Changes made to various sections of the AE Reporting Section to align with new protocol template. Section 8: Updated the Potential Cases of Drug-Induced Liver Injury language; Section 8: The active collection periods for recording non-serious AEs and serious adverse events (SAEs) on Case Report Forms and reporting SAEs to Pfizer Safety have been modified according to new protocol template; Section 9: updated to align with changes made to other sections of the protocol; Section 9.1 updated sample size to reflect the decreased number of patients needed in the 4th line cohort (from 75 to at least 45); Section 9.5 updated to clarify review conducted on unblinded data in an open label study (as per new protocol template); Section 9.6: Clarified that periodic safety review will be applied by an internal safety review team with medical and statistical capabilities; Section 10: Added the following sentence to the Quality Control and Quality Assurance section: The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. Statement added in conjunction with the *contrat unique* (France) process. Legal requested this sentence to be included in the protocol template; Section 13.2: Updated to clarify timeframe for End of

		Trial; Section 16, References: 2 new references added for ponatinib hydrochloride; 1 new reference added for the treatment with growth factors defined by ASCO guidelines; 2 new references added for the prior ELN recommendations (2006 and 2009); 1 new reference added for the definition of hematological response for AP and BP CML; Appendix 1 (former): Removed prior TKI guidelines defining resistance and intolerance to previous TKI and added guidelines for resistance or intolerance to previous TKIs; Appendix 2: Updated CYP3A4 inhibitors and inducers based on completion of recent bosutinib pharmacological studies; Appendix 7: Clarified criteria to Identify Phase of CML; Appendix 9: Updated text for Hy's Law, coagulation, pregnancy, glucose, HbA1C, and lipid tests due to inconsistencies, and added the requirement of monitoring potassium and magnesium levels to follow as clinically indicated; Appendix 11: Updated text for CP CML patients per ELN recommendations (2013), and added a new table to define hematological response for AP and BP CML; Minor administrative corrections adding clarifications and removing inconsistences made throughout the protocol; Updated language throughout the protocol related to changes in the Sponsor's clinical trial protocol template.

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

PROTOCOL SUMMARY

Background and Rationale:

Bosutinib (Bosulif®) is an orally bioavailable, potent, multi-targeted, dual Src-Abl tyrosine kinase inhibitor (TKI) that has been approved for the treatment of adult patients with Philadelphia chromosome positive (Ph+) chronic phase chronic myelogenous leukemia previously treated with other TKI therapy.

Chronic myelogenous leukemia (CML) is the fourth most commonly occurring adult leukemia. CML traditionally follows a triphasic course with most patients being diagnosed in an initial oligosymptomatic chronic phase (CP) which eventually progresses into a more advanced accelerated phase (AP) and culminates in a blast phase (BP), which resembles a highly treatment-refractory form of acute leukemia that generally shows either a myeloid or a lymphoid phenotype. The transformation of CML from a deadly cancer 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, including imatinib, bosutinib, dasatinib, nilotinib, and ponatinib.[1, 2, 3, 4, 5] The transition of patients with CML from CP to BP with an intermediate AP is becoming less standard with the chief determinants of survival being disease stage and TKI responsiveness.

On September 4, 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 (United States Prescribing Information BOSULIF®). More recently, on March 27, 2013, the European Medicines Agency (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 TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options (EMA Summary of Product Characteristics).

Furthermore, in 5%–10% of patients with of chronic myelogenous leukemia (CML), the Philadelphia chromosome (Ph) is not identified despite the presence of the associated BCR-ABL molecular abnormality (Ph-negative, BCR-ABL-positive CML) because of sub-microscopic rearrangements. Regardless, the presence of the BCR-ABL fusion gene will translate into a BCR-ABL fusion protein with dysregulated tyrosine kinase activity. Therefore, a TKI targeting BCR-ABL is also an effective treatment also for Ph negative CML patients. The FDA and EMA approvals were granted based on the results obtained from the single-arm, Phase 1/2 study (3160A4-200-WW, "Study-200") in adult patients with Ph+ leukemias who had failed prior TKI therapy, and with the support of the safety results obtained from the Phase 3 study (3160A4-3000-WW) comparing bosutinib with imatinib in newly diagnosed CP Ph+ CML patients. In addition, the EMA was provided with descriptive narrative information from the bosutinib compassionate use program in patients with Ph+CML who had received at least one prior TKI treatment and had progressed or were intolerant, and otherwise not considered suitable for other TKI therapy, as well as efficacy and safety analyses from a subset of Study-200 patients whose disease had failed prior imatinib and/or dasatinib or nilotinib and were contraindicated for treatment with dasatinib or nilotinib, as well as 4th-line CML patients on the study.

The purpose of this phase 4 study is to fulfill the post-authorization commitment made by Pfizer to the EMA in providing additional safety and efficacy data in approximately 150 Ph+ CML patients with high unmet medical need, including approximately 75 CP, AP or BP patients in the 2nd/3rd-line cohort and at least 45 patients in the 4th or later line treatment setting (i.e., after treatment with at least 3 other TKIs).

The EMA conditional approval requires completion of this post-authorization study in order to convert the conditional approval to a full marketing authorization approval.

Study Objectives:

Primary Objectives

- To estimate the 1-year (Week 52) probability of cumulative confirmed Major Cytogenetic Response (MCyR) in CP Ph+ CML patients with 1 or 2 prior lines of TKI therapy.

- To estimate the 1-year (Week 52) probability of cumulative confirmed MCyR in CP Ph+ CML patients with 3 or more prior lines of TKI therapy.

- To estimate the 1-year (Week 52) probability of cumulative confirmed Overall Hematological Response (OHR) in AP and BP Ph+ CML patients with any prior TKI therapy.

Secondary Objectives

- To estimate the probability of cumulative MCyR in each disease phase (CP, AP and BP) for Ph+ CML patients.

- To estimate the probability of cumulative confirmed OHR in each disease phase (AP and BP) for Ph+ CML patients by number of lines of prior therapy.

- To characterize the distributions of best response (molecular, cytogenetic, or hematologic) in the CP, AP, and BP Ph+ CML patient populations.

- To estimate the probability of MCyR at 3, 6, 12, 18, and 24 months in the CP, AP, and BP Ph+ CML patient populations.

- To estimate the probability of confirmed OHR at 3, 6, 9, 12, 18, and 24 months in the AP and BP Ph+ CML patient populations.

- To estimate the probability of cumulative confirmed Complete Hematological Response (CHR) in the CP, AP and BP Ph+ CML patient populations.

- To estimate the probability of cumulative major molecular response (MMR) in the CP, AP and BP Ph+ CML patient populations.

- To estimate the duration of Complete Cytogenetic Response (CCyR).

- To estimate the duration of MMR.
- To evaluate the overall safety profile of bosutinib in the study population.

Exploratory Objectives

- To obtain preliminary estimates of Progression Free Survival (PFS) and Overall Survival (OS) in 4th or later line CP, AP and BP Ph+ CML patients.
- To identify *BCR-ABL* mutations associated with sensitivity or resistance to bosutinib, as well as to catalog possible acquired resistance mutations.
- To explore efficacy (hematologic and molecular response) in Ph- CML patients.
- To evaluate patient reported outcomes measures.
- To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.

Primary Endpoints

- Cumulative confirmed MCyR defined as Complete Cytogenetic Response (CCyR) or Partial Cytogenetic Response (PCyR) by 1 year (52 weeks) in 2nd and 3rd line CP patients.
- Cumulative confirmed MCyR by 1 year (52 weeks) in 4th and later-line CP patients.
- Cumulative confirmed OHR defined as Complete Hematological Response (CHR) or Return to CP (RCP) by 1 year (52 weeks) in AP and BP patients.

Secondary Endpoints

- Cumulative MCyR in CP, AP, and BP patients.
- Cumulative confirmed OHR in AP and BP patients by line of therapy.
- Cumulative best response in CP, AP, and BP patients.
- MCyR at 3, 6, 12, 18, and 24 months in CP, AP, and BP patients.
- Confirmed OHR at 3, 6, 9, 12, 18, and 24 months in AP and BP patients.
- Cumulative confirmed CHR.
- Cumulative MMR in CP, AP, and BP patients.

- Duration of CCyR.
- Duration of MMR.
- Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v. 4.0), timing, seriousness, and relatedness; and laboratory abnormalities.

Exploratory Endpoints

- PFS in 4th or later line CP patients.
- OS in 4th or later line CP patients.
- Presence of BCR-ABL mutations.
- For Ph- CML patients, cumulative best response (CHR and MMR) anytime on treatment.
- Patients Reported Outcome (PRO) endpoints such as those measured by Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu).
- Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens section.

Study Design

This is a single-arm, open-label, non-randomized, multi-center Phase 4 study to evaluate bosutinib (Bosulif®) in patients with CP/AP/BP Ph+ CML whose disease has failed prior treatment with commercially available TKIs due to drug resistance or intolerance, or are otherwise contraindicated for treatment with commercially available TKIs such as imatinib, dasatinib, or nilotinib (i.e., presence of a BCR-ABL mutation or medical condition making commercially available TKIs unsuitable for a patient). Patients will receive bosutinib for at least 4 years from the time of first dose, unless disease progression, unacceptable toxicity, patient withdrawal of consent, death or Sponsor discontinuation of study. Patients discontinuing bosutinib prior to completing at least 4 years of therapy will be followed for survival until they complete at least 4 years of follow-up from the time of first dose. Patients completing at least 4 years of bosutinib with continued benefit may be switched to commercially available therapy at that time.

Cytogenetic and molecular assessments will be performed at baseline and every 3 months until Week 52, then at 6- month intervals during Years 2, 3, and 4 of treatment. Complete blood counts should be performed weekly for the first month, then 4 weeks later and thereafter per the visit schedule (Table 1), and as clinically indicated. Hematologic, cytogenetic and extramedullary disease assessments will be done locally, while molecular

monitoring of BCR-ABL transcript levels and mutational analysis of the BCR-ABL kinase domain will be performed by a central laboratory and carried out by independent central analysis. Patient participation will conclude not more than 4 years after the first dose.

Study Treatment

Patients will receive bosutinib 500 mg orally once dailywith food. Bosutinib commercial formulation of 100 mg and 500 mg tablets will be provided.

Statistical Methods

This study does not include any formal sample size determination. Approximately 150 patients with Ph+ CML will be enrolled including approximately 45 CP, AP, and BP patients in the 4th or later line treatment setting.

The primary analyses will be the percentage of cumulative confirmed MCyR (for CP Ph+ CML patients) and cumulative confirmed OHR (for AP and BP Ph+ CML patients) by 1 year of bosutinib treatment (week 52). Confirmed MCyR will be defined as (1) the attainment of confirmed MCyR (CCyR or PCyR) by 1 year for patients entering the study without CCyR achieved on the previous TKI therapy or (2) the maintenance of confirmed CCyR (achieved under the previous TKI therapy) for at least 1 year after starting treatment with bosutinib or (3) at least MMR by 1 year and a deeper molecular response compared to baseline. Patients with baseline PCyR that do not achieve CCyR are included in the analysis but they would be counted as non-responders. Initial cytogenetic (in the absence of MMR) and hematologic responses must be confirmed by 2 consecutive assessments at least 28 days apart.

Secondary efficacy analyses include the percentage of cumulative MCyR, cumulative confirmed OHR, cumulative MMR, cumulative best response, landmark MCyR and OHR, cumulative confirmed CHR, duration of CCyR and duration of MMR.

All treated Ph+ CML patients with a valid baseline efficacy assessment for the respective endpoint will be included in the molecular, cytogenetic, and hematologic efficacy analyses. All treated Ph+ CML patients will be included in the other efficacy analyses. Analyses will be presented by disease stage (e.g., CP, AP, BP) and/or line of therapy (e.g., CP 2nd line [CP2L], CP 3rd line [CP3L], CP 4th or later line [CP4L], AP2L, AP3L, AP4L, BP2L, BP3L, BP4L).

Ph- CML patients will be analyzed separately and only for cumulative CHR and molecular endpoints.

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

The exploratory time-to-event endpoints of OS and PFS will be summarized using the Kaplan-Meier method or by cumulative incidence, whichever is more relevant.

The Full Analysis Set (FAS) will include all patients who receive at least 1 dose of study drug. The Evaluable Population will include all patients with a valid baseline assessment for the respective endpoint. All molecular, cytogenetic, and hematologic statistical analyses will be based on the Evaluable Population and the remaining efficacy analyses will be based on the FAS.

The FACT-Leu will be scored according to the respective user's guides and validation papers. Summary statistics of the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) quality of life questionnaire will be calculated at baseline and approximately every 3 months for the first year, and then every 6 months during year 2, 3, and 4 of treatment on study.

All safety analyses will be based on the FAS.

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 sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

		On Treatment				End of Treatment	Follow-Up
Protocol Activity	**Screening**	**Week 1, Day 1 (pre-dose)**	**Weeks 1, 2, 3, 4, and 8 on Day 7**	**Weeks 13, 26, 39 and 52**	**Weeks 78, 104, 130, 156, and 182**	**Week[p]**	**Every 3 months up to 4 years after first dose**
Visit Time Window	30 days		+/- 1 day	+/- 7 days	+/- 21 days	+/- 7 days	+/- 7 days
Informed Consent	X						
Medical History	X						
Cancer Diagnosis/ History	X						
ECOG Performance Score	X			X	X	X	
Physical Examination	X			X	X	X	
Vital Signs (blood pressure, heart rate, height, weight)	X			X	X	X	
Smoking Status[a]	X			X	X	X	
Contraception Check[b]	X	X	X	X	X	X	
Laboratory							
Hematology[c]	X	X	X	X	X	X	
Blood Chemistry	X	X	X	X	X	X	
Liver Function[d]	X	X	X	X	X	X	
Coagulation Tests[e]	X	X	X	X	X	X	
Pregnancy Test[f]	X	X		X	X	X	
Chest X-ray[g]	X	As clinically indicated				X	
ECHO or MUGA scan[h]	X	As clinically indicated				X	
ECG	X	As clinically indicated				X	
Registration[i]	X[i]						
Bosutinib Treatment		Continuous Daily					
Efficacy Assessments							
Hematologic Assessment	X	X	X	X	X	X	
Cytogenetic Assessment[j]	X			X	X	X	
Molecular Assessment[k]	X			X	X	X	
Mutation Analysis[l]	X					X	
Extramedullary Disease Assessment[m]	X	As clinically indicated[m]				X	
Adverse Events		Continuous				X	
Concomitant Medications		Continuous				X	
FACT-Leu	X			X	X	X	
Blood and plasma for biobanking[n]	X	As clinically indicated[n]				X	
Hepatitis B serology[q]	X	As clinically indicated					
Survival							X[o]

The 3-monthly visits will be performed at approximately 13-week intervals.

a. The use of TKIs could lead to cumulative long-term cardiovascular disease therefore smoking status will be collected. Past and present smoking status will include: smoking type (if the patient ever smoked), if the patient is a current smoker, or ex-smoker and, if appropriate, duration since the patient last stopped smoking, and the number of units consumed/day (e.g. number of cigarettes; number of pipes; number of cigars, etc.).

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

c. Hematology to include complete blood count (CBC) including a WBC with differential, platelet count, and neutrophil count (see Appendix 9). Complete blood counts should be performed weekly for the first month, then 4 weeks later and thereafter per the visit schedule, and as clinically indicated.

d. Direct bilirubin must be collected if total bilirubin is > 1.5 x ULN and for any Hy's Law determination, if appropriate (see Section Appendix 9).

e. Coagulation tests including: either prothrombin time (PT) or international normalized ratio (INR); and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT).

f. A urine or serum pregnancy test should also be done whenever one menstrual cycle is missed during treatment (or potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of IRB/ECs or if required by local regulations.

g. Standard of care chest X-ray results may be used for screening if not longer than 12 weeks prior to the first bosutinib dose in the absence of past medical history of pulmonary disease. If the patient has past medical history of pulmonary disease or ongoing pulmonary co-morbidities chest X-ray should be obtained within 7 days prior to the first bosutinib dose.

h. Standard of care echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan results may be used for screening if not longer than 12 weeks prior to the first bosutinib dose in the absence of past medical history of cardiovascular disease and presence of normal left ventricular ejection fraction (LVEF). If the patient has past medical history of cardiovascular disease or ongoing cardiovascular co-morbidities, ECHO or MUGA scan should be obtained within 7 days prior to the first bosutinib dose. Screening, unplanned, and End of Treatment assessments should be consistent (e.g. assessment should be performed with the same test, ECHO or MUGA scan, to evaluate cardiac function).

i. Patients must be registered to the study after protocol eligibility is confirmed and within 3 days prior to receiving the first dose of bosutinib.

j. Conventional cytogenetic assessment:

- It is required for all patients at screening**, (unless** the CML disease status is proven **to be** MMR **by** quantitative reverse transcription polymerase chain reaction (q**RT-PCR).** Standard of care bone marrow analysis (morphology and G-banding) within 30 days prior to screening may be used for screening results; or bone marrow aspirate must be collected for morphological assessment (% of bone marrow differential) and local conventional cytogenetic assessment (with at least 20 metaphases), Percentage (%) of Ph+ metaphases, as well as any other chromosomal abnormalities, will be documented. Conventional Cytogenetic assessment should be continued until MMR. Only chromosome banding analysis of marrow cell metaphases can be used to assess the degree of cytogenetic response (CyR) (with at least 20 metaphases analyzed).

- Upon achieving CCyR by the conventional cytogenetic assessment, fluorescent in situ hybridization (FISH) of blood interphase cell nuclei with an appropriate probe (Dual-Color Dual-Fusion or Dual-Fusion FISH) could substitute for chromosome banding analysis of marrow cell metaphases for the assessment of maintenance of the CCyR (which is then defined by <1% BCR-ABL-positive nuclei of at least 200 nuclei) until MMR is reached, Loss of CCyR using FISH requires resumption of bone marrow conventional cytogenetic assessment.

- A bone marrow aspirate for morphology (% bone marrow differential) and conventional cytogenetic assessment is also required for all patients at the time of suspected progression and/or failure.

  Note:The cytogenetic assessment needs to be repeated at 28 days later to confirm CCyR CML disease status for Ph+CML patients (when the cytogenetic response is first observed in the absence of MMR, e.g once CCyR is achieved by G-banding, FISH is needed to confirm the achievement/maintenance of CCyR at least 28 days later).

  Note: In Ph- CML patients, conventional cytogenetic assessment (to detect other potential cytogenetic abnormalities) and molecular cytogenetic assessments using FISH are required only at screening and at time of suspected progression and/or failure.

k. qRT-PCR for molecular assessment (BCR-ABL fusion transcripts) will be performed by a central laboratory. For Chronic-Phase (CP) CML, the assessment will be performed using peripheral blood samples. For Advanced Phase CML (Accelerated Phase [AP] and Blast Phase [BP]) the assessment will be performed using peripheral blood and/or bone marrow samples.Confirmed loss of MMR requires resumption of bone marrow cytogenetic assessments.

l. Mutational analysis of the BCR-ABL kinase domain will be performed by an independent central laboratory at baseline and End of Treatment for CP, AP and BP CML patients and during treatment for patients with baseline mutations. Mutation analysis will also be performed if there is loss of response as indicated by a rise in BCR-ABL transcript levels of at least 5-fold that has been confirmed by more than one test and/or disease progression. For CP CML, the assessment will be performed using peripheral blood sample. For Advanced Phase (AP and BP) CML, the assessment will be performed using peripheral blood and/or bone marrow samples. Mutational analysis will be performed from the peripheral blood or bone marrow samples that were used for the molecular response assessment.

m. Patients presenting with symptoms or signs of CNS involvement at screening must be evaluated by lumbar puncture to confirm eligibility. Extramedullary disease will be evaluated by chest X-ray and physical examination (e.g., liver, spleen, lymph nodes). Sites of extramedullary disease identified at screening should be followed during the course of treatment. Patients should be evaluated upon suspicion of new extramedullary disease.

n. Blood and plasma samples will be collected for biobanking if specifically allowed by local EC/IRB; 1 tube of whole blood (prep D1) and 1 tube of plasma (prep B1) will be collected at the time points indicated in the Schedule of Activities. B1 and D1 samples will also be collected at the time of first response, where response is a major cytogenetic response for CP patients and a hematologic response for AP/BP patients when feasible. These additional biobank response samples should be obtained at the next scheduled visit if the next scheduled visit occurs within 2 months after the first response. If the next scheduled visit occurs >2 months after the first response, the sample should be collected at an unscheduled visit within 2 months after the first response, if feasible, unless this is the End of Treatment visit. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit.

o. End of Treatment visit should be done at Week 208 for those patients completing 4 years on bosutinib therapy, or at any time the patient meets any of the criteria for early discontinuation of bosutinib, whichever is earlier. Patients continuing to receive benefit from bosutinib at the time of study conclusion may switch to commercially available therapy. Note: 1 year = 52 weeks.

p. Patients discontinuing treatment prior to 4 years from first dose will be followed for survival (telephone contact acceptable) until the patient has completed at least 4 years on study (from time of first dose) or sooner if the patient withdraws consent for disclosure of future information.

q. Hepatitis B serology testing will be included in the screening tests and thorughtout the study as clinicaly indicated. Hepatitis B reactivation has been reported with Tyrosine Kinase Inhibitors (TKI's).

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APPENDICES

1. INTRODUCTION

1.1. Indication

Bosutinib (Bosulif®) is an orally bioavailable, potent, multi-targeted, dual Src-Abl tyrosine kinase inhibitor (TKI) that has been approved for the treatment of adult patients with Philadelphia chromosome positive (Ph+) chronic phase (CP), accelerated phase (AP) and blast phase (BP) chronic myelogenous leukemia (CML) previously treated with other TKI therapy.[6]

1.2. Background and Rationale

CML is the fourth most commonly occurring leukemia in adults. 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. The molecular product of the t(9;22) translocation is the BCR-ABL1 oncogene, which encodes the constitutively activated BCR-ABL1 kinase that activates several downstream signaling pathways that mediate myeloproliferation, resistance to apoptosis and genetic instability. In 5%–10% of patients with of chronic myelogenous leukemia (CML), the Philadelphia chromosome (Ph) is not identified, despite the presence of the associated BCR-ABL molecular abnormality (Ph-negative, BCR-ABL-positive CML) because of sub-microscopic rearrangements. Regardless, the presence of the BCR-ABL fusion gene will translates into a BCR-ABL fusion protein with dysregulated tyrosine kinase activity. Therefore, TKI targeting BCR-ABL is an effective treatment also for Ph negative CML patients.

The transition of patients with CML from CP to BP with an intermediate AP is becoming less standard with the chief determinants of survival being disease stage and TKI responsiveness.

1.2.1. Therapeutic Options for CML

Imatinib (Gleevec®, Glivec®) has improved the prognosis for many patients with CML worldwide. Imatinib was granted approval by the European Commission in November 2001 and by the United States Food and Drug Administration (FDA) in December 2002 for the treatment of newly diagnosed patients with CP Ph+ CML based on results from the IRIS trial.

However, after 8 years of follow-up, only 55% of the patients originally randomized to the imatinib arm remain on study drug chiefly due to failure to achieve CCyR (17%), loss of CCyR (15%), and intolerance to imatinib (approximately 5%).[7] While several mechanisms of imatinib resistance have been proposed, the best known and possibly the most clinically prevalent are lack of adherence/compliance (which may reflect adverse events in some patients) and/or the development of BCR-ABL1 mutations, which alter drug sensitivity and can be detected in approximately 40-50% of patients with CP CML in which imatinib has failed.[7]

In order to overcome these mechanisms of resistance, second-generation TKIs have been developed.[8] However, despite the success of imatinib and the second-generation TKIs nilotinib and dasatinib, some patients are intolerant to these drugs or have disease that

progresses despite therapy. As with imatinib, these second generation TKIs may have their therapeutic potential compromised by the development of resistance, including BCR-ABL1 mutations, and/or intolerance.

As dasatinib and nilotinib have only recently been approved for the first line treatment of CP CML, there are limited data regarding disease management and outcome after failure in the frontline treatment setting.[9, 10]

In the second-line treatment setting, between 40%-50% of patients with CP CML who are treated with dasatinib or nilotinib do not achieve a MCyR with either agent.[3, 4] In AP CML, 35% of patients treated with dasatinib and 65% of those treated with nilotinib do not achieve an MHR. In BP CML, for which dasatinib is an approved second-generation TKI, MHR is not achieved in over 50% of patients, and current therapies are inadequate.[11, 12, 13] Resistance to both these agents likely occurs through a variety of mechanisms, including Abl kinase domain mutations.[14]

Recently, the third-generation TKI inhibitor ponatinib hydrochloride (Iclusig®) was approved for the treatment of adult patients with T315I-positive chronic myeloid leukemia (CP, AP, or BP) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) and for treatment of adult patients with CP, AP, or BP CML or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated. On 20 December 2013, FDA began requiring several new safety measures for ponatinib hydrochloride to address the risk of life-threatening blood clots and severe narrowing of blood vessels with ponatinib hydrochloride treatment.[15, 16]

In addition, the safety profiles of dasatinib and nilotinib potentially limit their use. A known toxicity associated with dasatinib is serosal inflammation (pleural and/or pericardial effusion (Sprycel® United States Prescribing Information (USPI) or Summary of Product Characteristics (SmPC). In addition, uncommon cases (0.1 to 1%) of sudden deaths have been reported in patients with imatinib-resistant or intolerant CML in CP or AP with a past medical history of cardiac disease or significant cardiac risk factors when treated with nilotinib (Tasigna® USPI or SmPC). Myelosuppression, hepatic and/or pancreatic dysfunction, peripheral occlusive arterial disease, cardiac or pulmonary compromise, bleeding diatheses, autoimmune disorders, diabetes mellitus, and a history of other malignancy or immune suppression are all of concern in individual patients when considering dasatinib or nilotinib therapy.[17, 18, 19, 20, 21, 22, 23]

Therefore, there is a continued unmet medical need for CML patients, with an urgent need for new treatment options such as bosutinib for adult CML patients resistant or intolerant to currently available TKIs, which was recently approved as described below.

1.2.2. Bosutinib (BOSULIF®)

As of 01 September 2016, approximately 2033 patients have received at least 1 dose of bosutinib in 28 clinical studies. These included 19 clinical pharmacology studies (17 studies in healthy volunteers, 1 study in patients with hepatic impairment, and 1 study in patients with renal impairment) and 9 clinical studies in patients with cancer. Of the clinical studies

conducted in patients with cancer, 3 studies were conducted in patients with advanced malignant solid tumors who received bosutinib as a single agent, 3 studies were conducted in breast cancer patients with bosutinib in combination with another anticancer agent, and 3 studies were conducted in patients with Ph+ leukemias with bosutinib as a single agent.

On September 4, 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 March 27, 2013, the European Medicines Agency (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, "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 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 Study 200 patients.

Efficacy and safety data from the Phase 1/2 study, Study 200, and the Phase 3 study, Study 3000, are presented below according to phase of disease and line of therapy, as of 28 March 2011 for efficacy and 15 February 2012 for safety (Study 200) and as of 26 September 2011 (Study 3000). Pooled safety data from Study 200, Study 3000, and the Phase 1/2 Japanese study, Study 2203, are presented below as of 15 November 2010. The most current 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 Study 200. 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 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 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 (i.e., third line) and 3 CP CML patients who received imatinib followed by dasatinib and nilotinib (i.e., fourth line) were enrolled and treated in Study 200. 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 Study 200. 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%.

Pooled Second-line and Third-Line CP CML and Advanced Leukemias

Summary safety data across all patient cohorts in Study 200 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, 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 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 diarrhoea (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%), diarrhoea (9.1%), rash (6.1%), lipase increased (5.2%) and aspartate aminotransferase increased (5.0%).

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

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

Providing these biospecimens is a required study activity for study sites and patients, unless prohibited by local regulations or ethics committee (EC) decision.

1.2.3. Study Rationale

The purpose of this study is to fulfill the post-authorization commitment made by Pfizer to the EMA in providing additional safety and efficacy data in approximately 150 patients with Ph+ CML whose disease had failed or who are otherwise not appropriate for treatment with dasatinib, nilotinib or imatinib TKI, including at least 75 patients in the 4th line treatment setting (i.e., after treatment with at least 3 other TKIs). The EMA conditional approval requires completion of this post-authorization study in order to convert the conditional approval to a full marketing approval.

This study was initiated in November 2014 and the original target projection was 75 patients in each cohort. However, the 4th line cohort has not met its planned targeted enrollment objective; whereas, the 2nd /3rd-line cohort has overenrolled (n=106). Therefore, Pfizer decided based on CHMP feedback to stop recruitment after at least 45 patients have been enrolled in the 4th line cohort. It was further agreed, there are sufficient numbers of patients in each cohort to perform an informative descriptive analysis of the safety and efficacy and safety of bosutinib.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	**Primary Endpoint(s):**
To estimate the 1-year (52-week) probability of cumulative confirmed Major Cytogenetic Response (MCyR) in CP Ph+ CML patients with 1 or 2 prior lines of TKI therapy.	Cumulative confirmed MCyR defined as Complete Cytogenetic Response (CCyR) or Partial Cytogenetic Response (PCyR) by 1 year (52 weeks) in 2nd and 3rd line CP patients.
To estimate the 1-year (52-week) probability of cumulative confirmed MCyR in CP Ph+ CML patients with 3 or more prior lines of TKI therapy.	Cumulative confirmed MCyR by 1 year (52 weeks) in 4th and later line CP patients.
To estimate the 1-year (52-week) probability of cumulative confirmed Overall Hematological Response (OHR) in AP and BP Ph+ CML patients with any prior TKI therapy.	Cumulative confirmed OHR defined as Complete Hematological Response (CHR) or Return to Chronic Phase (RCP) by 1 year (52 weeks) in AP and BP patients.
Secondary Objective(s):	**Secondary Endpoint(s):**
Efficacy	
To estimate the cumulative probability of MCyR in each disease phase (CP, AP and BP) for Ph+ CML patients.	Cumulative MCyR in CP, AP and BP patients.
To estimate the cumulative probability of confirmed OHR in each disease phase (AP and BP) for Ph+ CML patients by number of lines of prior therapy.	Cumulative confirmed OHR in AP and BP patients by line of therapy.
To characterize the distributions of best response (molecular, cytogenetic, or hematologic) in the CP, AP, and BP Ph+ CML patient populations.	Cumulative best response in CP, AP, and BP patients.
To estimate the probability of MCyR at 3, 6, 12, 18, and 24 months in the CP, AP, and BP Ph+ CML patient populations.	MCyR at 3, 6, 12, 18, and 24 months in CP, AP, and BP patients.
To estimate the probability of confirmed OHR at 3, 6, 9, 12, 18, and 24 months in the AP and BP Ph+ CML patient populations.	Confirmed OHR at 3, 6, 9, 12, 18, and 24 months in AP and BP patients.
To estimate the probability of cumulative confirmed CHR in the CP, AP and BP Ph+ CML patient populations.	Cumulative confirmed CHR.
To estimate the probability of cumulative major molecular response (MMR) in the CP, AP, and BP Ph+ CML patient populations.	Cumulative MMR in CP, AP, and BP patients.
To estimate the duration of CCyR.	Duration of CCyR.
To estimate the duration of MMR.	Duration of MMR.

Safety	
To evaluate the overall safety profile of bosutinib in the study population.	Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v. 4.0), timing, seriousness, and relatedness; and laboratory abnormalities.
Tertiary/Exploratory Objective(s):	**Tertiary/Exploratory Endpoint(s):**
To obtain preliminary estimates of Progression Free Survival (PFS) and Overall Survival (OS) in 4th or later line CP, AP and BP Ph+ CML patients.	PFS in 4th or later- line CP patients. OS in 4th or later line CP patients.
To identify BCR-ABL mutations associated with sensitivity or resistance to bosutinib, as well as to catalog possible acquired resistance mutations.	Presence of BCR-ABL mutations.
To explore efficacy (hematologic and molecular response) in Ph- CML patients.	For Ph- CML patients, cumulative best response (CHR and MMR) anytime on treatment
To evaluate patient reported outcomes measures	PRO endpoints such as those measured by FACT-Leu.
To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.	Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens section.

Cytogenetic assessments will be carried out locally. The local cytogenetic assessments will be used for the primary endpoint analysis in CP patients. Molecular assessments will be performed at a central laboratory. Endpoint analysis for molecular response will be carried out by independent central analysis. The local hematologic assessments will be used for the primary endpoint analysis in AP and BP patients.

3. STUDY DESIGN

This is a single-arm, open-label, non-randomized, multi-center Phase 4 study to evaluate bosutinib (Bosulif®) in patients with chronic or advanced CP/AP/BP Ph+ CML who have failed prior treatment with TKIs which are commercially available, due to drug resistance or intolerance, or are otherwise contraindicated for treatment with commercially available TKIs such as imatinib, dasatinib, and nilotinib (i.e., presence of a BCR-ABL mutation or medical condition making commercially available TKIs unsuitable for a patient). Patients will receive bosutinib for at least 4 years from the time of first dose, unless disease progression, unacceptable toxicity, withdrawal of consent by patient, death or discontinuation of study by Sponsor. Patients discontinuing bosutinib prior to completing 4 years of therapy will be followed for survival until they complete at least 4 years on studyof follow-up from the time of first dose. Patients completing at least 4 years of bosutinib with continued benefit may be switched to commercially available therapy at that time.

Cytogenetic and Molecular assessments will be performed at baseline and every 3 months until Week 52, then at 6 -month intervals during Years 2, 3, and 4 of treatment. Complete blood counts should be performed weekly for the first month, then 4 weeks later and thereafter per the visit schedule (Table 1) and as clinically indicated.

Hematologic, cytogenetic and extramedullary disease assessments will be done locally, while molecular monitoring of BCR-ABL transcript levels and mutational analysis of the BCR-ABL kinase domain will be performed by a central laboratory and carried out by independent central analysis. Local cytogenetic assessment will be repeated at least 28 days later to confirm on-treatment CCyRCML disease status (when the CCyR is first observed in the absence of MMR). Patient participation will conclude no sooner than 4 years after first dose.

Approximate Duration of Study: The end of the study will be considered to be the last visit of the last patient for purposes of closing out sites, informing the site or regional institutional review board/ethics committee (IRB/EC), and terminating distribution of Council for International Organizations of Medical Sciences (CIOMS) reports; however, for other purposes the end of the study will be the last patient last visit.

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 participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

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. Cytogenetic or PCR-based diagnosis of Ph+ CML or BCR-ABL1+ if Ph- (from initial diagnosis). NOTE: Ph- CML patients will not count towards the 150 patients for primary and secondary analyses, which include Ph+ CML patients only.

   NOTE: All patients must have screening bone marrow (BM) cytogenetic analysis with conventional G banding performed within 30 days prior to study entry (unless CML disease status is proven to be MMR by quantitative reverse transcription polymerase chain reaction [qRT-PCR]). Examination of at least 20 metaphases is required.

2. Prior treatment with 1 or more TKIs for CML.

3. Any CML phase, as long as the patient is resistant to, intolerant of, or otherwise not appropriate for treatment with imatinib, dasatinib and/or nilotinib.

4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 for CP patients, or 0, 1, 2, or 3 for 4th line CP (and beyond) and AP/ BP patients.

5. Adequate bone marrow function:

   - For 2nd and 3rd line CP CML patients:

     - Absolute neutrophil count >1000/mm^3 (>1 x10^9/L).

     - Platelets ≥75,000/mm^3 (≥75 x10^9/L) absent any platelet transfusions during the preceding 14 days.

   - For 4th line CP and AP/BP CML patients:

     - Absolute neutrophil count >500/mm^3 (>0.5 x10^9/L).

     - Platelets ≥50,000/mm^3 (≥50 x10^9/L) absent any platelet transfusions during the preceding 14 days.

6. Adequate hepatic and renal function:

   - AST/ALT ≤2.5 x the upper limit of normal (ULN) or ALT/AST ≤5 x ULN if attributable to liver involvement of leukemia.

   - Total bilirubin ≤1.5 x ULN (unless the bilirubin is principally unconjugated and there is a strong suspicion of subclinical hemolysis (e.g. chronic hemolysis without clinical symptoms), or the patient has documented Gilbert's Disease);

   - Alkaline phosphatase ≤2.5 x ULN.

   - Creatinine ≤1.5 x ULN or estimated creatinine clearance (CrCL) ≥60 mL/min as calculated using the standard method for the institution.

7. Able to take daily oral tablets.

8. Age ≥18 years.

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

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

11. Male and female patients of childbearing potential must agree to use two 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.

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) (Phase 1-4) within 14 days or 3 half-lives (whichever is longer) prior to the first dose of bosutinib.

2. Prior bosutinib or ponatinib exposure.

3. Prior hydroxyurea or anagrelide exposure within 72 hours of the baseline CML disease assessment.

4. Known T315I or V299L mutation in BCR-ABL1.

5. Clinically active leptomeningeal leukemia. Patients must be free of central nervous system (CNS) involvement for a minimum of 2 months.

6. Hypersensitivity to the active substance or to any of the following excipients: Microcrystalline cellulose (E460), Croscarmellose sodium (E468), Poloxamer 188, Povidone (E1201), Magnesium stearate (E470b), Polyvinyl alcohol, Titanium dioxide (E171), Macrogol 3350, Talc (E553b), Iron oxide red (E172).

7. Pregnant or breastfeeding females.

8. Males and females of childbearing potential who are unwilling or unable to use two highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 28 days after last dose of investigational product.

9. 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.

10. 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.

4.2.1. Philadelphia Chromosome Negative (Ph-) CML Patients

Patients whose CML is BCR-ABL1 positive and Philadelphia chromosome negative (Ph-) will be permitted to enroll. These patients will be in addition to, and not contribute to analysis of, the approximately 150 Ph+ CML patients planned for this study. Due to the lack of data on and treatment options available for this small subset of CML patients, they will be classified and analyzed in a separate, stand-alone cohort. Patients must meet all other eligibility criteria based on their stage of disease, and will be treated in an identical manner as Ph+ CML patients. However, due to their lack of the Ph chromosome, they will be followed for hematologic and molecular response only, as well as safety.

4.3. Special Warnings and Precautions

The following are not exclusion criteria, however investigators are advised to proceed with caution and ensure appropriate monitoring if enrolling patients with any of the following (see Section 5.6.4 Interaction with other Medicinal Products and Other Forms of Interaction for more information and Appendix 1):

- Automated machine-read QTc prolongation without accompanying arrhythmia has been observed. Patients who have a history of or predisposition for corrected QT (QTc) prolongation, who have uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia, or who are taking medicinal products that are known to prolong the QT interval (e.g., anti-arrhythmic medicinal products and other substances that may prolong the QT interval. See Appendix 3. The presence of hypokalemia, hypocalcemia, and hypomagnesaemia may further enhance this effect. Monitoring for an effect on the QTc interval is advisable and a baseline electrocardiogram (ECG) is recommended prior to initiation of therapy and as clinically indicated. Hypokalemia, hypocalcemia, or hypomagnesaemia must be corrected prior to administration of bosutinib and should be monitored periodically during therapy.

- Patients with previous history of pancreatitis.

- Patients with recent (within 30 days of study entry) or ongoing clinically significant gastrointestinal disorder (e.g., severe vomiting, severe diarrhea, and/or malabsorption), or prior partial or total gastrectomy.

- Patients on proton pump inhibitors (PPIs) who cannot be switched to alternative medications that do not impact proton-pump activity.

- A concomitant strong or moderate CYP3A4 inhibitor (low or minimal inhibition potential) should be avoided as an increase in bosutinib plasma concentration will occur. Selection of an alternate concomitant medication with no or minimal CYP3A4 inhibition potential, if possible, is recommended. If a strong or moderate CYP3A4 inhibitor must be administered during bosutinib treatment, an interruption or dose reduction of bosutinib should be considered.

- A concomitant strong or moderate CYP3A4 inducer should be avoided as a decrease in bosutinib plasma concentration will occur.

- Caution is warranted if mild CYP3A4 inducers are used concomitantly with bosutinib.

- Treatment with bosutinib may result in a clinically significant decline in renal function in CML patients. A decline over time in estimated glomerular filtration rate (eGFR) has been observed in CML patients with bosutinib treatment. It is important that renal function is assessed prior to bosutinib treatment and closely monitored during therapy, with particular attention in those patients who have preexisting renal compromise or in those patients exhibiting risk factors for renal dysfunction, including concomitant use of medicinal products with potential for nephrotoxicity such as diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers and nonsteroidal anti-inflammatory drugs (NSAIDs). Bosutinib exposures were increased in patients with moderately and severely impaired renal function. Dose reduction is recommended for patients with moderate or severe renal impairment.

4.4. Life Style Guidelines

In this study, fertile male patients and female patients who are of childbearing potential will receive bosutinib, which has been associated with demonstrated teratogenicity/fetotoxicity. Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for at least 28 days after the last dose of investigational product.

The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected 2appropriate methods of contraception for the individual patient and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the patient of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the patient or partner.

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

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

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

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

4. Male sterilization with absence of sperm in the 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).

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

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

5. STUDY TREATMENTS

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

Starting dose of bosutinib therapy is 500 mg once daily (commercial formulation of 100 mg and 500 mg tablets provided), will be taken with food. Patients will be provided diary cards to record bosutinib administration, any adverse events that occur, and concomitant medications.

Bosutinib will be administered for at least 4 years from the date of first dose, unless treatment is discontinued early due to disease progression or unacceptable toxicity or other reasons outlined in Section 5.3. Patients discontinuing bosutinib prior to at least 4 years on treatment will be followed for survival until the patient has completed at least 4 years on study (from time of first dose). Patients still deriving benefit from bosutinib at the time of study discontinuation may switch to commercially available product.

5.1. Allocation to Treatment

When registering a patient, an email should be sent to the study team indicating when screening is beginning, when screen failure occurs (if there is a screen failure), and when dosing occurs. For patients being treated with bosutinib, the information in the email should include the eligibility worksheet, enrollment form, and patient summary. Sites will use their 4-digit site number and assign a 4-digit patient number as follows:

- The patients in 2nd- or 3rd- line Ph+ [Chronic Phase (CP), Accelerated (AP), Blast Phase (BP)] CML patients (e.g. 12341001 – 1234 being the site number and 1001 being the first Ph+ patient screened) and continue patient assignments in ascending order for subsequent patients in this line of treatment.
- For patients with Ph+ CML ≧4th-line Ph+ (CP, AP, BP) CML, the patient number will start with 2001 (e.g., 12342001) and subsequent assignments will continue in ascending order for patients in this line of treatment.
- For patients with Ph- CML, the patient number will start with 3001 (e.g. 12343001) and subsequent assignments will continue in ascending order for patients in this line of treatment.
- It is the investigator's determination if and when a patient meets criteria for enrollment.

5.2. Dose Modifications

The recommended starting bosutinib dosing has been defined as 500 mg once daily; however, the daily dose can vary as described in the table below:

Table 2. Available Dose Levels

Dose Level	Daily Bosutinib Dose
+1	600 mg[a]
0 (Starting 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. Consideration may be given to reducing bosutinib to 200 mg/day for CP CML patients who are not tolerating the 300 mg dose but otherwise benefiting from bosutinib. 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

Patients will be allowed to dose escalate to 600 mg/day in the absence of any grade 3/4 or persistent grade 2 adverse drug reaction (or adverse event), if the response is unsatisfactory or there are signs of disease progression. These include, but are not limited to:

- Failure to achieve complete hematologic response (CHR) by Week 8.
- Failure to achieve complete cytogenetic response (CCyR) by Week 13 (Ph+ CML patients only).

If it is determined via qRT-PCR that a patient who has achieved a previous MMR while on study now has a rising level of BCR-ABL transcripts (5 times rise, accompanied with loss of MMR) the investigator should contact the Sponsor to determine if the patient's dose should be escalated to further optimize their response.

Dose escalation to a dose greater than 600 mg is prohibited.

5.2.2. Dose Adjustments for Adverse Reactions

Bosutinib dosing may be interrupted with or without dose reduction in case of treatment-related toxicity according to the guidelines described in the following tables. Dosing interruption and dose reduction is advised for the management of hematologic and non-hematologic adverse drug reactions. Appendix 4 provides specific guidance to patients in the management of diarrhea.

Table 3. Non-Hematologic Treatment-Related Toxicity

Adverse Event Type and Severity	Action
Grade 1	Remain on current dose level.
Grade 2	For persistent clinically relevant toxicity not responding to optimal management: Interrupt bosutinib treatment, and reintroduce at the same dose or reduce dose by 1 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 treatment, 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 treatment. Investigator and Sponsor to review to determine if patient may continue on bosutinib with appropriate dose reduction.
Specific AEs	
Elevated liver transaminases[b]	If elevations in liver transaminases >5 × institutional upper limit of normal (ULN) occur, bosutinib treatment should be interrupted until recovery to ≤2.5×ULN and may be resumed at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, permanent discontinuation of bosutinib should be considered. If transaminase elevations ≥3×ULN occur concurrently with bilirubin elevations >2×ULN and alkaline phosphatase <2×ULN, bosutinib should be permanently discontinued.
Diarrhea	For Grade 3-4 diarrhea, bosutinib treatment should be interrupted and may be resumed at 400 mg once daily upon recovery to grade ≤1. See Appendix 4 for further guidance on diarrhea management.
Renal	For Grade 3 renal impairment (CrCL 30 to 50 mL/min calculated by the Cockroft-Gault formula), bosutinib treatment should be interrupted until recovery to Grade ≤ 1, then may be resumed at 400 mg once daily. For Grade 4 renal impairment (CrCL <30 mL/min, calculated by the Cockroft-Gault formula), bosutinib treatment should be interrupted until recovery to Grade ≤ 1, then may be resumed at 300 mg once daily.

a. Treatment should only be reintroduced when all toxicities are Grade ≤ 1 and the treating physician feels it is in the patient's best interest. Pfizer must be notified by email that treatment has been restarted. For patients who have required a dose reduction due to toxicity, but then have been free of the specific toxicity (Grade ≤1) and are otherwise tolerating bosutinib well, the investigator may choose to re-escalate the dose by 1 dose level (if it is in the patient's best interest) until the patient is back to the starting or previous dose (whichever is higher). See Table 2 for available dose levels.

b. For patients with pre-existing liver transaminase baseline values above the normal range (ALT/AST ≤5 x ULN if attributable to liver involvement of leukaemia) who subsequently present with AST or ALT ≥2 times the baseline values and ≥3 times the ULN, or ≥8 times the ULN (whichever is smaller), bosutinib should be interrupted until recovery to baseline levels.

Table 4. Hematologic Treatment-Related Toxicity

Adverse Event Severity	Action
Grade 1	Remain on current dose level
Grade 2	Remain on current dose level
Grade 3[a, b]	Interrupt bosutinib treatment: If recovered to grade ≤2 within 2 weeks of treatment hold: re-introduce bosutinib at same dose. If recovered within 4 weeks of treatment hold: reduce bosutinib by one dose level. In case of recurrent grade 3 toxicity, dose must be reduced upon recovery to grade ≤2. If recovery takes longer than 4 weeks, the investigator should contact the Sponsor to determine if the patient may continue on bosutinib.
Grade 4[a]	Withhold bosutinib treatment. Investigator and Sponsor to review to determine if patient may continue on bosutinib with appropriate dose reduction.

a. For patients requiring dose reduction due to toxicity, who have been free of the toxicity (grade ≤1) and are otherwise tolerating bosutinib well, the investigator may choose to re-escalate the dose by 1 dose level (if it is in the patient's best interest) until the patient is back to the starting or previous dose (whichever is higher) – see Table 2 for available dose levels.
b. For AP and BP patients who enter the study with Grade 3 neutropenia or anemia due to underlying disease, bosutinib dose does not require dosing interruption/reduction, unless, in the opinion of the investigator, the Grade 3 event is due to bosutinib toxicity, in which case the bosutinib dosing guidelines should be followed. If neutropenia, thrombocytopenia and/or anemia worsen to grade 4, bosutinib dosing should be interrupted, with subsequent dose reduction. Any Grade 3 hematologic toxicity occurring after 4 or more weeks on treatment should be managed by interrupting/reducing bosutinib dosing as recommended.

5.3. Bosutinib Treatment Discontinuation

Patients meeting any of the following criteria should permanently discontinue bosutinib treatment:

1. Unsatisfactory Response (after dose escalation or with no option to dose escalate due to ongoing toxicities).
    - For CP 2nd-line patients, please refer to European LeukemiaNet (ELN) definition of Failure (Appendix 5);
    - For CP 3rd or 4th-line patients, lack of CHR or lack of MCyR;
    - For AP and BP patients, lack of any hematologic response.
2. Disease Progression:
    - For CP, at least one of the following criteria:
        - Development of AP or BP CML;
        - Loss of CHR (in absence of cytogenetic response) confirmed by 2 complete blood counts (CBCs) at least 2 weeks apart; Loss of CHR is defined as:
            - WBC count that rises to > 20.0 x 10^9/L;

- Platelet count that rises to ≥ 600 x 10^9/L;
- Appearance of extramedullary disease not present at baseline including hepatosplenomegaly by palpation or other extramedullary involvement proven by biopsy;
- Appearance of ≥=5% myelocytes + metamyelocytes in the peripheral blood or appearance of blasts or promyelocytes in the peripheral blood.

- Loss of MCyR (loss of CCyR or loss of PCyR);
- Increasing white blood count (WBC) in a patient without CHR, defined as doubling of WBC, to >20 x 10^9/L on 2 occasions at least 2 weeks apart (after the first 4 weeks of treatment).

- For AP, at least one of the following criteria:
  - Development of confirmed BP;
  - Loss of previous hematologic response over a 2-week period;
  - Loss of CHR is defined as:
    - WBC count that rises to > 20.0 x 10^9/L;
    - Platelet count that rises to ≥ 600 x 10^9/L;
    - Appearance of extramedullary disease not present at baseline including hepatosplenomegaly by palpation or other extramedullary involvement proven by biopsy;
    - Appearance of ≥=5% myelocytes + metamyelocytes in the peripheral blood or appearance of blasts or promyelocytes in the peripheral blood.
  - No decrease from baseline levels (if considered clinically relevant) in percentage blasts in peripheral blood or bone marrow on all assessments over a 4-week period.

- For BP (of any phenotype):
  - Increasing blasts (if considered clinically relevant) peripheral blood or bone marrow over a 4-week period;

3. Symptomatic Deterioration:

   Symptomatic deterioration is a worsening of the disease under study that does not meet the definition of disease progression, but in the investigator's opinion, indicates the treatment is no longer effective and alternative therapeutic options should be undertaken, if dose escalation is not an option or has not been successful.

   Dose escalations up to 600 mg daily dose are permitted for patients with unsatisfactory response or who show signs of disease progression and do not have concurrent grade 3 or 4 treatment related adverse events as described in Section 5.2.1. The patient should be monitored closely to assess tolerability and any improvements in efficacy on the increased dose. If the patient's disease does not improve and/or continues to worsen, the patient should be permanently m bosutinib treatment.

4. 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).

5. Bosutinib dose reduction below 200 mg/day. No dose reductions below 200 mg/day will be permitted.

6. Withdrawal of consent.

7. Sponsor decision.

8. Pregnancy.

9. Death.

Survival follow-up information will be obtained for all patients who discontinue bosutinib treatment prior to completing at least 4 years of treatment from the time of first dose. See Section 6.4 for detailed procedures.

5.4. Investigational product Supplies

5.4.1. Formulation and Packaging

Bosutinib tablets (100 mg and 500 mg dosage strength) will be supplied by the Sponsor in high density polyethylene (HDPE) bottles or obtained through prescription if available locally. The commercial formulation of bosutinib will be used in this study. Bosutinib is commercially available and either central supply or locally obtained commercial supplies of Bosutinib will be used in accordance with local regulations.

Bosutinib will be labeled according to local regulations.

Specific countries in which approval has been granted, a prescription may be provided to the Ph+ CML patients to source bosutinib for the study as directed by local regulations. Ph- CML patients will receive bosutinib from Pfizer.

5.4.2. Preparation and Dispensing

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.

Patients will be given enough bosutinib to cover the period of administration between scheduled resupply visits. Any visit delays will need to be carefully evaluated to ensure adequate supply of bosutinib.

5.4.3. Administration

Bosutinib will be self-administered by the patient, once daily, orally, with food. Patients will swallow the investigational product whole and will not manipulate or chew the investigational product prior to swallowing. Both tolerance and absorption may be improved with food, including adequate dietary fats; no restriction is imposed on patient's food choice; with the exception of grapefruit or other foods known to inhibit cytochrome P450 3A (CYP3A). If a dose is missed the patient should be instructed not to double the dose the next day. The patient should take the usual prescribed dose on the following day. Any missed dose information must be indicated in the source documents and the case report forms (CRFs). 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.

5.4.4. 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 CRFs. Site personnel will monitor compliance by reviewing compliance with each patient and documenting appropriately in the CRF. Diary cards will be provided to patients as an aid for the recording of bosutinib compliance (Appendix 6).

5.5. Investigational Product Storage and Accountability

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

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

Bosutinib should be stored at controlled room temperature (between 15-25°C/59-77°F) in a secured area with controlled access. Freezing is not permitted.

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

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

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

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

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 investigational product disposition which at minimum consists of the date received, date dispensed, quantity dispensed and the patient to whom the investigational product was dispensed.

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

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

Patients will be required to return all unused IP at the time new IP bottles are dispensed and at the End of Treatment. Returned medication must not be re-dispensed. Site staff will instruct patients on the storage requirement for taking home medications including how to report temperature excursions outside the specified range.

5.5.1. Destruction of Investigational Product Supplies

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

5.6. Concomitant Medication(s)

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

In addition, any transfusion (red blood cells or platelets) within 1 week prior to screening and during the active study treatment period should be recorded on the CRF.

Growth factors required by the patient during the active study treatment period and the reason for administration must be recorded on the CRF.

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 (e.g., 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 medication restrictions apply only while the patient is on the active treatment phase of the study (i.e., 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;
- Prophylactic use of growth factors;
- Requiring concurrent treatment with immunosuppressive agents, other than corticosteroids prescribed for a short course of therapy (≤ 10 days).

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 (i.e., diarrhea will be monitored and managed using standards of care, including antidiarrheals, antiemetics, and/or fluid replacement). See Appendix 4 for a sample Patient Information Card (Guidelines for the Management of Diarrhea);

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

- Treatment with growth factors [according to American Society of Clinical Oncology (ASCO) guidelines].[25] No prophylactic use of growth factors will be allowed;

  NOTE: if an on-treatment BM assessment or CBC is scheduled within 1 week from the last dose of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (CM-CSF) growth factors, it should be considered "not evaluable" for response assessment, and a BM evaluation or CBC should be repeated at least 1 week from the last dose of growth factor;

- A short course of hydroxyurea or anagrelide for cytoreduction is allowed during the first month of treatment with bosutinib, provided that the last dose of hydroxyurea or anagrelide is stopped at least 72 hours before any CML disease assessment;

- 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

Patients should be cautioned on the following:

- Patients should be strongly encouraged to avoid herbal remedies, including St John's Wort. Grapefruit products should also be avoided.

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

- Inhibitors of platelet aggregation (e.g., 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 Section 5.4 dose modification tables.

5.6.4. 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 (See Appendix 2).

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.

In a study of 24 healthy patients in whom 5 daily doses of 400 mg ketoconazole were co-administered with a single dose of 100 mg bosutinib under fasting conditions, ketoconazole increased bosutinib Cmax by 5.2-fold, and bosutinib area under the curve (AUC) in plasma by 8.6-fold, as compared with administration of bosutinib alone.

CYP3A inducers

The concomitant use of bosutinib with strong CYP3A inducers should be avoided, as a decrease in bosutinib plasma concentration may occur (See Appendix 2).

Based on the large reduction in bosutinib exposure that occurred when bosutinib was co-administered with rifampicin, increasing the dose of bosutinib when coadministering with strong or moderate CYP3A inducers is unlikely to sufficiently compensate for the loss of exposure.

Caution is warranted if mild CYP3A inducers are used concomitantly with bosutinib.

Following concomitant administration of a single dose bosutinib with 6 daily doses of 600 mg rifampicin, in 24 healthy patients in fed state bosutinib exposure (C_{max} and AUC in plasma) decreased to 14% and 6%, respectively, of the values when bosutinib 500 mg was administered alone.

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 (e.g., take bosutinib in the morning and antacids in the evening) whenever possible.

Bosutinib displays pH-dependent aqueous solubility *in vitro*. When a single oral dose of bosutinib (400 mg) was coadministered with multiple-oral doses of lansoprazole (60 mg) in a study of 24 healthy fasting patients, bosutinib C_{max} and AUC decreased to 54% and 74%, respectively, of the values seen when bosutinib (400 mg) was given alone.

Effects of other medicinal products

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 3).

6. STUDY PROCEDURES

Refer to the Schedule of Activities (Table 1) for the complete list of procedures to be performed and associated timepoints. All patients will participate on study for at least 4 years. In view of the very refractory nature of the patients being treated on this study, the investigator may delegate certain specific tests/visits to be performed at other sites closer to the patient's home. The investigator will be responsible for capturing results of any study-specified tests and visits (e.g., AE/Adverse Drug Reaction data collection) that are performed outside his/her site in the relevant CRFs and in the source documents maintained on site. Disease assessments will be performed at the site at week 1, week 2, week 3, week 4 and week 8 during the first 2 months, afterwards (from week 13), the disease assessments will be performed during the 3 monthly visits and starting after week 52, performed during the 6-monthly visit.

6.1. Screening

Screening can be accomplished over one or multiple visits over a 4-week period (30 days). Stage of disease is defined as the worst phase of CML experienced by the patient, regardless of disease status at the time of study entry. For example, a patient whose disease is in CP at study entry, but who had been previously diagnosed in AP, will be classified as AP CML. Refer to Appendix 7 for specific criteria for CP, AP and BP phases of disease.

Prior cancer history, including CML and any other cancer will be collected. All treatments received by the patient for CML (CP, AP, and BP), including dates of administration, dose(s), best response and tolerability (including specific intolerance(s) to each therapy) will be collected from the time of original diagnosis of CML. Any additionally diagnosed malignancies will also be recorded at screening.

All relevant medical history and treatment received by the patient within 30 days before administration of bosutinib will be recorded on the patient's CRF, including the name of the procedure or drug and other related information.

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

- Signature of informed consent document (ICD);
- Review of patient's eligibility (i.e., protocol inclusion/exclusion criteria);
- Cytogenetic confirmation of Ph+ chromosome (or BCR-ABL1+ if Ph-) CML diagnosis and phase. Acceptable documentation includes results from primary CML diagnosis or results following discontinuation/ failure of prior CML therapy. Either traditional cytogenetics for the Ph+ chromosome or fluorescence in situ hybridization (FISH) for the BCR-ABL juxtaposition or PCR for BCR-ABL transcript quantification are acceptable for the diagnosis of CML;
- Medical history;

- Complete physical examination to include vital signs (sitting or supine blood pressure, heart rate, and height and weight);
- Smoking status at screening; (Note: the use of TKIs could lead to cumulative long-term cardiovascular disease therefore information of other risk cardiovascular factors like smoking status will be collected for this study);
- Extramedullary disease assessment (including assessment of liver, spleen and lymph nodes by physical examination as well as other potential sites of extramedullary involvement);
- ECOG performance status (Appendix 8);
- Electrocardiogram (ECG);
- Echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan; Standard of care echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan results may be used for screening if not longer than 12 weeks prior to the first bosutinib dose in the absence of past medical history of cardiovascular disease and presence of normal left ventricular ejection fraction (LVEF). If the patient has past medical history of cardiovascular disease or ongoing cardiovascular co-morbidities, ECHO or MUGA should be obtained within 7 days prior to the first bosutinib dose. Screening, unplanned, and End of Treatment assessments should be performed with the same test, ECHO or MUGA scan.
- Chest X-ray; Standard of Care chest X-ray results may be used for screening if not longer than 12 weeks prior to the first bosutinib dose in the absence of past medical history of pulmonary disease. If the patient has past medical history of pulmonary disease or ongoing pulmonary co-morbidities, then chest X-ray should be obtained within 7 days prior to the first bosutinib dose;
- Bone marrow aspirate sample for G-banding analysis (karyotype) and morphological assessment (% of bone marrow differential) is required at screening, unless the CML disease status is proven to be MMR by qRT-PCR. Conventional cytogenetic assessment will be done locally. If a bone marrow aspirate that meets all study requirements was obtained within 30 days prior to screening, these data may be used to replace the need for a bone marrow aspirate during screening. In Ph- CML patients, conventional cytogenetic assessments (to detect other potential cytogenetic abnormalities) and molecular cytogenetic assessments using FISH (to detect cryptic/variant translocations) are required at screening;
- qRT-PCR for molecular response assessment (BCR-ABL fusion transcript levels) and mutational analysis of the BCR-ABL kinase domain will be performed by a central laboratory. For CP CML, the assessments will be performed using peripheral blood sample. For Advanced Phase (AP and BP) CML, the assessments will be performed using peripheral blood and/or bone marrow samples; mutational analysis will be performed from the peripheral blood or bone marrow samples that were used for molecular response assessment;

- Hematology panel (Appendix 9);
- Chemistry panel (Appendix 9). In addition, baseline fasting glucose, glycosylated hemoglobin (HbA1c) , cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL), potassium and magnesium should be performed and repeated if abnormal;
- Liver Function Tests (LFTs) including: total bilirubin, AST and ALT, Alkaline Phosphatase (Appendix 9);
- Hepatitis B serology testing should be evaluated;
- 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) ;
- Urine or serum pregnancy test (for women of childbearing potential) (Appendix 9);
- Contraceptive check: patients of child-bearing potential will be required to affirm their use of 2 highly effective methods of contraception which will be documented in the patient's source document;
- Blood and plasma collection for biobanking if specifically allowed by local EC/IRB. If missed, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit;
- Patient diary card review and implementation (dosing, AEs and concomitant medications, Appendix 6);
- FACT-Leu administration (Appendix 10).

6.2. Study Period

The following procedures will be performed on treatment. Patients must be registered to the study after eligibility is confirmed within 3 days prior to receiving first dose of bosutinib.

Week 1 (Day 1, pre-dose and Day 7), Week 2, Week 3, Week 4 and Week 8 (±1 day) on Day 7

- Hematology panel (Appendix 9); complete hematological assessment response;
- Liver function tests (Appendix 9);
- Chemistry panel; including HbA1C, cholesterol, HDL, LDL, potassium, and magnesium, if clinically indicated (Appendix 9);
- Coagulation tests (Appendix 9);

- Urine or serum pregnancy test (for women of childbearing potential) (pre-dose Week1 Day 1 only) (Appendix 9);

- Contraceptive check: patients of child-bearing potential will be required to affirm their use of 2 highly effective methods of contraception which will be documented in the patient's source document;

- Extramedullary disease assessment, if clinically indicated. Sites of extramedullary disease identified at screening should be followed during the course of treatment. Patients should be evaluated upon suspicion of new extramedullary disease;

- Hepatitis B serology testing, as clinically indicated;

- Patient diary card review (Appendix 6);

- Bosutinib dispensation on Day 1.

Week 13, Week 26, Week 39, Week 52 (±7 days), Week 78, Week 104, Week 130, Week 156, and Week 182 (±21 days)

- Complete physical examination to include vital signs (sitting or supine blood pressure, heart rate and weight);

- Current smoking status.

- Extramedullary disease assessment, if clinically indicated. Sites of extramedullary disease identified at screening should be followed during the course of treatment. Patients should be evaluated upon suspicion of new extramedullary disease;

- Hepatitis B serology testing, as clinically indicated;

- ECG assessment, if clinically indicated;

- ECHO or MUGA scan assessment, if clinically indicated;

- Chest X-ray, if clinically indicated;

- ECOG Performance Status (Appendix 8);

- Bone marrow aspirate must be collected for local conventional cytogenetic assessment (with at least 20 metaphases). Percentage (%) of Ph+ metaphases, as well as any other chromosomal abnormalities, will be documented. Conventional cytogenetic assessment should be continued until MMR. Only chromosome banding analysis of marrow cell metaphases can be used to assess the degree of CyR (with at least 20 metaphases analyzed). Upon achieving CCyR by the conventional cytogenetic assessment, FISH of blood interphase nuclei with an appropriate probe (Dual-Color Dual-Fusion or Dual-Fusion FISH) could substitute for chromosome

banding analysis of marrow cell metaphases for the assessment of maintenance of the CCyR (which is then defined by <1% BCR-ABL1-positive nuclei of at least 200 nuclei) until MMR is reached. Loss of CCyR using FISH requires resumption of bone marrow conventional cytogenetic assessment (unless the CML disease status is proven to be MMR by qRT-PCR);

- Bone marrow aspirate for morphology (% bone marrow differential) and conventional cytogenetic assessment is required for all patients at the time of suspected progression and/or failure.

  Note: in Ph-CML patients, conventional cytogenetic assessment (to detect other potential cytogenetic abnormalities) and molecular cytogenetic assessments using FISH are required at the time of suspected progression and/or failure;

- qRT-PCR for molecular response assessment (BCR-ABL fusion transcript levels) and mutational analysis of the BCR-ABL kinase domain will be performed by a central laboratory. For CP CML, the assessments will be performed using peripheral blood sample. For Advanced Phase (AP and BP) CML, the assessments will be performed using peripheral blood and/or bone marrow samples; mutational analysis will be performed from the peripheral blood or bone marrow samples that were used for molecular response assessment. Loss of confirmed MMR requires resumption of conventional cytogenetic assessment;

- Hematology panel (Appendix 9); complete hematological assessment response;

- Liver function tests (Appendix 9);

- Chemistry panel; including HbA1C, cholesterol, HDL, LDL, potassium, and magnesium, if clinically indicated (Appendix 9);

- Coagulation tests (Appendix 9);

- Urine or serum pregnancy test (Appendix 9);

- Contraceptive check: patients of child-bearing potential will be required to affirm their use of 2 highly effective methods of contraception which will be documented in the patient's source document;

- Blood and plasma collection for biobanking, if specifically allowed by local EC/IRB; sample should be collected at the time of first response, where response there is response (e.g. MCyR, CCyR, MMR, depending on the baseline CML disease status) for CP patients and hematologic response for AP/BP patients when feasible. This sample should be obtained at the next scheduled visit if the next scheduled visit occurs within 2 months after the first response. If the next scheduled visit occurs >2 months after the first response, then the sample should be collected at an unscheduled visit within 2 months after the first response, if feasible;

- FACT-Leu administration (Appendix 10);
- Patient diary card review;
- Bosutinib dispensation.

6.3. End of Treatment Visit (±7 days)

The End of Treatment visit should be performed **for all patients** once they have permanently discontinued bosutinib. The visit should occur within the 28 days after the last dose of bosutinib. For patients who discontinue bosutinib prior to Week 208, all procedures listed should be performed, unless collected within the previous 6 weeks. The following procedures are required:

- Complete physical examination including vital signs (sitting or supine blood pressure, heart rate, and weight);
- Current smoking status;
- Extramedullary disease assessment;
- ECOG performance status (Appendix 7);
- FACT-Leu administration (Appendix 10);
- ECG;
- ECHO or MUGA scan; screening and End of Treatment tests to evaluate the cardiac function should use the same test in both visits);
- Chest X-ray;
- Bone marrow aspirate for morphology (% bone marrow differential) and conventional cytogenetic assessment is required if the discontinuation is due to progression and/or failure;
- qRT-PCR for molecular response assessment (BCR-ABL fusion transcript levels) and mutational analysis of the BCR-ABL kinase domain will be performed by a central laboratory. For CP CML, the assessments will be performed using peripheral blood sample. For Advanced Phase CML (AP and BP) the assessment will be performed using peripheral blood and/or bone marrow samples;
- Hematology panel (Appendix 9); complete hematological assessment response;
- Liver function tests (Appendix 9);

- Chemistry panel; including HbA1C, cholesterol, HDL, LDL, potassium and magnesium, if clinically indicated (Appendix 9);
- Coagulation tests (Appendix 9);
- Urine or serum pregnancy test (Appendix 9);
- Contraceptive check: patients of child-bearing potential will be required to affirm their use of 2 highly effective methods of contraception until 28 days after their final dose of bosutinib which will be documented in the patient's source document;
- Blood and plasma collection for biobanking, if specifically allowed by local EC/IRB, if feasible;
- Final review of patient diary card;
- Return of unused bosutinib. (Note: Ph+ CML patients who receive a prescription [per local regulations] will have a final compliance check for dose levels and duration of Bosutinib treatment).

6.4. Long-Term Follow-Up Visit

Patients who discontinue from treatment for any reason (except death, withdrawal of patient consent or termination of study by Sponsor) prior to completing at least 4 years will enter into the follow-up phase of the study. Patients will be followed for at least 4 years from the first dose of bosutinib and will be assessed for overall survival status only.

Follow-up will be conducted approximately every 3 months from the last dose of bosutinib (telephone calls acceptable). If bone marrow transplantation is performed after discontinuation, it should be captured during the long-term follow-up as well as treatment with another TKI, time to progression, and transformation to AP or BP.

Patient study participation will not conclude before 4 years after the first dose of bosutinib was administered.

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.

Potential reasons why a patient may permanently discontinue or be withdrawn from study treatment are provided in Section 5.4.

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

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the patient. When a protocol- required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions 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 assessments detailed in this protocol are aligned with the European LeukemiaNet (ELN) guidelines.[26] Refer to the SCHEDULE OF ACTIVITIES for assessment of time points.

7.1.1.1. Cytogenetic Response Assessment

Cytogenetic analysis will be performed by conventional cytogenetics from bone marrow, requiring at least 20 metaphases in order to evaluate number of Ph+ cells to determine cytogenetic response. Conventional cytogenetic assessment will be performed at scheduled visits until MMR is observed.

Only chromosome banding analysis of marrow cell metaphases will be used to assess the degree of CyR. Upon achieving CCyR by the conventional cytogenetic assessment, FISH of blood interphase nuclei with an appropriate probe (Dual-Color Dual-Fusion or Dual-Fusion FISH) could substitute for chromosome banding analysis of marrow cell metaphases for the assessment of maintenance of the CCyR (which is then defined by <1% BCR-ABL1-positive nuclei of at least 200 nuclei) until MMR is reached. Loss of CCyR using FISH will require resumption of bone marrow conventional cytogenetic assessment (unless the CML disease status is proven to be MMR by qRT-PCR).

For Ph- CML patients, conventional cytogenetic analysis will be performed only at screening and at the time of suspected progression and/or failure. Conventional cytogenetic assessment will be used to detect other potential cytogenetic abnormalities and molecular cytogenetic assessment (FISH) will be used to detect cryptic/variant translocations. Cytogenetic analysis will be conducted locally. Note: The cytogenetic assessment needs to be repeated at least 28 days later to confirm CCyR CML disease status for Ph+CML patients (when the cytogenetic response is first observed in the absence of MMR, e.g once CCyR is achieved by G-banding,

FISH is needed to confirm the achievement/maintenance of CCyR at least 28 days later). Loss of cytogenetic response must be confirmed by 2 assessments at least 4 weeks apart. (Note: if confirmation is lacking and the patient goes off treatment due to progressive disease, the assumption is that loss of cytogenetic response (CyR) is confirmed for this study; therefore, the confirmation of loss of CyR 4 weeks apart is not required in this clinical context).

Karyotypic abnormalities in Ph- subclones should be recorded. See Appendix 11 for CyR criteria definitions.

7.1.1.2. Hematologic Response Assessment

Complete blood counts and differentials and extramedullary disease assessment (liver and spleen assessment) from the physical examination and bone marrow differentials will be used to determine response to treatment.

Hematologic responses must be of at least 4 weeks duration confirmed by 2 assessments at least 4 weeks apart. Complete hematologic response (CHR) and OHR (defined as CHR or RCP) will be evaluated by peripheral blood, and bone marrow differential (to define RCP) when available, only utilizing local laboratory results. Loss of hematologic response must be confirmed by 2 assessments at least 2 weeks apart. Note: if confirmation is lacking and the patient goes off treatment due to progressive disease, the assumption is that loss of hematologic response is confirmed for this study; therefore, the confirmation of loss of hematologic response 2 weeks apart is not required in this clinical context.

The definition of CHR for CP CML is outlined in Appendix 11.

CHR for AP and BP CML is defined as white blood cell (WBC) count less than or equal to the institutional upper limit of normal (ULN); absolute neutrophil count (ANC) 1.0 x 10^9/L or higher, platelet count 100 x 10^9/L or higher; marrow blasts 5% or less with no peripheral blasts or promyelocytes; peripheral myelocytes + metamyelocytes less than 5%; basophils in peripheral blood less than 5%; and no evidence of extramedullary involvement.

> Note: If an on-treatment CBC is scheduled within 1 week from the last platelet transfusion, it should be considered “Not Evaluable” for hematological response assessment, and a CBC should be repeated at least 1 week from the last platelet transfusion received.
>
> Note: If an on treatment CBC is scheduled within 1 week from the last dose of G-CSF or GM-CSF growth factor, it should be considered “Not Evaluable” for response assessment and CBC should be repeated at least 1 week from the last dose of growth factor.

7.1.1.3. Extramedullary Disease

Physical examination will be carried out as part of the extramedullary disease response assessment to confirm hepatic, spleen or other organ involvement by CML. Chest X-ray may also be performed, when clinically indicated.

7.1.1.4. Molecular Response Assessment

Blood samples (for CP, AP, and BP CML patients) and bone marrow samples (for AP and BP CML patients) will be collected at each efficacy time point for qRT-PCR analysis of BCR-ABL transcript levels that will be reported using the International Scale.

See Appendix 11for response criteria definitions.

A BCR-ABL1 expression of ≤0.1% corresponds to MMR with >5,000 ABL1 transcripts.

The following criteria will be used to define deep molecular response (MR):

- MR4 = either (i) detectable disease with <0.01% BCR-ABL1^{IS} or (ii) undetectable disease in cDNA with >10 000 ABL1 transcripts.

- MR4.5 = either (i) detectable disease with <0.0032% BCR-ABL1^{IS} or (ii) undetectable disease in cDNA with >32,000 ABL1 transcripts in the same volume of cDNA used to test for BCR-ABL1.

Samples with a total of <10,000 ABL1 transcripts (i.e., sum of the replicates if replicate analysis is performed) should be considered as not evaluable for MR4 and samples with a total of <32,000 ABL1 transcripts should be considered as not evaluable for MR4.5.

MMR is MR3. For all patients, MR1/MR2, MR3 will be used and have a working definition of ≤ 10%/1%/0.1% BCR-ABL1^{IS}with >5 000 ABL1 transcripts.

Molecular response assessments will be carried out by an independent central laboratory at baseline and every 3 months until Week 52, then at 6-month intervals during Years 2, 3, and 4 and End of Treatment, and any time there is treatment failure and/or disease progression.

Loss of MMR must be confirmed by 2 consecutive assessments, one of which is ≥ 1% on the International Scale. Note: if confirmation is lacking and the patient goes off treatment due to progressive disease, the assumption is that loss of MMR is confirmed for this study.

7.1.1.5. BCR-ABL Mutation Testing

Samples will be collected at screening to identify pre-bosutinib exposure point mutations in the BCR-ABL kinase domain.

In addition, mutational analysis of the BCR-ABL kinase domain will be performed during bosutinib treatment for patients with baseline mutations and for all patients at End of Treatment, and any time if treatment failure occurs (as indicated by a rise in BCR-ABL transcript levels of at least 5-fold that has been confirmed by more than one test) and/or disease progression.

Mutational analysis of the BCR-ABL kinase domain will be performed by an independent central laboratory. For CP CML, the assessment will be performed using peripheral blood samples. For Advanced Phase (AP and BP) CML, the assessments will be performed using peripheral blood and/or bone marrow samples. Mutational analysis will be performed from the peripheral blood or bone marrow samples that were used for molecular response assessment.

BCR-ABL mutation analysis and molecular response assessment will be performed by the same central laboratory.

7.2. Safety Assessment Methods

Safety will be assessed by physical examination (including vital signs) and laboratory tests, including chest X-ray and ECHO/MUGA scans. All safety assessments are outlined in the SCHEDULE OF ACTIVITIES which includes adverse event and concomitant medication review, assessment of disease status, and ECG monitoring. Patient Diary cards and FACT-Leu should be reviewed by site staff to verify presence of any reportable safety information that should be assessed by the investigator and reported according to guidelines provided in adverse event section.

7.3. Safety Laboratory Determinations

The investigator will review laboratory test results to determine the occurrence of clinically important abnormalities (i.e., adverse events [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.

7.4. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a further negative pregnancy result will then be required at the baseline visit before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated every 3 or 6 months at scheduled visits during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/ECs or if required by local regulations.

7.5. Banked Biospecimens

7.5.1. Markers of Investigational Product Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited as such by local regulations or ethics committee decision.

To protect patients' confidentiality, the banked biospecimens and data generated from them will be coded with the patient's study ID number. Samples will be kept in a facility accessible only by badge-swipe. Data will be stored on password-protected computer systems. The key between the code and the patient's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Patients can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Patients are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the patient's medical record. There is no intention to contact patients after completion of the clinical trial.

A 4 mL blood biospecimen **Prep D1 (K_2 EDTA whole blood collection optimized for DNA analysis)** will be collected at Baseline, time of response (MCyR for CP patients, CHR/MHR for AP/BP patients), and at the End of Treatment visits to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. Additional biospecimens to be retained for exploratory analyses in this study include **Prep B1** plasma samples.

Prep B1 (K2 EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis): a 10 mL blood biospecimen will be collected at screening, at the time of first response, and at End of Treatment (unless within 6 weeks of prior sample collection). This sample should be obtained at the next scheduled visit if the next scheduled visit occurs within 2 months after the first response. If the next scheduled visit occurs >2 months after the first response, then the sample should be collected at an unscheduled visit within 2 months after the first response, if feasible, unless it is the End of Treatment Visit.

The Banked Biospecimens will be collected from all patients **unless prohibited by local regulations or ethics committee decision.** Detailed collection, processing, storage and shipment instructions are provided in the independent central laboratory manual.

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

7.5.2. Additional Research

Unless prohibited by local regulations or IRB/EC decision, patients will be asked to indicate on the consent form whether they will allow the Banked Biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical trial, and related conditions;
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to Pharmacogenomics/biomarkers.

Patients need not provide additional biospecimens for the uses described in this section; the biospecimens specified in Markers of Investigational Product Response Section will be used. Patients may still participate in the clinical trial if they elect not to allow their Banked Biospecimens to be used for the additional purposes described in this section.

7.6. Biological Samples

Peripheral blood and bone marrow aspirate samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the patient's identity. Some of the samples may be stored by Pfizer for additional testing. The samples will not be used for any unrelated research and no genetic testing will be performed. The samples will be stored for up to 15 years after the end of the study and then destroyed.

The patient or legal guardian may request that the samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained.

7.7. Health Outcomes Assessment

Cancer and its treatment often have significant effects on patients as measured by patient-reported outcomes (PROs) (e.g., symptoms, concerns, overall well-being). Health outcomes assessments will be conducted with the FACT-Leu administered at screening, Weeks 13, 26, 39, 52, 78, 104, 130, 156, 182, and 208 (End of Treatment), where the appropriate translations are available. The health outcomes assessment surveys are for the purpose of exploring the patient's own perceptions about his or her quality of life, disease symptoms, aspects of their treatment, and should be completed by the patient only prior to interaction with health care professionals at assigned study visits. The investigator must not influence the patient's assessments. Every effort should be made to maintain an unbiased assessment.

7.7.1. Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)

The FACT-Leu (see Appendix 10) is a 44-item, self-reported, reliable and valid assessment of quality of life in patients with leukemia.[23] The FACT-Leu consists of measures health related quality of life across 4 domains : Physical Well-being (7 items; score range, 0–28), Social/Family Well-being (7 items; score range, 0–28), Emotional Well-being (6 items; score range, 0–24), Functional Well-being (7 items; score range, 0–28 and a leukemia-specific subscale, which consists of 17 items (score range, 0–68) that assess patient concerns relating to leukemia. The total score (range, 0-176) can also be calculated. Patients are asked rate on a scale from '0' ("not at all") to '4' ("very much"), regarding how much each item (i.e., pain, fatigue, etc.) was present in the last 7 days; higher scores reflect better quality of life. The minimally important difference (MID), defined as the smallest change in a PRO measure that is perceived by patients as beneficial, or that would result in a clinician considering a change in treatment for this instrument are defined as: 2-3 (PWB), N/A (SWB), 2 (EWB), 2-3 (FWB), 3-7 (FACT-G), 4-7 (Leus-specific subscale) and 6-12 (FACT-Leu Total).

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 treatment group or suspected causal relationship to the investigational product will be reported as described in the following paragraphs.

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

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to

the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient/legally acceptable representative/legal guardian. In addition, each study patient/legally acceptable representative/legal guardian 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 Section on Patient Withdrawal)

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

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

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

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include the signs or 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 reported 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 reporting as an AE.Serious Adverse Events

8.2.3. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

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

Or that is considered to be:

- An important medical event.

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

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 reporting 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 Section on Severity Assessment).

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.

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 (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, 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 (e.g., 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 (e.g., for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (e.g., patient has no place to sleep);
- Administrative admission (e.g., for yearly physical examination);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);

- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive 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

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE Version 4.0, Publish Date: May 28, 2009, *http://ctep.cancer.gov/reporting/ctc.html*) will be used to assess the severity of AEs and SAEs.

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.0 document but may be used in certain circumstances.)
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO Adverse Event

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). 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 patient’s individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

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

- For patients with baseline ALT **or** AST **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:

    - Pre-existing AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 x ULN, or >8 x 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 x ULN **or** the value reaches >3 x ULN (whichever is smaller).

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

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

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase, direct and indirect bilirubin, gamma-glutamyl transferase, 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 (e.g., 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 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 (e.g., 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 (e.g., because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

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

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

If the outcome of the pregnancy meets the criteria for an SAE (i.e., 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 (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source document that the patient was given 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 adverse event.

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

8.4.4. Medication Errors

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

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

8.4.4.1. Medication errors

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

Medication errors include:

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

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

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

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

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

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 primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

This study does not include any formal sample size determination. Approximately 150 patients with Ph+ CML will be enrolled including at least 45 CP, AP, and BP patients in the 4th or later line treatment setting. With a subset of 45 patients, the standard deviation of an estimate of the probability of response is at most 0.075.

9.2. Efficacy Analysis

All treated Ph+ CML patients with a valid baseline efficacy assessment for the respective endpoint (Evaluable Population) will be included in the molecular, cytogenetic, and hematologic efficacy analyses. All treated Ph+ CML patients (Full Analysis Set [FAS]) will be included in the other efficacy endpoints. Analyses will be presented by disease stage (e.g., CP, AP, BP) and/or line of therapy (e.g., CP 2nd line [CP2L], CP 3rd line [CP3L], CP 4th or later line [CP4L], AP2L, AP3L, AP4L, BP2L, BP3L, BP4L) for Ph+ CML patients. All Ph- CML patients will be analyzed separately and only for cumulative CHR and molecular endpoints.

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

9.2.1. Analysis of Primary Endpoint

The primary efficacy analyses are the percentage of cumulative confirmed MCyR in CP 2nd and 3rd line patients, cumulative confirmed MCyR in 4th and later line patients and the cumulative confirmed OHR in AP and BP patients by 1 year of bosutinib treatment (Week 52) assessed from the local laboratory data. The primary analyses will be the percentage of cumulative confirmed MCyR (for CP Ph+ CML patients) and cumulative confirmed OHR

(for AP and BP Ph+ CML patients) by 1 year of bosutinib treatment (week 52). Confirmed MCyR will be defined as (1) the attainment of confirmed MCyR (CCyR or PCyR) by 1 year for patients entering the study without CCyR achieved on the previous TKI therapy or (2) the maintenance of confirmed CCyR (achieved under the previous TKI therapy) for at least 1 year after starting treatment with bosutinib or (3) at least MMR by 1 year and a deeper molecular response compared to baseline. Patients with baseline PCyR that do not achieve CCyR are included in the analysis but they would be counted as non-responders. Initial cytogenetic (in the absence of MMR) and hematologic responses must be confirmed by 2 consecutive assessments at least 28 days apart.

9.2.2. Analysis of Secondary Endpoints

Percentages for the following secondary endpoints will be calculated:

- Cumulative MCyR anytime on treatment in the CP, AP and BP Ph+ CML patient populations.
- Cumulative confirmed OHR anytime on treatment in the different advanced phase (AP, BP) Ph+ CML patient populations by lines of prior of therapy.
- Cumulative best response anytime on treatment in the different CP, AP, and BP Ph+ CML patient populations, also in the 4^{th}- or later-line treatment setting. The hierarchy to assess for best response is MR4.5, MR4, MMR, CCyR, PCyR, CHR, and OHR.
- Landmark MCyR at 3, 6, 12, 18, and 24 months in the different CP, AP and BP Ph+ CML patient populations.
- Landmark confirmed OHR at 3, 6, 9, 12, 18, and 24 months in the AP and BP Ph+ CML patient populations.
- Cumulative confirmed CHR anytime on treatment in the CP, AP and BP Ph+ CML patient populations.
- Cumulative MMR anytime on treatment in the CP, AP and BP Ph+ CML patient populations.
- Duration of CCyR.
- Duration of MMR.

Analyses of hematologic and cytogenetic response will be based on the data from the local laboratory assessment. Analyses of molecular response will use the data from the independent central laboratory.

Duration of response is defined as the interval from the date of first on-treatment response to the date of confirmed loss of response, death within 28 days of last dose, or treatment discontinuation due to disease progression. Responders without loss of response will be censored at the last valid assessment for the respective endpoint.

The secondary time-to-event endpoint duration of response will be summarized using the Kaplan-Meier method or by cumulative incidence, whichever is more appropriate, depending on the competing risks (e.g., treatment discontinuation without disease progression in the analysis).

9.3. Analysis of Other Endpoints

OS or survival time is defined as the interval from the date of first dose of bosutinib to the date of death due to any cause. Patients not known to have died will be censored at the last known alive date. The OS distribution up to at least 4 years will be provided.

PFS is the interval from the date of first dose of bosutinib until the earlier date of disease progression or death from any cause. Patients without PFS events will be censored at the last evaluation date. The PFS distribution up to at least 4 years will be provided.

The exploratory time-to-event endpoints of OS and PFS will be summarized using the Kaplan-Meier method or by cumulative incidence, whichever is more appropriate, depending on the competing risks (e.g., treatment discontinuation without progression in PFS analysis).

For Ph- CML patients, cumulative best response anytime on treatment will be provided. The hierarchy to assess for best response is MR 4.5, MR4, MMR, MR2, MR1, CHR, and OHR.

The percentage of patients with baseline and emergent Bcr-Abl kinase-domain mutations, along with the specific types of mutations, will be summarized.

The FACT-Leu will be scored according to the respective user's guides and validation papers. Summary statistics of the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) quality of life questionnaire will be calculated at baseline and approximately every 3 months for the first year, and every 6 months during year 2, 3 and 4 of treatment on study. The mean and 95% CI and median of the observed scores and the changes from baseline will be reported for the FACT-Leu, individual domains, and items.

9.4. Safety Analysis

AE incidence rates will be described both with and without regard to causality. The frequency of occurrence of overall toxicity, categorized by toxicity grades (NCI CTCAE v4.0), 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 safety analyses will be based on the FAS.

9.5. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating pharmacokinetic (PK)/pharmacodynamic (PD) modeling, and/or to support clinical development.

9.6. Data Monitoring Committee

This study will not use an external Data Monitoring Committee. The Sponsor's procedures for ongoing monthly 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. This verification may also occur after study completion.

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

In most cases, the source documents are the hospital'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, e.g., 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 (e.g., 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 (e.g., 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)/Ethics Committee (EC)

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with 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 1996 and 2008 versions).

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.

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

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

The informed consent document(s) used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

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 (eg, 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 (eg, 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, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative or legal guardian when applicable before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

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

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable regulatory 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

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (i.e., Clinical Trial Application (CTA) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all other Participating Countries

The end of the trial for each patient occurs no more than 4 years after the date of his/her first dose of study drug. The overall End of Trial for this study in all other participating countries is defined as the Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, 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 14 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

PCD is defined as the date that the final patient was examined or received an intervention for 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 wwwclinicaltrials.gov.

15.2. Publications by Investigators

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

Investigator 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, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator 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, Investigator agrees 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, Investigator is free to publish separately, subject 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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Appendix 1. Guidelines for Identifying Resistance and Intolerance

Definition criteria for Resistance

There are two categories of resistance:

- Primary resistance is the failure to achieve a response as established by the European LeukemiaNet (ELN) or National Comprehensive Cancer Network (NCCN) guidelines. Primary resistance will be further divided into primary hematologic resistance, which occurs in cases who fail to normalize peripheral counts within 3–6 months of initiation of treatment; or primary cytogenetic resistance, in patients who fail to achieve any level of cytogenetic response (CyR) at 6 months, a major CyR (MCyR) at 12 months or a CCyR at 18 months.[30]

- Secondary resistance is defined as those who have previously achieved and sub sequently lost their hematologic, molecular, or cytogenetic response in accordance with ELN/NCCN guidelines.[31, 32]

Definition of Intolerance to therapy:[33,34]

A patient is deemed to be intolerant to a TKI if one or more of the following criteria are met:

- Any life threatening Grade 4 non hematological toxicity.

- Any Grade 3 or 4 non hematological toxicity that persists despite dose reduction and optimal symptomatic measures.

- Grade 3 or 4 hematological toxicity that is unresponsive to supportive measures and would require dose reduction below the accepted minimal effective dose.

- Any combination of non hematological toxicities of any grade that persist despite supportive measures and in the patients and physician's opinion compromise quality of life to such an extent that a change of therapy is justified.

Appendix 2. 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	atazanavir
itraconazole	Aprepitant
voriconazole	Amprenavir
posaconazole	Fosamprenavir
conivaptan	Imatinib
clarithromycin	Verapamil
telithromycin	tofisopam
boceprevir	Ciprofloxacin
telaprevir	
mibefradil	
nefazodone	
grapefruit products including grapefruit juice	

Inducers:

Strong CYP3A inducers	Moderate CYP3A inducers
rifampicin	Bosentan
phenytoin	Nafcillin
carbamazepine	Efavirenz
St. John's Wort	Modafinil
	Etravirine

Appendix 3. Summary of Drugs That Are Generally Accepted to Have a Risk of Causing QTc Prolongation Potentially Causing Torsades de Pointes

Generic Name	Brand Name	EU and Other Regions (Common Tradenames)
Amiodarone	Coradone/Pacerone	Coradone
Arsenic trioxide	Trisenox	Trisenox
Bepridil	Vascor (no longer sold in the theUS)	-
Chloroquine	Aralen	Avlocor, Nivaquine
Chlorpromazine	Thorazine	Largactil / Megaphen
Clarithromycin	Biaxin	Binoclar, Crixan, Claritt, Clarac, Biaxin, Klaricid, Klacid, Klaram, Klabax, Claripen, Clarem, Claridar, Fromilid, Clacid, Clacee, Vikrol, Infex, Clariwin, Resclar, Clarihexal
Disopyramide	Norpace	Rythmodan
Dofetilide	Tikosyn	-
Domperidone	Motilium	Motilium
Droperidol	Inapsine	Xomolix
Erythromycin	Erythrocin/E.E.S.	-
Halofantrine	Halfan	Halfan
Haloperidol	Haldol	Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Haldol, Halosten, Keselan, Linton
Ibutilide	Corvert	Corvert
Levomethadyl	Orlaam (discontinued in the US)	-
Mesoridazine	Serentil	-
Methadone	Methadose/Dolophine	Methadose
Moxifloxacin	Avelox, Moxeza, Vigamox	-
Pentamidine	NebuPent/Pentam	-
Pimozide	Orap	Orap
Procainamide	Pronestyl/Procan	-
Quinidine	Cardioquin/Quinaglute	-
Sotalol	Betapace	Sotacor
Sparfloxacin	Zagam	-
Thioridazine	Mellaril	-

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

See the following websites for an updated List – Drugs with Risk of Torsades de Pointes:
http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm#
http://www.medicines.org.uk/emc/
http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&murl=&mid=&jsenabled=true

Appendix 4. Patient Information Card

Guidelines for the Management of Diarrhea

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

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

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

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

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

Recommendations

1. 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.

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.

2. 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.

Appendix 5. European Leukemia Net Definition of Response to Second-Generation TKIs for Chronic Phase Second-line CML Patients

If first-line treatment was changed because of INTOLERANCE, the following table defines Optimal Response, Warning, and Failure corresponding to SECOND-LINE TREATMENT for all CML patients in CP, AP, and BP[26]

Evaluation Time Months	Optimal Response	Warning	Failure
Baseline	NA	High Risk OR CCA/Ph+, major route	NA
Month 3	BCR-ABL1^{IS} ≤10%, AND/OR Ph+ ≤35% (PCyR)	BCR-ABL^{IS} >10% AND/OR Ph+ 36-95%	Non CHR AND/OR Ph+ >95%
Month 6	BCR-ABL1^{IS} <1%, AND/OR Ph+ 0 (CCyR)	BCR-ABL1^{IS} 1-10%, AND/OR Ph+ 1-35%	BCR-ABL1^{IS} >10% AND/OR Ph+ > 35%
Month 12	BCR-ABL1^{IS} ≤ 0.1% (MMR)	BCR-ABL1^{IS} > 0.1-1%	BCR-ABL1^{IS} >1% AND/OR Ph+ >0
Any Time	MMR or better**	CCA/Ph- (-7, or 7q-)	Loss of CHR Loss of CCyR Confirmed Loss of MMR* Mutations CCA/Ph+

Abbreviations: TKIs, tyrosine kinase inhibitors; NA, not applicable; Ph+, Philadelphia chromosome positive; Ph-, Philadelphia chromosome negative; CCA/Ph+, Clonal Chromosome Abnormalities in Ph+ cells; CCA/Ph-, Clonal Chromosome Abnormalities in Ph- cells; IS, BCR-ABL transcripts on International Scale,

* In two consecutive tests, of which one has a BCR-ABL1 transcripts level ≥ 1% on International Scale.
** "Better" is defined as MR4 or MR4.5 or MR5

If first-line treatment was changed because of FAILURE, the following table defines Optimal Response, Warning, and Failure corresponding to SECOND-LINE TREATMENT for all CML patients in CP AP, and BP[26]

Time	Optimal Response	Warning	Failure
Baseline	NA	No CHR or Loss of CHR on first-line treatment or Lack of CCyR to first-line TKI or High Risk	NA
3 months	BCR-ABL1^{IS} ≤10% AND/OR Ph+ <65%	BCR-ABL1^{IS} >10% AND/OR Ph+ 65-95%	No CHR, or Ph+ >95%, or New mutations
6 months	BCR-ABL1^{IS} ≤10% AND/OR Ph+ <35% (PCyR)	Ph+ 35-65%	BCR-ABL1^{IS} >10% AND/OR Ph+ >65% AND/OR New mutations
12 months	BCR-ABL1^{IS} <1% AND/OR Ph+ 0 (CCyR)	BCR-ABL1^{IS} 1-10-% AN/OR Ph+ 1-35%	BCR-ABL1^{IS} >10% AND/OR Ph+ >35% AND/OR New mutations
Any Time	MMR or better**	CCA/Ph-(-7 or 7q-) or BCR-ABL1^{IS} > 0.1%	Loss of CHR, or Loss of CCyR, or PCyR New mutations, or Loss of MMR*, or CCA/Ph+

Abbreviations: TKIs, tyrosine kinase inhibitors; NA, not applicable; Ph+, Philadelphia chromosome positive; Ph-, Philadelphia chromosome negative; CCA/Ph+, Clonal Chromosome Abnormalities in Ph+ cells; CCA/Ph-, Clonal Chromosome Abnormalities in Ph- cells; IS, BCR-ABL transcripts on International Scale,
* In two consecutive tests, of which one has a BCR-ABL1 transcripts level ≥ 1% on International Scale.
** "Better" is defined as MR4 or MR4.5 or MR5.

Appendix 6. Sample Patient Diary Card

Take ____mg of the study medication every morning with food This means _____(#) of tablets			
DATE	**DOSE**	**CHECK IF DOSE MISSED**	**REASON FOR MISSED DOSES** **SYMPTOMS/COMMENTS** **CONCOMITANT MEDICATIONS**
Example: 4Jul07-16Jul07	500 mg		Mild headache; Tylenol 250mg tablet
17Jul07 + 18Jul07	0	yes	Forgot meds

SAMPLE

Date of your next visit: _____

Appendix 7. Criteria to Identify Phase of CML

Phase [a, 27,28,]	Findings
Blast Phase	≥30% Blasts in blood or bone marrow Extramedullary Blasts proliferation, apart from spleen If either of these 2 criteria is present, the patient is classified as Blast Phase regardless of other criteria.
Accelerated Phase	15-29% Blasts in blood or bone marrow OR >30% Blasts + Promyelocytes (with Blasts <30%) in blood or bone marrow OR ≥20% Basophils in blood or bone marrow OR Persistent platelets <100 x 10^9/L (not related to therapy)OR Clonal chromosomal abnormalities in Ph+ cells (CCA/Ph +), major route, on treatment
Chronic Phase	<15% Blasts <20% Basophils ≤30% Blasts + Promyelocytes (with Blasts <15%) in blood or bone marrow AND Platelets ≥100 x 10^9/L (unless related to therapy) AND No Extramedullary Blasts (except spleen)

[a] Observance of any one criterion in the worse disease phase achieves that phase as the diagnosis (e.g., 20% basophils alone elevates the diagnosis from CP to AP).

Appendix 8. Eastern Cooperative Oncology Group (ECOG) Performance Status

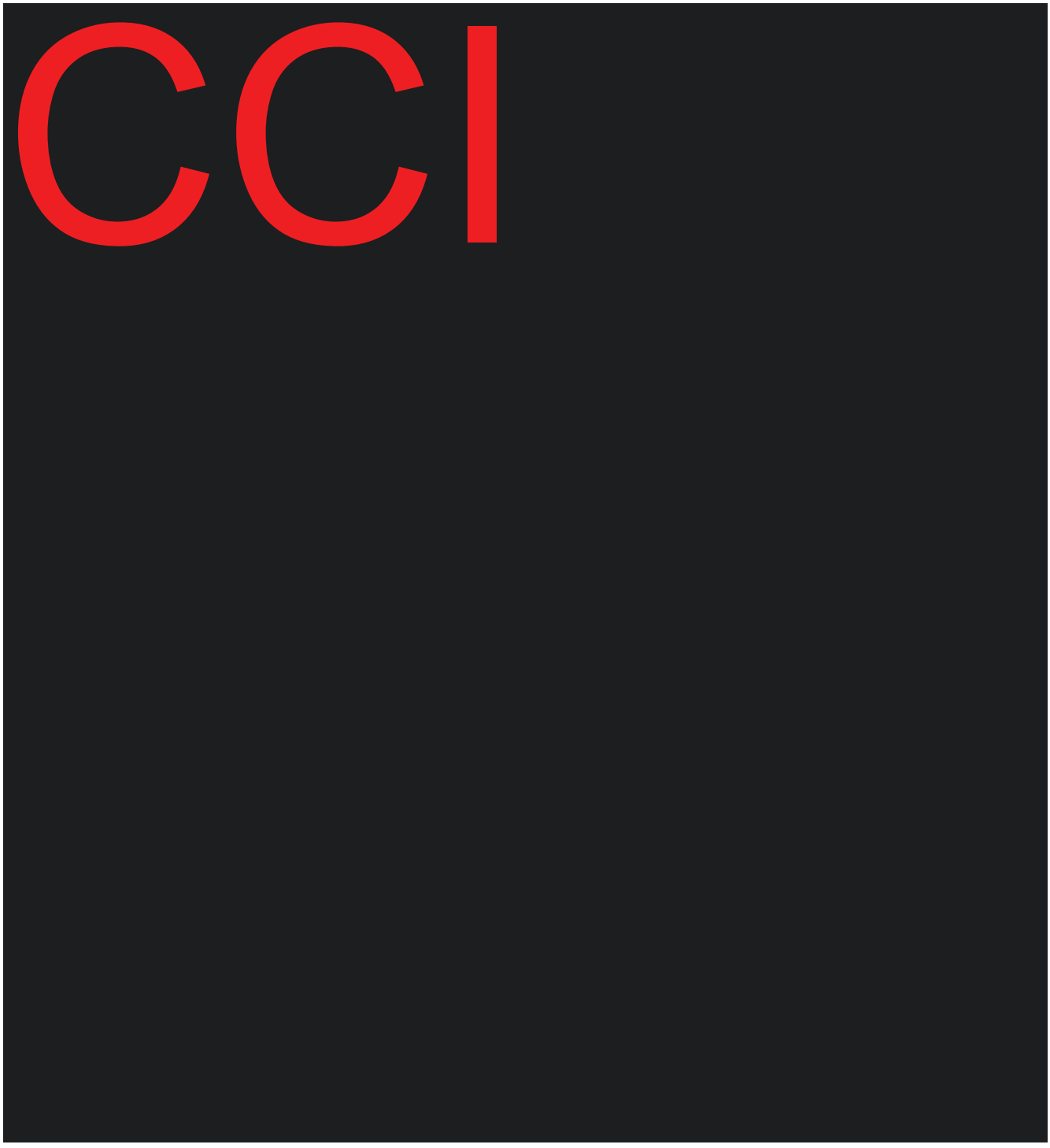
ECOG Grade	Description	Karnofsky Score*
0	**Fully active, able to carry on all pre-disease activities without restriction.**	100
1	**Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (light house work, office work).**	80 or 90
2	**Ambulatory 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.**	10, 20 or 30

* Karnofsky Score is provided for comparison purposes only. Please record ECOG Grade only.

Appendix 9. Local Laboratory Collection Requirements

Hematology Panel
CBC (including Hemoglobin and Hematocrit)
WBC with differential
Platelets
Neutrophils
Liver Function Tests
ALT
AST
Alkaline Phosphatase
Total Serum Bilirubin *
Direct bilirubin*
Indirect bilirubin**
Gamma-glutamyl transferase (GGT)**
Total bile acids**
Acetaminophen drug test and/or protein adduct levels**
Blood Chemistry Panel
Total Calcium
Cholesterol (as clinically indicated)
HDL (as clinically indicated)
LDL (as clinically indicated)
Sodium
BUN or Urea
Creatinine kinase** (as clinically indicated)
Creatinine
Albumin
Potassium (as clinically indicated)
Magnesium (as clinicallyindicated)
Glucose
HbA1C (as clinically indicated)
Phosphorous
Lipase
Amylase
Uric acid
Coagulation Tests
PT or INR
PTT or aPTT
Pregnancy Test
Serum OR Urine (sensitivity of at least 25 mIU/mL)

* Direct bilirubin must be collected if total serum bilirubin is >1.5 x ULN and for Hy's law determination, if appropriate.
** Collected for Hy's Law determination, if appropriate
Note: Hy's Law definition is defined in Section 8.4.1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CCI

Appendix 11. European LeukemiaNet Guidelines for Response in CML

Definitions of Hematologic, Cytogenetic, and Molecular Response[26]

Response by Type	Definitions
Hematologic Complete (CHR)	 WBC <10 x 10^9/L Peripheral Blood Basophils <5% No Peripheral Blood myelocytes, promyelocytes, myeloblasts in the differential Platelet count <450 x 10^9/L Spleen nonpalpable
Cytogenetic * Complete (CCyR) Partial (PCyR) Minor (mCyR) Minimal (minCyR) None (noCyR)	 No Ph+ metaphases 1% to 35% Ph+ metaphases 36% to 65% Ph+ metaphases 66% to 95% Ph+ metaphases >95% Ph+ metaphases
Molecular Deep Molecular Response (MR4, MR4.5) Major (MMR)	 MR4= either (i) detectable disease with <0.01% BCR-ABL1 ^{IS} or (ii) undetectable disease in cDNA with >10 000 ABL1 transcripts MR4.5 =either (i) detectable disease with < 0.0032% BCR-ABL1 ^{IS} or (ii) undetectable disease in cDNA with >32,000 ABL1 transcripts in the same volume of cDNA used to test for BCR-ABL1. Ratio of $BCR\text{-}ABL^{IS}$ ≤0.1%**.

Abbreviations: CHR, complete hematologic response; CCyR, complete cytogenetic response, PCyR, partial cytogenetic response; Ph+, Philadelphia Chromosome positive; MCyR, major cytogenetic response; mCyR, minor cytogenetic response; minCyR, minimal cytogenetic response; noCyR, no cytogenetic response; MR4, MR4.5, deep molecular response; MMR, major molecular response;.

*If bone marrow metaphases cannot be obtained or evaluated by chromosome banding analysis, the definition of CCyR (defined as <1% for FISH) may be based on interphase FISH of blood cells, provided that it is performed with Dual-Color Dual-Fusion or Dual-Fusion FISH probes and at least 200 nuclei are scored. PCyR and CCyR are counted together and reported as MCyR.

**With >=5,000 ABL1 transcripts.

Definitions of Hematologic Response for AP and BP CML[29]*

CHR**	WBC ≤ institutional upper limit of normal (ULN) ANC ≥ 1.0 x 10^9/L Platelet count ≥ 100 x 10^9/L BM Blasts ≤ 5% *** No peripheral blood blasts or promyelocytes; Peripheral blood myelocytes + metamyelocytes < 5%; Basophils in peripheral blood < 5%* No evidence of extramedullary involvement

*The maximum % of basophils in peripheral blood was modified from < 2 to <5% for a less restrictive constraint and alignment with the CHR criteria for CP CML patients according to ELN guidelines.

**If an on- treatment CBC is scheduled within 1 week from the last platelet transfusion or last dose of G-CSF, it should be considered "Not Evaluable" for hematological response assessment, and a CBC should be repeated at least 1 week from the last platelet transfusion or last dose of G-CSF received.

***CHR for AP/BP that the 5% BM blasts is only required when a BM differential is available.

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