NON-INTERVENTIONAL (NI) STUDY REPORT (ABBREVIATED)

PASS information

Title	A Non-Interventional Study of Bosutinib in Patients With Previously Treated Chronic Phase Chronic Myelogenous Leukemia (CML)
Protocol number	B1871042
Version identifier of the final study report	23 June 2015
Date of last version of the final study report	Not Applicable
EU Post Authorisation Study (PAS) register number	ENCEPP/SDPP/5461
Active substance	Bosutinib
Medicinal product	Bosulif®
Product reference	EU/1/13/818/001 -04
Procedure number	EMEA/H/C/002373
Marketing Authorisation Holder (MAH)	Pfizer Limited
Joint PASS	No

Research question and objectives	This Non-Interventional Study (NIS) will aim to capture real-world treatment related adverse events (AEs) and discontinuation rates and evaluate effective dosing strategies employed in clinical practice when managing these AEs.
Country of study	United States
Author	NI Study Lead: Fiona An, MD, Senior Director, US Oncology Medical, Pfizer, Inc.

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	Pfizer Limited Ramsgate Road, Sandwich, Kent CT130NJ United Kingdom
MAH contact person	NI Study Lead: Graciela Mabel Woloj PhD, Senior Director, Team Leader Oncology, Pfizer, Inc.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

None

Annex 1. List of stand-alone documents

1. ABSTRACT (STAND-ALONE DOCUMENT)

Not Applicable.

2. LIST OF ABBREVIATIONS

	Definition
AE	**Adverse event**
Bcr-Abl	**Breakpoint cluster region-Abelson**
CCyR	**Complete cytogenic response**
CI	**Confidence intervals**
CIOMS	**Council for International Organizations of Medical Sciences**
CML	**Chronic myelogenous leukemia**
CP	**Chronic phase**
CRF	**Case report form**
DC	**Discontinuation**
EIU	**Exposure in-utero**
ELN	**European LeukemiaNet**
GEP	**Good Epidemiological Practice**
GPP	**Good Pharmacoepidemiology Practices**
IEA	**International Epidemiological Association**
IEC	**Independent Ethics Committee**
IRB	**Institutional Review Board**
IRIS	**International Randomized Study of Interferon Versus STI571**
ISPE	**International Society for Pharmacoepidemiology**
ISPOR	**International Society for Pharmacoeconomics and Outcomes Research**

MCyR	**Major cytogenic response**
NI	**Non-interventional**
PASS	**Post-Authorisation Safety Study**
PDGFR	**Platelet derived growth factor receptor**
SAE	**Serious adverse event**
SAP	**Statistical Analysis Plan**
SEER	**Surveillance Epidemiology and End Results**
TKIs	**Tyrosine kinase inhibitors**

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site that enrolled subjects are listed in Appendix 3.1.

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Fiona An, MD	Pfizer NI study lead, Senior Director, US Oncology Medical	Pfizer, Inc.
Graciela Mabel Woloj, PhD	Senior Director, Team Leader, Global Oncology	Pfizer, Inc.

Lead Country Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Jorge E. Cortes, MD	Lead Investigator, Distinguished Professor, Leukemia Research Deputy Chairman, Section of AML, CML, Department of Leukemia	MD Anderson Cancer Center

4. OTHER RESPONSIBLE PARTIES

Not Applicable.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of Institutional Review Board (IRB) approval of protocol The IRB approval dates for the protocol and any amendments is provided in Appendix 3.2 for the site that enrolled subjects.	27 February 2014	27 February 2014	Not applicable
Start of data collection	01 May 2014	27 August 2014	Not applicable
End of data collection	27 August 2016	07 May 2015	This study was terminated early. Termination date is 11 March 2015
Registration in the EU PAS register	23 December 2013	23 December 2013	Not applicable
Abbreviated report of study results	15 February 2017	23 June 2015	Study was terminated early due to recruitment difficulty

6. RATIONALE AND BACKGROUND

Chronic myelogenous leukemia is a hematopoietic stem cell disease that accounted for 11.5% of new leukemia cases in 2012.[1] According to Surveillance Epidemiology and End Results (SEER) data, the incidence of CML between 2005 and 2009 was 1.6 cases per 100,000 persons.[2] In 2012, the American Cancer Society estimated 5,430 new cases of CML.[1]

SEER data also estimated the prevalence of CML to be over 29,000 cases in 2012.[2] However, this figure may represent an underestimate of CML prevalence due to two factors. First, SEER CML prevalence data are placed in the common category of leukemia.[2] Second, SEER estimates do not account for the reduction in all-cause mortality rate of CML resulting from the availability and use of TKIs over the last decade.[3]

In 2012, Huang and colleagues[4] developed a model to estimate the prevalence of CML in the US, which took into account the incidence and mortality rate of CML, as well as projections of growth in the overall and aging population. The model estimated 70,000 cases of CML in 2010. Prevalence is projected to steadily increase until reaching a near plateau of over 180,000 cases in 2050.[4]

Treatment for CML has improved substantially in the past 20 years, especially since the introduction of oral BCR-ABL tyrosine kinase inhibitors (TKIs) more than a decade ago. Before the advent of therapy with TKIs, the median survival of subjects with CML was approximately 6 years.[5] International Randomized Study of Interferon Versus STI571 (IRIS) trial[6] published in 2003, imatinib (Gleevec®, Novartis Pharmaceuticals Corporation, East Hanover, NJ), the first TKI to be approved to treat Ph+ CML, quickly replaced interferon-□ as the standard of care. Subjects from the IRIS study have been followed for 8 years and data show that imatinib prolongs survival in newly diagnosed subjects with CP CML with an overall survival rate of 85% and 93% when only subjects with CML-related deaths and those who have not received stem cell transplant are considered.[7] The more potent second generation TKIs, dasatinib (Sprycel®, Bristol-Myers Squibb Company, Princeton, NJ) and nilotinib (Tasigna®, Novartis Pharmaceuticals Corporation, East Hanover, NJ), were approved by the US Food and Drug Administration (FDA) in 2006 and 2007, respectively, as second-line agents in subjects with imatinib resistance or intolerance, and in 2010 both agents received FDA approval for treatment of newly diagnosed adults with Ph+ CML in CP CML.[8,9]

Despite these advances in the treatment of CML treatment, an unmet need remains for many CML subjects who are resistant or intolerant to one or more TKIs. Approximately one-third of CML subjects treated with imatinib fail to achieve an optimal endpoint.[10] Among subjects who are resistant or intolerant to imatinib and require treatment with dasatinib or nilotinib, approximately half of them do not maintain durable cytogenetic response. A clinical study evaluating second-line treatment with dasatinib (n=91) or nilotinib (n=25) in 119 CP CML subjects who failed imatinib therapy reported that 52% of subjects discontinued therapy due to the development of resistance or intolerance.[11]

Bosutinib offers another treatment option for subjects who are resistant or intolerant to a prior therapy. Bosutinib, a member of the dual ABL/SRC family of kinases was approved in the US on September 4, 2012 for the treatment of adult subjects with chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy.[12] Later in 2012, two more therapies for the treatment of previously treated CML subjects were approved by FDA, omacetaxine (Synribo®, Teva Pharmaceuticals USA Inc, North Wales, PA) and ponatinib (Iclusig®, ARIAD Pharmaceuticals Inc, Cambridge, MA). Omacetaxine is indicated for the treatment of adult subjects with chronic or accelerated phase\CML with resistance and/or intolerance to two or more TKIs.[13] Ponatinib is a kinase inhibitor indicated for the treatment of adult subjects with chronic, accelerated or blast phase CML or Ph+ acute lymphoblastic leukemia (Ph+ ALL) that are resistant or intolerant to prior TKIs.[14]

Bosutinib has demonstrated activity against many of the BCR/ABL kinase domain mutations resistant to imatinib, nilotinib and dasatinib, except T315I, with minimal inhibition of mast/stem cell growth factor receptor (KIT) and Platelet Derived Growth Factor Receptor (PDGFR). Bosutinib showed efficacy in chronic, accelerated and blast phase CML when evaluated in a single arm multi-center Phase I-II trial that enrolled 570 subjects with resistance or intolerance to prior TKI therapy. In the cohort of subjects with CP CML treated with first-line imatinib and second-line bosutinib (n=288), major cytogenetic response (MCyR) at 24 weeks was achieved in 31% of subjects (33% of subjects resistant to imatinib, n=200; and 27% of subjects intolerant to imatinib, n=88). Complete hematologic response (CHR), MCyR and complete cytogenetic response (CCyR) were achieved in 86%, 53%, and 41% of subjects respectively in this cohort after a median followup of 24 months. In the cohort of subjects with CP CML pretreated with more than one TKI (n=118), CHR, MCyR and CCyR were achieved in 73%, 32%, and 24% of subjects respectively with a median follow-up of 28.5 months of bosutinib therapy. Bosutinib has a favorable safety profile. Diarrhea, nausea, vomiting and rash were the most frequently reported non-hematological Grade 1 and 2 adverse events. Grade 3 or 4 diarrhea was reported in 8% and 4% of subjects, respectively. Thrombocytopenia (25%), neutropenia (19%) and anemia (8%) were the most frequent Grade 3 and 4 hematological adverse events. Bosutinib was also associated with minimal effect in QTc interval prolongation and a low incidence of pleural effusions, muscle cramps, musculoskeletal events and cardiac toxicities that may be seen with other TKIs.[12,15] Approximately 20% of subjects in this clinical trial discontinued bosutinib due to AEs. Given the importance of persistence and adherence to therapy in maintaining a durable response,

this NIS will aim to capture real world discontinuation rates and evaluate effective dosing strategies employed in clinical practice when managing treatment related AEs.

CP CML is now a highly treatable chronic disease with a potential "functional cure". As with choice of front-line therapy, optimal therapy for previously treated CML requires a high degree of tolerability and adherence. Subjects transition to further lines of therapy due to resistance or intolerance and selection of therapy depends on previous lines of therapy, subjects' co-morbidities, and individual preferences.

Given the availability of multiple targeted agents for CML, each with their own unique safety and tolerability profile, it is important to understand real world practice patterns in the US. This NIS will evaluate real world practices by collection of data in subjects with CP CML resistant or intolerant to previous treatments who are treated with bosutinib. The main objectives are to describe the safety profile and discontinuations from treatment due to adverse events in a real world setting. Adverse events data as well as treatment monitoring and response assessments will be collected during the first 12 months of bosutinib treatment in approximately 170 CP CML subjects from academic and community centers in the US. It is important to note that subjects enrolled in clinical trials may not fully represent real world populations of subjects given the preselection criteria outlined in the inclusion and exclusion criteria of these types of studies. The data captured in this NIS will assist in a better understanding of AE early identification of successful AE management strategies, and to detect areas of concern where consistent treatment is not maintained. The study will also collect data on type and frequency of treatment response monitoring that will provide documentation of how efficacy is assessed in treated CP CML subjects, and if National Comprehensive Cancer Network (NCCN)[15] or European LeukemiaNet (ELN)[16] guidelines recommendations are being used in real world practice.

The most frequent AEs observed with bosutinib (ie, gastrointestinal and liver toxicity) primarily occurred during the first 6 months of treatment in the clinical trials. There is mounting evidence that early response to TKI (at 3 and/or 6 months) predicts for stable response, further reduction in minimal residual disease, and freedom from relapse/ progression events.[17] The 12 month duration of the study was selected to allow adequate time to collect safety, and response assessments in this real world setting.

Baseline characteristics of subjects prescribed bosutinib provided information on sequence of therapeutic choices, previous regimen(s), and duration and reason for switching therapies. Data from this study helps to understand the reasons physicians change therapy to and from bosutinib in the current US environment.

These data and results help to provide clinically important information on bosutinib.

This NIS has no directed diagnostics, interventions, or visits. Usual care practice determined the schedule of visits as well as monitoring for safety and efficacy.

This NIS is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. The primary objectives of this NIS are to:

1. Determine the rate of treatment related AEs in CP CML subjects treated with bosutinib.
2. Observe the discontinuation (DC) rate due to treatment related AEs and compare with the DC rate in subjects with chronic phase CML resistant or intolerant to previous treatment(s) observed in the clinical trials.

7.2. Secondary objectives will include a descriptive assessment of:

1. Safety (treatment emergent AEs, treatment related AEs, AEs leading to treatment modification, management of selected AEs).
2. Subject self-reported adherence information via the Morisky scale and quality of life via a leukemia specific quality of life questionnaire (FACT-leu_v4).
3. Treatment with bosutinib in a real world setting (dosing, treatment duration, adherence, reasons for dose reductions/ delay/ discontinuations, timing and tests performed during treatment, concomitant medications).
4. Responses (results of hematological, cytogenetic and/or molecular testing, and best response by investigator assessment).
5. Baseline information/prior treatments to describe the subject population treated with bosutinib (demographics, medical history, time from diagnosis to enrollment, prior treatments and best response to prior treatments, reason for switching of prior therapies, last known hematological, cytogenetic and/ or molecular response status).

8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

9.1. Study design

The study is terminated early by the sponsor due to slow enrollment. This was a prospective, observational, non-interventional study of previously treated subjects with CP CML who were prescribed or started with bosutinib. The study was designed to collect real world data in community and academic centers. One hundred seventy subjects were planned to enroll to 30 sites in the US. Study duration was planned for 2.5 years, assuming 18 months of recruitment and 12 months of subject follow-up. All treatment decisions and type and timing of disease monitoring were at the discretion of the treating physician and subject. Data was to be recorded for 12 months after starting bosutinib or until subject withdrawal from the study, death or study discontinuation. Because of the early termination, only 3 subjects were enrolled into the study. Subjects IDs are 10021001, 10121001 and 10161001, respectively.

9.2. Setting

The study planned to enroll subjects according to the eligibility criteria in the US. Every subject who met eligibility criteria could participate in the study. Subjects with active cardiovascular disease or other comorbidities that may have been excluded to participate in another bosutinib clinical trial were not excluded. The study population included men and women ages 18 years and older with the diagnosis of CP CML that had been treated with at least one previous TKI and had been prescribed or started treatment with bosutinib. Baseline visit should occur within 7 days of starting bosutinib. Approximately 170 subjects were planned to enroll into this NIS over an 18 month enrollment period followed by a 12 month observation period. Physicians prescribed bosutinib and any other therapy to subjects at their discretion, and assessed subjects per their usual practice. Data were collected from medical records used in routine medical practice. Due to the sponsor decision to terminate the study early, only 3 subjects enrolled into the study.

9.3. Subjects

Subjects included those who had not yet started treatment or may have taken bosutinib for no more than 7 days at the time of baseline visit. This study excluded newly diagnosed CML subjects who had not received any previous TKI treatment, concomitant use of any FDA approved or investigational agents for Ph+ CML (eg, omacetaxine), and subjects in accelerated or blast phase CML at screening/baseline.

9.4. Variables

AE rates and discontinuation rates due to treatment related AEs were be recorded along with bostutinib dose, regimen and duration including dose reductions, discontinuations and doses withheld due to AEs during the 12 month follow-up period.

9.5. Data sources and measurement

Management of bosutinib toxicities and hematological, cytogenetic and molecular testing to monitor subject response were conducted according to a site's routine medical practice and were captured on a standardized case report form for this study.

9.6. Bias

Subject selection constitutes a potential selection bias classically associated with NI studies. Subjects who agreed to participate may differ from those who declined to participate.

Measurement Bias

Measurement biases may relate to site-specific differences in subject management. As no guidelines existed for the monitoring and follow-up of subjects, and no schedule of visits was planned, therapeutic management and safety/efficacy monitoring, as well as investigator assessment of subject response can differ from one site to another.

9.7. Study Size

Approximately 170 subjects from 30 US sites (academic and community centers) were planned for the study. However, only 3 subjects completed the study at the time of study termination.

9.8. Data transformation

No data transformations were performed in this study.

9.9. Statistical methods

9.9.1. Main summary measures

Descriptive statistics was planned in the SAP for the study. However, due to the small sample size, 3 subjects, all subjects' data is listed and no summary is provided.

9.9.2. Main statistical methods

None.

9.9.3. Missing values

Missing values are not imputed.

9.9.4. Sensitivity analyses

None.

9.9.5. Amendments to the statistical analysis plan

None.

9.10. Quality control

Appropriate training relevant to the study was given to site's investigational staff. Regular contact with the sites and remote review of data was performed to verify that study site procedures were compliant with the protocol and that data was accurately recorded in the CRFs. The investigators' had the responsibility for the collection and reporting of all clinical safety and laboratory data entered in the CRFs and any other data collection forms.

9.11. Protection of human subjects

Subject information and consent

Written informed consent (Appendix 6) was obtained prior to the subject entering the study (before initiation of study protocol-specified procedures) by study personnel; the nature, purpose, and duration of the study was explained to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

Institutional Review Board (IRB)

The final protocol, any amendments, and informed consent documentation were reviewed and approved by an Institutional Review Board(s) (IRB) for each site participating in the study.

Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Outcomes Research Practices issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Draft Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

10. RESULTS

10.1. Participants

The study was terminated early due to slow enrollment. At the time of termination, 3 subjects were enrolled and completed the end of the study termination page.

10.2. Descriptive data

Three subjects enrolled into the study, 1 is a male and 2 are females. Basic demographic information is provided in Appendix 7.4.

10.3. Outcome data

Primary analyses were the AE rate and discontinuation rate due to treatment related AEs. Due to the small sample sizes, the summary statistics is not provided.

Of the 3 subjects, 2 (10021001 and 10161001) subjects had at least one AE related to the study drug. Subject 10021001 had Diarrhea started on 07Jan2015, no action was taken, severity is mild and the AE is not serious. Subject 10161001 reported 7 AEs, all are related to the treatment, and one of them, abdominal pain, is serious.

None of the subjects discontinued from the study due to treatment related AEs.

10.4. Main results

The study is terminated early. There is no sufficient data to present meaningful result.

10.5. Other analyses

None.

10.6. Adverse events / adverse reactions

Two out of the 3 subjects developed AEs, 10021001 had 1 non-serious AE, diarrhea; 10161001 had 1 serious and life-threatening AE, abdominal pain, and 6 non-serious AEs. Listing of AEs is available in Appendix 7.7.

Subject 10161001, a 47-year-old Hispanic female subject started to receive bosutinib orally from 10 Oct2014 and ongoing at 500 mg daily for chronic myeloid leukemia (CML), experienced Grade 4 Abdominal Pain from 10 November 2014 through 11 November 2014 with associated non-serious events of vomiting and diarrhea. The subject was hospitalized for two days and received IV Opioid Medication. The outcome of the SAE abdominal pain and non-serious event vomiting/diarrhea was recovered with sequel on 11Nov2014. The study drug was not interrupted. Relevant medical history included chronic myeloid leukemia ongoing from 2001 and gastro esophageal reflux disease (GERD) ongoing from 2012. The event, per Investigator, was considered related to the study drug. Serious adverse event is found in Table 15.3.9.

11. DISCUSSION

11.1. Key results

Sample size is small in assessing the impact of the AE rate related to the treatment or the discontinuation rate related to the treatment on the risk-benefit balance of the product.

11.2. Limitations

The biggest limitation of the study is the small sample size, n=3.

11.3. Interpretation

The primary objective of the study is to assess the safety profile in CML subjects who developed resistance to the prior therapy and who were treated with bosutinib in the real world practice. However, the study is terminated early and no meaningful interpretation can be drawn from the 3 subjects' data.

11.4. Generalisability

Not Applicable.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

The study is not conclusive due to small sample size.

14. REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10-29.
2. Surveillance Epidemiology and End Results. SEER Stat Fact Sheets: chronic myeloid leukemia. http://seer.cancer.gov/statfacts/html/cmyl.html. Accessed February 19, 2013.
3. Rohrbacher M, Hasford J. Epidemiology of chronic myeloid leukemia (CML). *Best Pract Res Clin Haematol*. 2009;22(3):295-302.
4. Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy.*Cancer*. 2012;118(12):3123-3127.
5. Hehlmann R, Heimpel H, Hasford J, et al. Randomized comparison of interferon-a with busulfan and hydroxyurea in chronic myelogenous leukemia. *Blood*. 1994;84(12):4064-4077.
6. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and lowdose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia*. N Engl J Med* 2003; 348(11): 994–1004.
7. Deininger M, O'Brien SG, Guilhot F, et al. International Randomized Study of Interferon vs. ST1571 (IRIS) 8-year follow-up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase treated with imatinib [abstract]. *Blood*. 2009;114 (22 suppl):462. Abstract 1126.
8. Sprycel (dasatinib) Prescribing Information. Princeton, NJ: Bristol Myers-Squibb Company, 2013.
9. Tasigna (nilotinib) Prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2013.
10. Alvarado Y, Kantarjian H, O'Brien S, et al. Significance of suboptimal response to imatinib, as defined by the European LeukemiaNet, in the long-term outcome of patients with early chronic myeloid leukemia in chronic phase. *Cancer*.2009;115(16):3709–3718.
11. Milojkovic D, Apperley JF, Gerrard G, et al. Responses to second-line tyrosine kinase inhibitors are durable: an intention-to-treat analysis in chronic myeloid leukemia patients. *Blood.* 2012;119(8):1838–1843.
12. Bosulif (bosutinib) Prescribing Information. New York, NY: Pfizer Pharmaceuticals Corporation, 2013.
13. Omacetaxine (Synribo) Prescribing Information Teva Pharmaceuticals USA, Inc. North Wales, PA, 2012.
14. Ponatinib (Iclusig) prescribing information. ARIAD Pharmaceuticals, Inc, 2013.
15. NCCN Clinical Practice Guidelines in Oncology. Chronic Myelogenous Leukemia. V.4.2013. NCCN.org.
16. Baccarani M, Deininger MW, Rosti G, Hochhaus A, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: *Blood*.2013;122(6):872-84.
17. Milojkovic D, Nicholson E, Apperley JF, et al. Early prediction of success or failure of treatment with second-generation tyrosine kinase inhibitors in patients with chronic myeloid leukemia. *Haematologica* 2010;95(2):224-231.

15. LIST OF SOURCE TABLES AND FIGURES

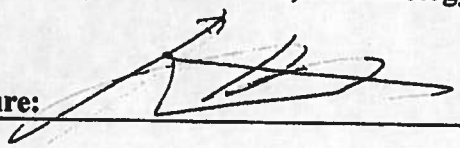
APPENDIX 1. SIGNATURES

PROTOCOL NUMBER: B1871042

TITLE OF STUDY: A Non-Interventional Study of Bosutinib in Patients With Previously Treated Chronic Phase Chronic Myelogenous Leukemia (CML)

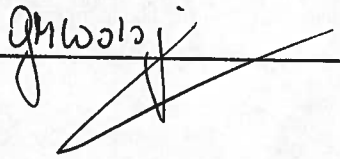
Confirmation: I confirm that this Non-Interventional (NI) study report, which is final in content and has been printed from its definitive source, is a complete and accurate representation of the data and statistical analyses from this study.

Pfizer NI Study Lead
Fiona An, MD, Senior Director, US Oncology, Medical, Pfizer, Inc.

Signature:  **Date:** June 30, 2015

Approval of non-interventional study report

Pfizer NI CSR Approver
Graciela Mabel Woloj, PhD, Senior Director, USMA, OBU, Pfizer, Inc.

Signature:  **Date:** July 20, 2015

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A Non-Interventional Study of Bosutinib in Patients With Previously Treated Chronic Phase Chronic Myelogenous Leukemia (CML)
Protocol number	B1871042
Protocol version identifier	28 October 2013
Date of last version of protocol	Non Applicable
EU Post Authorisation Safety Study (PASS) register number	Study not registered
Active substance	Bosutinib
Medicinal product	Bosulif®
Product reference	EU/1/13/818/001 -04
Procedure number	EMEA/H/C/002373
Marketing Authorisation Holder (MAH)	Pfizer Limited
Joint PASS	No
Research question and objectives	This Non-Interventional Study (NIS) will aim to capture real-world treatment related adverse events (AEs) and discontinuation rates and evaluate effective dosing strategies employed in clinical practice when managing these AEs.
Country of study	United States

Author	NI Study Lead: Graciela Mabel Woloj, Senior Director, USMA, OBU, Pfizer

Marketing Authorisation Holder

Marketing Authorisation Holder	Pfizer Limited Ramsgate Road, Sandwich, Kent CT130NJ United Kingdom
MAH contact person	NI Study Lead: Graciela Mabel Woloj, Senior Director, USMA, OBU, Pfizer

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
Bcr-Abl	Breakpoint cluster region-Abelson
CCyR	Complete cytogenic response
CHR	Complete hematologic response
CI	Confidence intervals
CIOMS	Council for International Organizations of Medical Sciences
CML	Chronic myelogenous leukemia
CP	Chronic phase
CRF	Case report form
DC	Discontinuation
DCF	Data clarification form
EIU	Exposure in-utero
ELN	European LeukemiaNet
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRIS	International Randomized Study of Interferon Versus STI571
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KIT	A mast/stem cell growth factor receptor
MCyR	Major cytogenic response
NCCN	National Comprehensive Cancer Network
NI	Non-interventional

NIS	Non-interventional study
PASS	Post-Authorisation Safety Study
PDGFR	Platelet derived growth factor receptor
Ph+	Philadelphia chromosome-positive
Ph+ALL	Ph+ acute lymphoblastic leukemia
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SEER	Surveillance Epidemiology and End Results
TKIs	Tyrosine kinase inhibitors

3. RESPONSIBLE PARTIES

Lead Principal Investigator of the Protocol

Name, degree(s)	Title	Affiliation	Address
Jorge E. Cortes, MD	Distinguished Prof. Leukemia Research Deputy Chairman, Section of AML CML, Department of Leukemia	MD Anderson Cancer Center	1515 Holcombe Boulevard ,Unit 428, Houston, TX 77030

4. ABSTRACT

A Non-Interventional Study of Bosutinib in Patients With Previously Treated Chronic Phase Chronic Myelogenous Leukemia (CML)

BACKGROUND: Despite the advances in CML treatment, an unmet need remains for many patients who are resistant or intolerant to one or more tyrosine kinase inhibitors (TKIs). Bosutinib offers another treatment option for patients who are resistant or intolerant to a prior therapy. Given the availability of multiple targeted agents for CML, each with their own unique safety and tolerability profile, it is important to understand real world practice patterns in the US. This Non-Interventional Study (NIS) will evaluate real world practices by collection of data in patients with chronic phase (CP) CML resistant or intolerant to previous treatments who are treated with bosutinib.

OBJECTIVES: The main objectives are to describe the safety profile and discontinuations from treatment due to treatment related adverse events (AEs) in a real world setting. Adverse events as well as treatment monitoring and response assessments will be collected during the first 12 months of bosutinib treatment.

STUDY DESIGN: A prospective, observational, NIS

POPULATION: Enrolled patients resistant or intolerant to previous therapy for Philadelphia chromosome-positive (Ph+) or Breakpoint Cluster Region-Abelson (BCR-ABL) CP CML who are prescribed bosutinib. Patients include those who have not yet started treatment or may have taken bosutinib for no more than 7 days at the time of baseline visit. This study excludes newly diagnosed CML patients who have not received any previous TKI treatment, concomitant use of any FDA approved or investigational agents for Ph+ CML (eg, omacetaxine), and patients in accelerated or blast phase CML at screening/baseline.

VARIABLES: AE rates and discontinuation rates due to treatment related AEs will be recorded along with bostutinib dose, regimen and duration including dose reductions, discontinuations and doses withheld due to AEs during the 12 month follow-up period.

DATA SOURCES: Management of bosutinib toxicities and hematological, cytogenetic and molecular testing to monitor patient response will be conducted according to a site's routine medical practice and will be captured on a standardized case report form for this study.

STUDY SIZE: Approximately 170 patients from 30 US sites (academic and community centers) will be enrolled. Study duration will be approximately 2.5 years, assuming 18 months of recruitment and 12 months of patient follow-up.

DATA ANALYSIS: Primary analysis of AE rates and DC rates due to treatment related AEs will be summarized with descriptive statistics and 95% confidence intervals. Descriptive statistics will be used to summarize all other endpoints. These analyses will be stratified by type of centers, previous treatment, and line of therapy separately and then for all patients together.

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned date
Start of data collection	February 2014
End of data collection	August 2016
Registration in the EU PAS register	December 2013
Final clinical study report	February 2017

7. INDICATION

Bosulif® (bosutinib) is a kinase inhibitor indicated for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy.

8. RATIONALE AND BACKGROUND

Chronic myelogenous leukemia is a hematopoietic stem cell disease that accounted for 11.5% of new leukemia cases in 2012.[1] According to Surveillance Epidemiology and End Results (SEER) data, the incidence of CML between 2005 and 2009 was 1.6 cases per 100,000 persons.[2] In 2012, the American Cancer Society estimated 5,430 new cases of CML.[1]

SEER data also estimated the prevalence of CML to be over 29,000 cases in 2012.[2] However, this figure may represent an underestimate of CML prevalence due to two factors. First, SEER CML prevalence data are placed in the common category of leukemia.[2] Second, SEER estimates do not account for the reduction in all-cause mortality rate of CML resulting from the availability and use of TKIs over the last decade.[3]

In 2012, Huang and colleagues[4] developed a model to estimate the prevalence of CML in the US, which took into account the incidence and mortality rate of CML, as well as projections of growth in the overall and aging population. The model estimated 70,000 cases of CML in 2010. Prevalence is projected to steadily increase until reaching a near plateau of over 180,000 cases in 2050.[4]

Treatment for CML has improved substantially in the past 20 years, especially since the introduction of oral BCR-ABL tyrosine kinase inhibitors (TKIs) more than a decade ago. Before the advent of therapy with TKIs, the median survival of patients with CML was approximately 6 years.[5] International Randomized Study of Interferon Versus STI571 (IRIS) trial[6] published in 2003, imatinib (Gleevec®, Novartis Pharmaceuticals Corporation, East Hanover, NJ), the first TKI to be approved to treat Ph+ CML, quickly replaced interferon-α as the standard of care. Patients from the IRIS study have been followed for 8 years and data show that imatinib prolongs survival in newly diagnosed patients with CP CML with an overall survival rate of 85% and 93% when only patients with CML-related deaths and those

who have not received stem cell transplant are considered.[7] The more potent second generation TKIs, dasatinib (Sprycel®, Bristol-Myers Squibb Company, Princeton, NJ) and nilotinib (Tasigna®, Novartis Pharmaceuticals Corporation, East Hanover, NJ), were approved by the US Food and Drug Administration (FDA) in 2006 and 2007, respectively, as second-line agents in patients with imatinib resistance or intolerance, and in 2010 both agents received FDA approval for treatment of newly diagnosed adults with Ph+ CML in CP CML.[8,9]

Despite these advances in the treatment of CML treatment, an unmet need remains for many CML patients who are resistant or intolerant to one or more TKIs. Approximately one-third of CML patients treated with imatinib fail to achieve an optimal endpoint.[10] Among patients who are resistant or intolerant to imatinib and require treatment with dasatinib or nilotinib, approximately half of them do not maintain durable cytogenetic response. A clinical study evaluating second-line treatment with dasatinib (n=91) or nilotinib (n=25) in 119 CP CML patients who failed imatinib therapy reported that 52% of patients discontinued therapy due to the development of resistance or intolerance.[11]

Bosutinib offers another treatment option for patients who are resistant or intolerant to a prior therapy. Bosutinib, a member of the dual ABL/SRC family of kinases was approved in the US on September 4, 2012 for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy.[12] Later in 2012, two more therapies for the treatment of previously treated CML patients were approved by FDA, omacetaxine (Synribo®, Teva Pharmaceuticals USA Inc, North Wales, PA) and ponatinib (Iclusig®, ARIAD Pharmaceuticals Inc, Cambridge, MA). Omacetaxine is indicated for the treatment of adult patients with chronic or accelerated phase\CML with resistance and/or intolerance to two or more TKIs.[13] Ponatinib is a kinase inhibitor indicated for the treatment of adult patients with chronic, accelerated or blast phase CML or Ph+ acute lymphoblastic leukemia (Ph+ ALL) that are resistant or intolerant to prior TKIs.[14]

Bosutinib has demonstrated activity against many of the BCR/ABL kinase domain mutations resistant to imatinib, nilotinib and dasatinib, except T315I, with minimal inhibition of mast/stem cell growth factor receptor (KIT) and Platelet Derived Growth Factor Receptor (PDGFR). Bosutinib showed efficacy in chronic, accelerated and blast phase CML when evaluated in a single arm multi-center Phase I-II trial that enrolled 570 patients with resistance or intolerance to prior TKI therapy. In the cohort of patients with CP CML treated with first-line imatinib and second-line bosutinib (n=288), major cytogenetic response (MCyR) at 24 weeks was achieved in 31% of patients (33% of patients resistant to imatinib, n=200; and 27% of patients intolerant to imatinib, n=88). Complete hematologic response (CHR), MCyR and complete cytogenetic response (CCyR) were achieved in 86%, 53%, and 41% of patients respectively in this cohort after a median followup of 24 months. In the cohort of patients with CP CML pretreated with more than one TKI (n=118), CHR, MCyR and CCyR were achieved in 73%, 32%, and 24% of patients respectively with a median follow-up of 28.5 months of bosutinib therapy. Bosutinib has a favorable safety profile. Diarrhea, nausea, vomiting and rash were the most frequently reported non-hematological Grade 1 and 2 adverse events. Grade 3 or 4 diarrhea was reported in 8% and 4% of patients, respectively. Thrombocytopenia (25%), neutropenia (19%) and anemia (8%) were the most

frequent Grade 3 and 4 hematological adverse events. Bosutinib was also associated with minimal effect in QTc interval prolongation and a low incidence of pleural effusions, muscle cramps, musculoskeletal events and cardiac toxicities that may be seen with other TKIs.[12,15] Approximately 20% of patients in this clinical trial discontinued bosutinib due to AEs. Given the importance of persistence and adherence to therapy in maintaining a durable response, this NIS will aim to capture real world discontinuation rates and evaluate effective dosing strategies employed in clinical practice when managing treatment related AEs.

CP CML is now a highly treatable chronic disease with a potential "functional cure". As with choice of front-line therapy, optimal therapy for previously treated CML requires a high degree of tolerability and adherence. Patients transition to further lines of therapy due to resistance or intolerance and selection of therapy depends on previous lines of therapy, patients' co-morbidities, and individual preferences.

Given the availability of multiple targeted agents for CML, each with their own unique safety and tolerability profile, it is important to understand real world practice patterns in the US. This NIS will evaluate real world practices by collection of data in patients with CP CML resistant or intolerant to previous treatments who are treated with bosutinib. The main objectives are to describe the safety profile and discontinuations from treatment due to adverse events in a real world setting. Adverse events data as well as treatment monitoring and response assessments will be collected during the first 12 months of bosutinib treatment in approximately 170 CP CML patients from academic and community centers in the US. It is important to note that patients enrolled in clinical trials may not fully represent real world populations of patients given the preselection criteria outlined in the inclusion and exclusion criteria of these types of studies. The data captured in this NIS will assist in a better understanding of AE early identification of successful AE management strategies, and to detect areas of concern where consistent treatment is not maintained. The study will also collect data on type and frequency of treatment response monitoring that will provide documentation of how efficacy is assessed treated CP CML patients, and if National Comprehensive Cancer Network (NCCN)[15] or European LeukemiaNet (ELN)[16] guidelines recommendations are being used in real world practice.

The most frequent AEs observed with bosutinib (ie, gastrointestinal and liver toxicity) primarily occurred during the first 6 months of treatment in the clinical trials. There is mounting evidence that early response to TKI (at 3 and/or 6 months) predicts for stable response, further reduction in minimal residual disease, and freedom from relapse/ progression events.[17] The 12 month duration of the study was selected to allow adequate time to collect safety, and response assessments in this real world setting.

Baseline characteristics of patients prescribed bosutinib will provide information on sequence of therapeutic choices, previous regimen(s), and duration and reason for switching therapies. Data from this study will help to understand the reasons physicians change therapy to and from bosutinib in the current US environment.

These data and results will help to provide clinically important information on bosutinib.

This NIS has no directed diagnostics, interventions, or visits. Usual care practice will determine the schedule of visits as well as monitoring for safety and efficacy.

This NIS is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

9. RESEARCH QUESTION AND OBJECTIVES

The primary objectives of this NIS are to:

1. Determine the rate of treatment related AEs in CP CML patients treated with bosutinib.

2. Observe the discontinuation (DC) rate due to treatment related AEs and compare with the DC rate in patients with chronic phase CML resistant or intolerant to previous treatment(s) observed in the clinical trials.

Secondary objectives will include a descriptive assessment of:

1. Safety (treatment emergent AEs , treatment related AEs, AEs leading to treatment modification, management of selected AEs).

2. Patient self-reported adherence information via the Morisky scale and quality of life via a leukemia specific quality of life questionnaire (FACT-leu_v4).

3. Treatment with bosutinib in a real world setting (dosing, treatment duration, adherence, reasons for dose reductions/ delay/ discontinuations, timing and tests performed during treatment, concomitant medications).

4. Responses (results of hematological, cytogenetic and/or molecular testing, and best response by investigator assessment).

5. Baseline information/prior treatments to describe the patient population treated with bosutinib (demographics, medical history, time from diagnosis to enrollment, prior treatments and best response to prior treatments, reason for switching of prior therapies, last known hematological, cytogenetic and/ or molecular response status).

10. RESEARCH METHODS

10.1. Study Design

This is a prospective, observational, non-interventional study of previously treated patients with CP CML who are now prescribed or started with bosutinib. The study is designed to collect real world data in community and academic centers. Approximately 170 patients will be enrolled at approximately 30 sites in the US. Study duration will be approximately 2.5 years, assuming 18 months of recruitment and 12 months of patient follow-up. All treatment decisions and type and timing of disease monitoring are at the discretion of the treating physician and patient. Data will be recorded for 12 months after starting bosutinib or until patient withdrawal from the study, death or study discontinuation.

10.2. Setting

The study will enroll patients according to the eligibility criteria in the US. Every patient who meets eligibility criteria can participate in the study. Patients with active cardiovascular disease or other co morbidities that may have been excluded to participate in another bosutinib clinical trial will not be excluded. The study population will be men and women ages 18 years and older with the diagnosis of CP CML that have been treated with at least one previous TKI and have been prescribed or started treatment with bosutinib. Baseline visit should occur within 7 days of starting bosutinib. It is expected that approximately 170 patients will be enrolled into this NIS over an 18 month enrollment period followed by a 12 month observation period. Physicians will prescribe bosutinib and any other therapy to patients at their discretion, and will assess patients per their usual practice. Data will be collected from medical records used in routine medical practice.

10.3. Screening Visit

Screening visit could be performed to confirm eligibility criteria.

10.4. Baseline Visit

Baseline visit will be performed after eligibility criteria have been confirmed and the patient has signed informed consent. Baseline visit must occur anytime 30 days before starting bosutinib to 7 days after starting bosutinib. FACT-Leu (Version 4) questionnaire (see Appendix 3) will be collected at baseline visit.

Study Period

No scheduled visits are required in this protocol. Interim follow-up visits will coincide with those that occur in accordance with a site's routine medical practice based on medical and therapeutic need. FACT-Leu (Version 4) questionnaires will be collected at baseline. Morisky 8-Item Medication Adherence and FACT-Leu (Version 4) questionnaires (see Appendix 3) will be collected at least one time in Weeks 4, 8 and 12 and every 12 weeks thereafter for the reminder of the follow up period.

10.5. Follow-up Visit

There shall be no additional visits necessary as a result of the patient's participation in this study. Reporting of non-serious and serious adverse events, will continue for 28 calendar days after the last administration of the study drug within the 12 month observational period.

10.6. 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, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved 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.

10.6.1. Inclusion Criteria

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

1. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
2. Age 18 years or older.
3. Philadelphia chromosome positive or BCR-ABL positive CP ML.
4. Resistant or intolerant to previous therapy for CP CML.
5. Has been prescribed bosutinib for the treatment of previously treated CP CML, who has either not started treatment or has not taken bosutinib for more than 7 days at the time of baseline visit.
6. Prior history of malignancy is permitted.

10.6.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Newly diagnosed CML patient who has not received any previous TKI treatment.
2. Patient in accelerated or blast phase CML at screening/baseline.
3. Patient who is pregnant or breast-feeding.
4. Concomitant use of any FDA approved (eg, omacetaxine) or investigational agents for Ph+ CML.

10.7. Variables

The following data will be collected for this study:

Variable	Role	Data Source(s)
Demographics (year of birth, gender, race, height, weight)	Baseline characteristics	Baseline Visit
Performance status	Baseline characteristics	Baseline Visit
Concomitant medications	Baseline characteristics/ Follow-up visits	Baseline and Follow-up Visits
Previous treatment/s for CML (type/ dose and regimen/ duration)	Baseline characteristics	Baseline Visit
Best response to previous treatment/s	Baseline characteristics	Baseline Visit
Reason for switching previous treatment/s	Baseline characteristics	Baseline Visit
Hematological, cytogenetic and/ or molecular results at baseline	Baseline characteristics	Baseline Visit
Investigator assessment of CML phase at baseline	Baseline characteristics	Baseline Visit
AEs and serious adverse events (SAEs) reported during bosutinib therapy	Outcome	Follow-up Visits
Bosutinib dose/ regimen/ duration	Outcome	Follow-up Visits
Bosutinib dose reductions, discontinuations and withheld due to AEs/ SAEs	Outcome	Follow-up Visits
Management of bosutinib toxicities (concomitant medications, additional measures)	Outcome	Follow-up Visits

Variable	Role	Data Source(s)
Bosutinib patient adherence	Outcome	Follow-up Visits
Health related quality of life via leukemia specific quality of life questionnaire (FACT-leu_v4)	Baseline characteristics Outcome	Baseline Visit Follow-up Visits
Hematological, cytogenetic and molecular testing performed to monitor patient response (type and frequency of monitoring, results)	Baseline characteristics Outcome	Baseline and Follow-up Visits
Investigator assessment of best response during treatment.	Outcome	Follow-up Visits

10.8. Data Sources

A case report form (CRF) will be used for data collection. As used in this protocol, the term CRF should be understood to refer to either a paper or electronic data record or both, depending on data collection method used in this study:

- For physicians: electronic CRF(eCRF).
- For patients: paper or electronic questionnaires (see Appendix 3).

This is a prospective NIS with patient characteristics and outcomes that will be observed during the study period which reflect current practice procedures. Interim follow-up visits will coincide with those that occur in accordance with site's routine medical practice based on medical and therapeutic need.

It is the investigator's responsibility to ensure data entry completion and to review and approve all CRFs. CRFs must be signed by the investigator or by authorized staff member(s). These signatures serve to attest that the data contained in the CRFs are true. At all times the investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

10.9. Study Size

Assuming the discontinuation rate due to treatment related AEs in the real world setting to be similar as the observed in the clinical trial in resistant or intolerant CP CML, (ie, 20%). In order to have a 95% confidence interval and a margin of error ≤6% for the discontinuation rate, a total of 170 patients will be needed. Approximately 30 sites in the US (10 academic

and 20 community) should contribute similar number of patients (ie, 85 patients from each type of center).

10.10. Data Management

The database and data management plan will be generated to include the following as a minimum:

- Data Flow Plan;
- Case Report Form Completion Guidelines;
- Data Entry Methods and Guidelines;
- Data Validation Document;
- Data Handling Conventions.

A data clarification form (DCF) process will be used for handling data discrepancies related to SAEs.

10.11. Data Analysis

Analysis will be based on the safety population, which includes all enrolled patients who received at least one dose of bosutinib. Patients who signed informed consent but who were not treated will be reported with a reason(s) why treatment was not received.

Analysis will be based on observed data. Incomplete dates will be imputed and details will be included in the SAP.

10.11.1. Primary Analysis

Rates of treatment related AEs will be summarized with descriptive statistics and their 95% confidence intervals (CI).

Discontinuation rates of bosutinib due to treatment related AEs will be summarized with descriptive statistics and their 95% CI.

10.11.2. Secondary Analysis

Logistic regression will be used to analyze association between baseline factors and discontinuation of bosutinib due to treatment related AEs.

Descriptive statistics (number of patients, mean, standard error, median and range for continuous variables; number of patients, percentage and 95% CI for categorical variables) will be used to summarize all other endpoints. These analyses will be performed by type of centers, previous treatment, and line of therapy separately and then for all patients together.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol. Any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

10.12. Quality Control

Investigator Site Set Up

Appropriate training relevant to the study will be given to a site's investigational staff. Any new information relevant to the performance of this NIS will be forwarded to the site during the study.

Investigational Site Monitoring

Regular contact with the site will occur to provide information and support to the investigator(s) and verify that study site procedures are compliant with the protocol and that data are being accurately recorded in a timely manner in the CRFs.

Additional monitoring tasks will be described in a monitoring plan according to Pfizer SOPs; monitoring visit(s) at investigator sites will be triggered if certain milestones that indicate low compliance have been reached and will ensure that the study is conducted accordingly with the protocol.

Quality and Accuracy of Records

The investigator will have the responsibility for the collection and reporting of all clinical, safety and laboratory data entered in the CRFs and any other data collection forms (eg, source documents). The investigator should ensure the data are accurate, authentic/original, attributable, complete, consistent, legible timely, enduring and available when required.

To enable evaluations and/ or audits from Regulatory Authorities and/or Pfizer, the investigator will agree to keep records, including the identity of all participating patients (ie, sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse events forms, source documents, and detailed record of treatment disposition and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone call reports). The records should be retained by the investigator according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

Storage of Records

Archival of the statistical programming will be performed according to Pfizer SOPs.

10.13. Limitations of the Research Methods

Investigational Site Selection

The voluntary participation of physicians as investigators constitutes a selection bias observed for this type of study. Investigational sites will be selected to represent both academic and community center practices. Investigators may have varying experience with the use of bosutinib.

Patient Selection

Patient selection constitutes a potential selection bias classically associated with NI studies. Patients who agree to participate may differ from those who decline to participate.

Measurement Bias

Measurement biases may relate to site-specific differences in patient management. As no guidelines exist for the monitoring and follow-up of patients, and no schedule of visits is planned, therapeutic management and safety/efficacy monitoring, as well as investigator assessment of patient response can differ from one site to another.

10.14. Other Aspects

N/A

10.15. Study Treatment and Duration

In this study, the use and dosage of Bosulif® (bosutinb) will be prescribed according to the discretion of the treating physician as per their usual clinical practice. As such, the potential risks and benefits for patients who participate in the study will be no different than for patients receiving usual medical care.

Medication will not be provided to patients, or reimbursed, as part of the study, but will be prescribed in the usual manner by the treating physician. All aspects of care, including diagnostic and therapeutic interventions, will be conducted at the discretion of the participating study physician according to his/her clinical judgment and routine practice of care. The US package insert includes additional information that patients and physicians may find valuable including safety and patient management guidelines.

Data will be recorded for 12 months after the patient initiates bosutinib or until patient withdrawal from the study, death, or study discontinuation.

11. PROTECTION OF HUMAN PATIENTS

11.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or any other identifying information on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

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

11.2. 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, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason(s) for withdrawal and follow-up with the patient regarding any unresolved adverse events.

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.

11.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

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

11.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Outcomes Research Practices issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Draft Guidance for Industry and FDA Staff: Best

Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

ADVERSE EVENT REPORTING

ADVERSE EVENTS

All observed or volunteered adverse events and suspected causal relationship to bosutinib will be recorded on the adverse event page(s) of the case report form (CRF) as follows.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (see section "Serious Adverse Events") requiring immediate notification to Pfizer or a Pfizer-designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship *to* bosutinib, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

REPORTING PERIOD

For non-serious and serious adverse events, the reporting period to Pfizer or its designated representative begins from the time of the patient's first dosing in the 12 month observational period as per study design through and including 28 calendar days after the last administration of the study drug within the observational period. If the investigator becomes aware of a SAE that is considered related to study drug occurring at any other time after completion of the study, the SAE is also reportable.

Reports of overdose, misuse, extravasations associated with the use of a Pfizer product will be recorded on the adverse event page(s) of the case report form, irrespective of the presence of an associated AE/SAE. The investigator must submit reports of overrode, misuse, extravasations to Pfizer within 24 hours of awareness, irrespective of the presence of an associated AE/SAE. Reports of occupational exposure to a Pfizer product are to be submitted within 24 hours of awareness, irrespective of the presence of an associated AE.

DEFINITION OF AN ADVERSE EVENT

An AE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including infant and toddler formulas [hereinafter "pediatric formulas"]) or medical device. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

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

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

ABNORMAL TEST FINDINGS

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- 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 or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

- Test result is considered to be an adverse event by the investigator or sponsor.

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

SERIOUS ADVERSE EVENTS

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;

- Is life-threatening;

- Requires inpatient hospitalization or prolongation of hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with severity Grade 5.

Lack of efficacy should be reported as an adverse event when it is associated with a serious adverse 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 outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from

clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

HOSPITALIZATION

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly exam);
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

CAUSALITY ASSESSMENT

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). The investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that bosutinib caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether bosutinib caused the event, then the event will be handled as related to bosutinib for reporting purposes. If the investigator's causality assessment is unknown but not related to bosutinib his should be clearly documented in the CRF.

EXPOSURE DURING PREGNANCY

An exposure during pregnancy (also referred to as exposure in-utero [EIU]) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) bosutinib or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to bosutinib (maternal exposure).

2. A male has been exposed, either due to treatment or environmental exposure to bosutinib <7 days prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposures during pregnancy reports from any source are reportable irrespective of the presence of an associated AE/SAE.

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).

If a study patient or study patient's partner becomes, or is found to be, pregnant during the study patient's treatment with bosutinib the investigator must submit this information to Pfizer within 24 hours of awareness of the pregnancy, irrespective of whether an adverse event has occurred.

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (eg, induced abortion) and then notify Pfizer of the outcome. The investigator will provide this information as a follow-up to the initial Exposure in Utero report.

For clinical studies conducted in pregnant women, data on the pregnancy outcome and non-serious AEs are expected to be collected and analyzed in the clinical database. In such instances only EIUs associated with a SAE are to be reported.

MEDICATION ERROR

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer within 24 hours of awareness, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

REPORTING REQUIREMENTS

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events.

If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

SERIOUS ADVERSE EVENT REPORTING REQUIREMENTS

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure during breast feeding and medication error cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of 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 or its designated representative.

12.1. Single Reference Safety Document

The single reference safety document to be used for the study will be the current US Package Insert.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final clinical study report will present the results of analysis of baseline and follow-up data and will address all study objectives.

A planned description of baseline characteristics that includes prior therapies will be conducted after enrollment has completed and an interim analysis will be performed after approximately 100 patients have completed the study. The interim analysis is not intended to be used for a decision to discontinue the study or stop enrollment.

14. REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10-29.

2. Surveillance Epidemiology and End Results. SEER Stat Fact Sheets: chronic myeloid leukemia. http://seer.cancer.gov/statfacts/html/cmyl.html. Accessed February 19, 2013.

3. Rohrbacher M, Hasford J. Epidemiology of chronic myeloid leukemia (CML). *Best Pract Res Clin Haematol*. 2009;22(3):295-302.

4. Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. *Cancer*. 2012;118(12):3123-3127.

5. Hehlmann R, Heimpel H, Hasford J, et al. Randomized comparison of interferon-a with busulfan and hydroxyurea in chronic myelogenous leukemia. *Blood*. 1994;84(12):4064-4077.

6. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003; 348(11): 994–1004.

7. Deininger M, O'Brien SG, Guilhot F, et al. International Randomized Study of Interferon vs. ST1571 (IRIS) 8-year follow-up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase treated with imatinib [abstract]. *Blood*. 2009;114 (22 suppl):462. Abstract 1126.

8. Sprycel (dasatinib) Prescribing Information. Princeton, NJ: Bristol Myers-Squibb Company, 2013.

9. Tasigna (nilotinib) Prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2013.

10. Alvarado Y, Kantarjian H, O'Brien S, et al. Significance of suboptimal response to imatinib, as defined by the European LeukemiaNet, in the long-term outcome of patients with early chronic myeloid leukemia in chronic phase. *Cancer*. 2009;115(16):3709–3718.

11. Milojkovic D, Apperley JF, Gerrard G, et al. Responses to second-line tyrosine kinase inhibitors are durable: an intention-to-treat analysis in chronic myeloid leukemia patients. *Blood.* 2012;119(8):1838–1843.

12. Bosulif (bosutinib) Prescribing Information. New York, NY: Pfizer Pharmaceuticals Corporation, 2013.

13. Omacetaxine (Synribo) Prescribing Information Teva Pharmaceuticals USA, Inc. North Wales, PA, 2012.

14. Ponatinib (Iclusig) prescribing information. ARIAD Pharmaceuticals, Inc, 2013.

15. NCCN Clinical Practice Guidelines in Oncology. Chronic Myelogenous Leukemia. V.4. 2013. NCCN.org.

16. Baccarani M, Deininger MW, Rosti G, Hochhaus A, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: *Blood*. 2013;122(6):872-84.

17. Milojkovic D, Nicholson E, Apperley JF, et al. Early prediction of success or failure of treatment with second-generation tyrosine kinase inhibitors in patients with chronic myeloid leukemia. *Haematologica* 2010;95(2):224-231.

15. LIST OF TABLES

Tables will be specified upon finalization of study protocol, SAP, and CRFs.

16. LIST OF FIGURES

N/A

APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

None

APPENDIX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

N/A

APPENDIX 3. ADDITIONAL INFORMATION

Morisky 8-Item Medication Adherence Questionnaire — Patient Answer Score (Yes No Y=1 N=0)

Do you sometimes forget to take your medicine?

People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?

Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?

When you travel or leave home, do you sometimes forget to bring along your medicine?

Did you take all your medicines yesterday?

When you feel like your symptoms are under control, do you sometimes stop taking your medicine?

Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?

How often do you have difficulty remembering to take all your medicine?

__ A. Never/rarely

__ B. Once in a while

__ C. Sometimes

__ D. Usually

__ E. All the time

A = 0;
B-E = 1
Total score

Scores: >2 = low adherence
1 or 2 = medium adherence
0 = high adherence

Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence.
Med Care. 1986;24:67-74.

FACT-Leu (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
HRM2	I am bothered by the chills	0	1	2	3	4
HS3	I have night sweats	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
HMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU5	I feel uncertain about my future health	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
HRM9	I have emotional ups and downs	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4

Appendix 3.1 LIST OF INVESTIGATORS BY COUNTRY

Total Number of Sites (Per Study) : 3
Total Number of Patients Enrolled (Per Study) : 3

United States

Coordinating Investigators:
<None Entered>

Number of Sites (Per Country) : 3
Number of Patients (Per Country) : 3

Center	Principal Investigator	Sub-Investigator(s)	Study Conducted At Address(es)	Patients Enrolled per site
1002	Dr. Ajit S. Maniam	Maria T. Ampudia Dr. Veena P. Charu Shelton Jim Colinco Karen Dawson Alpa Mehul Patel Dr. Reena Vora Sharon A. Westerberg	Pacific Cancer Medical Center, Inc Suite 203 1801 West Romneya Drive Anaheim, CA 92801 UNITED STATES	1
1012	Sarah I. Vidito	Dr. James D. Bearden III Dr. James D. Bearden III Dr. Charles Edward Bowers Dr. Charles Edward Bowers Dr. Steven William Corso Dr. Steven William Corso Dr. Colin P. Curran Dr. Colin P. Curran Dr. Sharmila Mehta Dr. Sharmila Mehta Dr. Eric Charles Nelson Dr. Asim Ranjan Pati	Spartanburg Regional HealthCare System Gibbs Cancer Center and Research Institute 101 East Wood Street Spartanburg, SC 29303 UNITED STATES	1

Center	Principal Investigator	Sub-Investigator(s)	Study Conducted At Address(es)	Patients Enrolled per site
1016	Dr. Ravin M. Rupani Dr. Daniel Changhyon Kim (Previous PI)	Dr. Richy Agajanian Dr. David Berz Dr. Swapna Boppana Dr. Arsinur Burcoglu-Oral Dr. Eric Cheung Dr. Michael Chung Anais Cunha Dr. Jack H. Freimann Jr. Dr. Alexander Gaitanis Dr. Youssef Gamal Lauren Gillan Dr. Daniel Huang Dr. Stephen Huang Dr. Reza Mostofi Son Nguyen Hannah Prawat Dr. Thomas F. Reynolds Merrill Kingman Shum Tania Tatoyan Dr. Rodina Vatanparast Dr. Deepika Wali	The Oncology Institute of Hope and Innovation 1184 North Euclid Street Anaheim, CA 92801 UNITED STATES The Oncology Institute of Hope and Innovation Suite 240 1510 South Central Avenue Glendale, CA 91204 UNITED STATES The Oncology Institute of Hope and Innovation Suite 100 3628 East Imperial Highway Lynwood, CA 9062 UNITED STATES The Oncology Institute of Hope and Innovation Suite A 1970 Old Tustin Avenue Santa Ana, CA 927052 UNITED STATES The Oncology Institute of Hope and Innovation Suite D 530 West Badillo Street Corvina, CA 91722 UNITED STATES The Oncology Institute of Hope and Innovation Suite 3750 1700 East Cesar Chavez Avenue Los Angeles, CA 90033 UNITED STATES The Oncology Institute of Hope and Innovation Suite 309	1

Center	Principal Investigator	Sub-Investigator(s)	Study Conducted At Address(es)	Patients Enrolled per site
			11480 Brookshire Avenue Downey, CA 90241 UNITED STATES	
			The Oncology Institute of Hope and Innovation Suite 304 3300 East South Street Long Beach, CA 90805 UNITED STATES	
			The Oncology Institute of Hope and Innovation Suite 200 101 East Beverly Boulevard Montebello, CA 90640 UNITED STATES	
			The Oncology Institute of Hope and Innovation Suite103 8135 South Painter Avenue Whittier, CA 90602 UNITED STATES	
			The Oncology Institute of Hope and Innovation Suite 109 4305 Torrance Boulevard Torrance, CA 90503 UNITED STATES	

Appendix 3.2 - List of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and Corresponding Protocol Approval Dates

United States

Center	IRB approval date for protocol	IEC or IRB Address(es)
1002	13-Mar-2014	Western IRB Suite 120 1019 39th Avenue SE Puyallup, WA 98374 UNITED STATES
1012	21-May-2014	Western IRB Suite 120 1019 39th Avenue SE Puyallup, WA 98374 UNITED STATES
1016	23-Jul-2014	Western IRB Suite 120 1019 39th Avenue SE Puyallup, WA 98374 UNITED STATES

02/Sep/2011

STATISTICAL ANALYSIS PLAN TEMPLATE

FOR NON-INTERVENTIONAL STUDIES

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Version 1	28 MAR 2014	Kongming Wang	Original

.

Non-Interventional Study Protocol
B1871042

A Non Interventional Study of Bosutinib in Patients with Previously Treated Chronic Phase Chronic Myelogenous Leukemia (CML)

Statistical Analysis Plan
(SAP)

Version: 1

Author: Kongming Wang (OBU Statistics, Pearl River)

Date: 28-MAR-2014

CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADI	Actual dose intensity
AE	Adverse event
Bcr-Abl	Breakpoint cluster region-Abelson
CCyR	Complete cytogenic response
CHR	Complete hematologic response
CI	Confidence intervals
CML	Chronic myelogenous leukemia
CP	Chronic phase
CRF	Case report form
DC	Discontinuation
DI	Dose intensity
EAS	Efficacy analysis set
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia questionnaire
FAS	Full analysis set
IRIS	International Randomized Study of Interferon Versus STI571
MCyR	Major cytogenic response
MedDRA	Medical Dictionary for Regulatory Activities
MMAS-8	Morisky 8-Item Medication Adherence Scale
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NI	Non-interventional
NIS	Non-interventional study
PASS	Post-Authorisation Safety Study
Ph+	Philadelphia chromosome-positive
Ph+ALL	Ph+ acute lymphoblastic leukemia
RDI	Relative dose intensity
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SD	Standard deviation
SEER	Surveillance Epidemiology and End Results
TEAE	Treatment emergent adverse event
TKIs	Tyrosine kinase inhibitors
WHODD	World Health Organization Drug Dictionary

1 AMENDMENTS FROM PREVIOUS VERSION(S)

This is the original version.

2 INTRODUCTION

Note: in this document any text taken directly from the Non-Interventional Study (NIS) Protocol is ***italicised***.

.

This Statistical Analysis Plan (SAP) describes the planned analyses, the statistical methods and guidelines to be used in the analysis of bosutinib Protocol B1871042: *A Non Interventional Study of Bosutinib in Patients With Previously Treated Chronic Phase Chronic Myelogenous Leukemia (CML)*. Definitions of the efficacy and safety endpoints and descriptions of the statistical methods to be used to analyze each endpoint are also included. Any post-hoc, or unplanned, analyses not described in this SAP will be clearly identified in the clinical study report (CSR). The protocol provides details on the conduct of this study, the operational aspects of clinical assessments, and timing for completing a subject in this study.

2.1 STUDY DESIGN

This is a prospective, observational, non-interventional study of previously treated patients with CP CML who are treated with bosutinib. The study is designed to collect real world data in community and academic centers. Approximately 170 patients will be enrolled at approximately 30 sites in the US. Study duration will be approximately 2.5 years, assuming 18 months of recruitment and 12 months of patient follow-up. All treatment decisions and type and timing of disease monitoring are at the discretion of the treating physician and patient. Data will be recorded for 12 months after starting bosutinib or until patient withdrawal from the study, death or study discontinuation.

Screening visit could be performed to confirm eligibility criteria.

Baseline visit will be performed after eligibility criteria have been confirmed and the patient has signed informed consent. Baseline visit must occur anytime 30 days before starting bosutinib to 7 days after starting bosutinib.

No scheduled visits are required in this protocol. Interim follow-up visits will coincide with those that occur in accordance with the site's routine medical practice based on medical and therapeutic need. FACT-Leu (Version 4) questionnaires will be collected at baseline. Morisky 8-Item Medication Adherence and FACT-Leu (Version 4) questionnaires will be collected at least one time in Weeks 4, 8 and 12 and then every 12 weeks thereafter for the reminder of the follow up period.

There shall be no additional visits necessary as a result of the patient's participation in this study. Reporting of non-serious and serious adverse events, will continue for 28 calendar days after the last administration of the study drug within the 12 month observational period.

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, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal and follow up with the patient regarding any unresolved 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.

Study population

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

1. *Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.*
2. *Age 18 years or older.*
3. *Philadelphia chromosome positive or BCR-ABL positive CP CML.*
4. *Resistant or intolerant to previous therapy for CP CML.*
5. *Has been prescribed bosutinib for the treatment of previously treated CP CML, who has either not started treatment or has not taken bosutinib for more than 7 days at the time of baseline visit.*
6. *Prior history of malignancy is permitted.*

Patients meeting any of the following criteria will not be included in the study:

1. *Newly diagnosed CML patient who has not received any previous TKI treatment.*
2. *Patient in accelerated or blast phase CML at screening/baseline.*
3. *Patient who is pregnant or breast-feeding.*

4. *Concomitant use of any FDA approved (e.g. omacetaxine) or investigational agents for Ph+ CML.*

Data source

A case report form (CRF) will be used for data collection. As used in this protocol, the term CRF should be understood to refer to either a paper or electronic data record or both, depending on data collection method used in this study:

- *For physicians: paper or electronic CRF(eCRF)*
- *For patients: paper or electronic questionnaires* (MMAS-8, FACT-Leu).

It is the investigator's responsibility to ensure data entry completion and to review and approve all CRFs. CRFs must be signed by the investigator or by authorized staff member(s). These signatures serve to attest that the data contained in the CRFs are true. At all times the investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

The following data will be collected for this study:

Variable	***Role***	***Data Source(s)***
Demographics (year of birth, gender, race, height, weight)	*Baseline characteristics*	*Baseline Visit*
ECOG performance status and Sokal score	*Baseline characteristics*	*Baseline Visit*
Concomitant medications	*Baseline characteristics/ Follow Up visits*	*Baseline and Follow up Visits*
Previous treatment/s for CML (type/ dose and regimen/ duration)	*Baseline characteristics*	*Baseline Visit*
Best response to previous treatment/s	*Baseline characteristics*	*Baseline Visit*
Reason for switching previous treatment/s	*Baseline characteristics*	*Baseline Visit*
Hematological, cytogenetic and/ or molecular results at baseline	*Baseline characteristics*	*Baseline Visit*
Investigator assessment of CML phase at baseline	*Baseline characteristics*	*Baseline visit*
AEs and serious adverse events (SAEs) reported during bosutinib therapy	*Outcome*	*Follow up visits*
Bosutinib dose/ regimen/ duration	*Outcome*	*Baseline and Follow up visits*

Variable	***Role***	***Data Source(s)***
Bosutinib dose reductions, discontinuations and withheld due to AEs/ SAEs	*Outcome*	*Follow up visits*
Management of bosutinib toxicities (concomitant medications, additional measures)	*Outcome*	*Follow up visits*
Bosutinib patient compliance (MMAS-8)	*Outcome*	*Follow up visits*
Hematological, cytogenetic and molecular testing performed to monitor patient response (type and frequency of monitoring, results)	*Baseline characteristics Outcome*	*Baseline and Follow up visits*
Investigator assessment of best response during treatment.	*Outcome*	*Follow up visits*
Quality of life (FACT-Leu)	Baseline characteristics Outcome	Baseline and Follow up visits

Treatment labels

Not applicable.

2.2 STUDY OBJECTIVES

The primary objectives of this NIS are to:

1. *Determine the rate of treatment related Adverse Events in CP CML patients treated with bosutinib.*

2. *Observe the* treatment *discontinuation (DC) rate due to treatment related AEs and compare with the DC rate in patients with chronic phase CML resistant or intolerant to previous treatment(s) observed in the clinical trials.*

Secondary objectives will include a descriptive assessment of:

1. *Safety (treatment emergent AEs* (TEAE) *, AEs leading to treatment modification, management of selected AEs)*

2. *Treatment with bosutinib in a real world setting (dosing, treatment duration, adherence, reasons for dose reductions/ delay/ discontinuations, timing and tests performed during treatment, concomitant medications)*

3. *Responses (results of hematological, cytogenetic and /or molecular testing, and best response by investigator assessment)*

4. *Baseline information/ prior treatments to describe the patient population treated with bosutinib (demographics, medical history, time from diagnosis to enrollment, prior treatments and best response to prior treatments, reason for switching of prior therapies, last known hematological, cytogenetic and/ or molecular response status).*

3 INTERIM AND FINAL ANALYSES

A planned description of baseline characteristics that includes prior therapies will be conducted after enrollment has completed and an interim analysis will be performed after approximately 100 patients have completed the study. The interim analysis is not intended to be used for a decision to discontinue the study or stop enrollment. The purpose of the interim analysis is for abstracts and/or publications describing patient population and baseline characteristics.

The final analysis will be when every subject has completed a 12-month follow-up after starting bosutinib or discontinued the study (withdrawal from the study, death), whichever is earlier.

4 HYPOTHESES AND DECISION RULES

The hypothesis is that the 12-month treatment discontinuation rate due to treatment related AEs in the real world setting is the same as that observed in the clinical trial in resistant or intolerant CP CML, (i.e. 20%).

4.1 STATISTICAL HYPOTHESES

The null hypothesis is H_0: p=.2.

4.2 STATISTICAL DECISION RULES

Testing of the null hypothesis will be done at the two-sided .05 level. The hypothesisis rejected if the 95% confidence interval for the discontinuation rate due to treatment related AEs does not cover 20%.

5 ANALYSIS SETS/ POPULATIONS

5.1 FULL ANALYSIS SET

The full analysis set (FAS) includes all subjects who took at least one dose of bosutinib. All analyses (safety, dosing, baseline/prior data), except response, will be based on the FAS.

5.2 SAFETY ANALYSIS SET

<

Safety analyses will be based on the FAS.

5.3 EFFICACY ANALYSIS SET

The efficacy analysis set (EAS) includes all subjects who took at least one dose of bosutinib and had adequate baseline assessment (hematologic, cytogenetic, or molecular).

5.4 SUBGROUPS

Subgroup analyses will be based on the following subgroups: type of centers (academic, community); prior TKI treatment (imatinib only, dasatinib only, nilotinib only, other).

6 ENDPOINTS AND COVARIATES

6.1 EFFICACY/ EFFECTIVENESS ENDPOINT(S)

Hematologic, cytogenetic, and molecular responses are defined in Appendix (section 11.3). Response is assessed by investigator during the study.
Hematologic testing (WBC counts, platelet counts, peripheral blood blasts %, etc), cytogenetic testing (Ph-positive metaphases %) and molecular testing (ratio of BCR-ABL/control gene) will be performed at baseline and post-baseline. Post-baseline testing and response assessment will be conducted according to a site's routine medical practice. Response assessments will be collected during the first 12 months of bosutinib treatment.

Cytogenetic response will also be derived based on Ph+ metaphases %. For subjects whose molecular tests were done on international scale, molecular response will also be derived.

6.2 SAFETY ENDPOINTS

An AE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including infant and toddler formulas [hereinafter "pediatric formulas"]) or medical device. The event need not necessarily have a causal relationship with the product treatment or usage. Signs or symptoms resulting from overdose, misuse, extravasation associated with the use of bosutinib will be recorded on the AE page(s) of the CRF, irrespective of an association with bosutinib.

A treatment-emergent AE is an AE that

- started inclusively in the period after the start of study treatment and through 28 days after the last study treatment administration,

- OR where the specific incidence of the event started prior to study medication administration, but worsened (became more severe) after study medication started.

An AE is treatment-related if it has a suspected causal relationship to bosutinib.

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

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

Safety variables/endpoints include the following:

- Demographic characteristics
  - age
  - gender
  - race
  - height
  - weight
- Incidence and severity of TEAEs
  - all causality
  - treatment-related
- Incidence and severity of SAEs
  - all causality
  - treatment-related
- Subject status at end of study
  - completed 12 months treatment
  - discontinued bosutinib less than 12 months after initiation (less than one year treatment)
  - reasons for discontinuing bosutinib earlier
    - all reasons
    - due to treatment-related AEs
- Death
  - all deaths on treatment or within 28 days of last dose of bosutinib
  - deaths within 30 days of first bosutinib dose
- Bosutinib dosing
  - Treatment duration
  - Total dose
  - Dose intensity (DI), actual dose intensity (ADI) and relative dose intensity (RDI) as defined in Appendix A1.3.

- number (%) of subjects with dose reductions and reasons for dose reductions
- number (%) of subjects with dose delays and reasons for dose delays

6.3 OTHER ENDPOINTS

Additional variables/endpoints include the following:

- Baseline disease characteristics
  - Sokal score
  - ECOG performance status
  - Medical history
- Prior treatment for CML
  - treatment regimen
  - dose
  - duration
  - best response to prior treatment(s)
  - reason for switching prior treatment(s)
- Concomitant medications. A medication is defined as concomitant if either the start date or the stop date is during study treatment with bosutinib.
  - concomitant medications for managing bosutinib related toxicities
  - all concomitant medications
- Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) questionnaire
  - The FACT-Leu is a 44 item questionnaire with 5 sub-scales: 7 items for physical well-being (PWB), 7 items for social well-being (SWB), 6 items for emotional well-being (EWB), 7 items for functional well-being (FWB), and 17 items corresponding to Leukemia Subscale (LeuS). Each item can take on integral values from 0 (“not at all”) to 4 (“very much”). Scale scoring is described in Section 8.1.1.
- Medication Adherence
  - Morisky 8-Item Medication Adherence Scale (MMAS-8). Seven questions are yes/no questions (yes=1, no=0) and the last question is a multiple choice question (A=0, B-E=1). Scoring is described in Section 8.1.2.

6.4 COVARIATES

Baseline characteristics that will be used as covariates in logistic regression are: age (≤65, >65), gender (male, female), Sokal risk group (low/intermediate, high), ECOG (0/1, >1), number of prior TKIs (1, >1), and reason for discontinuing prior TKI (lack of response/loss of response, other).

7 HANDLING OF MISSING VALUES

Only year of birth is required to calculate age ([year of first dose] – [year of birth] + 1).

A medication is defined as concomitant if either the start date or the stop date is during study treatment. A medication with a completely missing end date will be considered concomitant. For partial date missing day, if start month/year or stop month/year is the same as a month/year during study treatment, it will be considered concomitant. Similar rule if only start or stop year is available.

Start date is required for determining whether an AE is TEAE. If the start date of an event is completely missing, then the event will be classified as treatment-emergent given one of the following three criteria:

1. the event stop date is after first dose of study medication
2. the event stop date is completely missing
3. the event stop date is partially missing but classified as occurring after the start of treatment (e.g., stop month/year is after month/year of first dose)

For partial start dates, an adverse event with starting month and year the same as a month and year during study treatment will be considered treatment emergent as will an adverse event with only starting year the same as a year during study treatment as long as event stop dates meet one of the three criteria defined above.

Scoring of FACT-Leu and MMAS-8 with missing values is defined in sections 8.1.1 and 8.1.2 respectively.

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

Selected data (e.g., TEAE, death, subjects who signed informed consent and were not treated) will be presented in listings for the CSR. Data listings will be sorted for presentation by site, patient identification, and date/time order of assessments, as appropriate. Summary tables will be presented for safety and efficacy endpoints, patient demographics, baseline characteristics, patient disposition, and study drug exposure.

All analyses will be produced using SAS version 9.1.3 or higher. Means and medians will be reported to one decimal place greater than that reported on the CRF or by the laboratory/vendor. Standard deviations will be reported to two decimal places greater than that reported in the data. Minimum and maximum values will be reported to the same number of decimal places displayed on the CRF or by the laboratory/vendor.

Descriptive summaries of categorical outcomes will include the number and percent of patients. Confidence intervals for the percentage will be included for some endpoints as specified in section 8.2 of this SAP. Descriptive summaries of continuous measures will include the number of patients, mean, standard error, median, minimum and maximum.

Logistic regression will be used to analyze association between baseline factors and discontinuation of bosutinib due to treatment related AEs.

Duration in days is calculated as [end date] – [start date] + 1 except age which is calculated by [year of first dose] – [birth year] + 1. For example, treatment duration in days = [date of last dose] – [date of first dose] + 1. In addition,

- Duration in weeks = duration in days / 7
- duration in months = duration in days / 30.4

In general, all categories that appear on the CRF and in summary table templates (if applicable) will be reported even if no patients are reported in that category (e.g., if there are no patients of a particular race). The "Missing" category displayed for categorical variables in summary table templates will only be displayed if missing observations are present. If no observations meet the criteria for inclusion in a data display (e.g., if there re no SAEs), the table or listing will be generated with a line in the body of the listing such as "none observed."

8.1.1 Scoring FACT-Leu

Score of each sub-scale is the sum of its own item-scores. These scores are calculated by the following formula such that the higher the score, the better the quality of life is of the subject (Note: In the formula below, the (4-X) contributions are only used if the question was answered, i.e., the 'item score or 4' is not counted if the question is missing). Subscale scores are prorated if there are less than 50% of missing items in the subscales. Prorated subscale score is calculated by multiplying the sum of non-missing items by the number of items in the subscale, then dividing by the number of non-missing items. If there are 50% or more missing items in the subscale, then the subscale score at the assessment point is set to missing.

PWB = {(4-GP1)+(4-GP2)+(4-GP3)+(4-GP4)+(4-GP5)+(4-GP6)+(4-GP7)} × 7 / # of non-missing items (score range 0-28)

SWB = (GS1+GS2+GS3+GS4+GS5+GS6+GS7) × 7 / # of non-missing items (score range 0-28)

EWB = {(4-GE1)+GE2+(4-GE3)+(4-GE4)+(4-GE5)+(4-GE6)} × 6 / # of non-missing items (score range 0-24)

FWB = (GF1+GF2+GF3+GF4+GF5+GF6+GF7) × 7 / # of non-missing items (score range 0-28)

LeuS= {(4-BRM3) + (4-P2) + (4-BRM2) + (4- ES3) + (4-LEU1) + (4-TH1) + (4-TH2) + (4-HI12) + (4-BMT6)+ (4-C2) +C6+ An7 + (4-N3) +(4-LEU5) + (4- LEU6) + (4-BRM9) + (4-LEU7))}× 17 / # of non-missing items (score range 0-68)

The following composite scores will be calculated from the subscale scores:

FACT-G score is the sum of scores of the first four sub-scales (PWB, SWB, EWB, FWB), with score range 0-108: FACT-G=PWB+SWB+EWB+FWB.

FACT-Leu score (overall score) is the sum of FACT-G and LeuS scores, with score range 0-176: FACT-Leu=FACT-G+LeuS.

FACT-Leu TOI (The FACT-Leukemia Trial Outcome Index) is the sum of the PWB, FWB, and LeuS scores, with score range 0-124: TOI-FACT-Leu=PWB+FWB+LeuS.

8.1.2 Scoring MMAS-8

The score of MMAS-8 is the sum of all correct answers (yes=1, no=0). The degree of adherence was determined according to the score: high adherence (0 score), medium adherence (0 < scores ≤ 2) and low adherence (scores > 2). In this study, patients were considered adherent when they had a score of zero in the MMAS-8.

The score of MMAS-8 is prorated if there are missing values. Pro-rating dealt with missing items in the computation of the score at a time point for each subject, so long as there were fewer than 3 missing items at the time point for that subject; otherwise, the score was set to missing at the assessment time point. Prorated score = [score of non-missing items] x 8 / [# of non-missing items].

8.2 STATISTICAL ANALYSES

All safety summaries will be presented for the FAS, and response summaries will be presented for the EAS (primary analysis). *Patients who signed informed consent but who were not treated will be reported with reason(s) why treatment was not received.*

8.2.1 Safety Analyses

AE and SAE will be classified using MedDRA System Organ Class (SOC) and preferred term (PT). Toxicity will be graded according to the NCI CTCAE. Concomitant Medications will be classified using WHODD dictionary. All summaries will include the number and percent of patients reporting each AE.

All safety endpoints, except FACT-Leu and MMAS-8, will be summarized using descriptive statistics. In addition, 95% confidence intervals will be presented for rate of treatment discontinuation due to treatment related AEs and percentage of subjects with treatment related AEs.

Additional safety analyses are specified in sections 8.2.2.

8.2.2 Additional safety analyses

Association of treatment discontinuation due to treatment related AEs and baseline characteristics will be analyzed using logistic regression, with covariates as listed in section 6.4.

Treatment related AEs and treatment discontinuation due to treatment related AEs will also be summarized by subgroups, as defined in section 5.4, using descriptive statistics.

8.2.3 Analysis of FACT-Leu

Descriptive statistics (mean, standard error, median, minimum and maximum) will be presented for FACT-Leu scales (PWB, FWB, EWB, SWB, LeuS, FACT-G, FACT-Leu, and Fact-Leu TOI) at each assessment point as defined in the next paragraph. The mean FACT- Leu score will be plotted versus assessment points.

FACT-Leu data will be collected at baseline, at least one time in Weeks 4, 8 and 12 and every 12 weeks thereafter for the reminder of the follow up period.

The mean change from baseline (along with the standard error, median, minimum and maximum) in subscale scores (PWB, FWB, EWB, SWB, LeuS, FACT- G, FACT-Leu, Fact-Leu TOI) will be summarized by assessment points.

The overall score (FACT-Leu) will also be summarized by subgroups, as defined in section 5.4, using descriptive statistics.

8.2.4 Analysis of MMAS-8

Descriptive statistics will be presented for the MMAS-8 score (prorated score if there is missing value) and degrees of adherence (high, medium, low) by assessment time points as defined in the following paragraph.

MMAS-8 data will be collected at least one time in Weeks 4, 8 and 12 and every 12 weeks thereafter for the reminder of the follow up period.

8.2.5 Summary of Efficacy/ Effectiveness Analyses

Response is summarized by number of responders, response rate and 95% CI. A subject had an **overall response** if the subject had a hematologic, cytogenetic, or molecular response. Sensitivity analysis, which is based on a subset of EAS and excludes subjects without post-baseline tumor assessment, will be performed.

Endpoint	Analysis Set	Subgroups	Statistical Method	

Response by investigator		See section 5.4 for subgroups. EAS population only.	N, %, 95% CI	
Hematologic	EAS, sensitivity analysis			
Cytogenetic	EAS, sensitivity analysis			
Molecular	EAS, sensitivity analysis			
Overall	EAS, sensitivity analysis			
Derived response				
Cytogenetic	EAS	No subgroup analysis		
Molecular	EAS	No subgroup analysis		

Response will also be summarized by response categories (complete/partial cytogenetic response; complete/major molecular response) by number and percentage of responders.

Baseline FACT- Leu score will be summarized by response categories (hematologic response (yes/no), cytogenetic response (yes/no), molecular response (yes/no), overall (yes/no)) using descriptive statistics to assess the relationship between baseline FACT-Leu score and response by investigator.

9 LIST OF TABLES AND DATA SUMMARIES

A separate LOT and specification document will be provided.

10 REFERENCES

None.

11 APPENDICES

11.1 APPENDIX 1: DATA DERIVATION DETAILS

More details will be provided in a separate LOT and specification document.

A1.1 Definition and use of visit windows in reporting

Visit Label	Endpoint	Definition [Day window]
Baseline	All	Baseline visit will be performed after eligibility criteria have been confirmed and the patient has signed informed consent. Baseline visit must occur anytime 30 days before starting bosutinib to 7 days after starting bosutinib.
Date of first dose (Day 1)	All	Date of first bosutinib medication was taken. This date could be before baseline visit by 1 to 7 days as defined in protocol.
Follow-up	All	Office visits are based on the practice of the participating sites. No additional visit is necessary. Safety and response assessments will be conducted according to a site's routine medical practice. Dates of visits will be recorded.

A1.2 Definition of Analysis Populations/Sets

No additional detail required.

A1.3 Further Definition of Endpoints

Dose intensities will be calculated for each 30-day intervals from date of first dose (days 1-30, 31-60, etc) and overall.

If a 30-day interval ends before treatment discontinuation, then
DI = Starting dose of the 30-day period
ADI=[total bosutinib dose actually taken in the 30-day interval]/30
RDI=ADI/DI.

If treatment discontinued during a 30-day interval, then

DI = Starting dose at beginning of the interval
ADI=[total bosutinib dose actually taken from beginning of the interval to treatment discontinuation]/[number of days from beginning of the interval to treatment discontinuation]
RDI=ADI/DI.

Overall,
DI = average of the DIs for the 30-day intervals
ADI = average of the ADIs for the 30-day intervals
RDI=ADI/DI.

11.2 NCCN GUIDELINES VERSION 1.2014: CHRONIC MYELOGENOUS LEUKEMIA

Criteria for hematologic, cytogenetic, and molecular response

Hematologic response
Complete hematologic response if all of the followings are met:

- Complete normalization of peripheral blood counts with leukocyte count < 10 cells x 10^9/L
- Platelet count < 450 cells x 10^9/L
- No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood
- No signs or symptoms of disease with disappearance of palpable splenomegaly

Cytogenetic response

- Complete response: No Ph-positive metaphases
- Partial response: 1% - 35% Ph-positive metaphases

Molecular response

- Complete molecular response: no detectable BCR-ABL mRNA by QPCR (IS) using an assay with a sensitivity of at least 4.5 logs below the standardized baseline
- Major molecular response: ≥ 3-log reduction in IS of BCR-ABL mRNA

Document Approval Record

Document Name:	B1871042 Statistical Analysis Plan v1
Document Title:	B1871042 Statistical Analysis Plan v1

Signed By:	Date(GMT)	Signing Capacity
Pavlov, Dmitri	09-Jun-2014 18:52:56	Author Approval
Pavlov, Dmitri	09-Jun-2014 18:54:12	Author Approval

Patient CaseBook

Trial: A Non-Interventional Study of Bosutinib, Version: MSC002	Patient Type: NEWPAT	Version Date: 12/04/2014
Site: (Casebook Version MSC002)	Patient: New Patient	Date Generated:12/12/2014

Trial

Trial

1.	Trial Name	A Non-Interventional Study of Bosutinib
2.	Trial Number	B1871042
3.	Trial Caption	Chronic Phase CML NIS
4.	Sponsor	
5.	Start Date	DD/MON/YYYY(EN)
6.	End Date	DD/MON/YYYY(EN)
7.	Email From Name	
8.	Email From Address	
9.	Export Password	
10.	Trial Time Zone	(GMT-05:00) Eastern Time (US & Canada)
11.	Message of the Day	Please have the patient complete only the Fact-Leu Questionnaire at the Baseline Visit and not the Morisky.

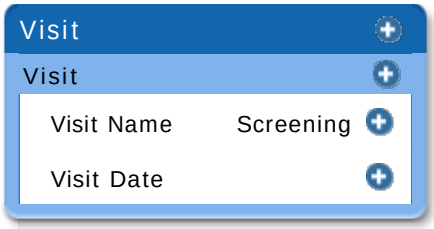
Site Setup & Information

Site Information

Site Name	Casebook Version MSC002
Site Number	
Site Caption	
Please provide the type of center for your site:	Academic Community
Address 1	
Address 2	
City	
State	
Postal Code	
Country	
Time Zone	
Contact First Name	
Contact Last Name	
Phone	
Target Enroll	
Target Enroll Date	TODAY DD/MON/YYYY(EN)

Subject Information

Subject Number
Subject ID
Informed consent date
Signed and dated copy of Informed Consent document was provided to participant ☐


Visit
Visit
Visit Name
Screening
Visit Date

Trial Name: A Non-Interventional Study of Bosutinib Site Name: Casebook Version MSC002
Subject ID: Visit Name: Screening

Inclusion and Exclusion Criteria

Did the subject meet all eligibility criteria?

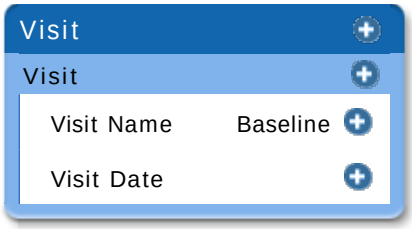
- Yes
- No

Inclusion Criteria

1.	Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
2.	Age 18 years or older.
3.	Philadelphia chromosome positive or BCR-ABL positive CP ML.
4.	Resistant or intolerant to previous therapy for CP CML.
5.	Has been prescribed bosutinib for the treatment of previously treated CP CML, who has either not started treatment or has not taken bosutinib for more than 7 days at the time of baseline visit.
6.	Prior history of malignancy is permitted.

Exclusion Criteria

1.	Newly diagnosed CML patient who has not received any previous TKI treatment.
2.	Patient in accelerated or blast phase CML at screening/baseline.
3.	Patient who is pregnant or breast-feeding.
4.	Concomitant use of any FDA approved (eg. omacetaxine) or investigational agents for Ph+ CML.


Visit
Visit
Visit Name
Baseline
Visit Date

Trial Name: A Non-Interventional Study of Bosutinib Site Name: Casebook Version MSC002
Subject ID: Visit Name: Baseline

Demography

Date of Birth: *(For partial dates use UN for missing day and month. Example: UN/MAR/2013)*	
Age:	
Sex:	☐ Male ☐ Female
Height:	
Unit	
Weight:	
Unit	
Race:	☐ White ☐ Black ☐ Asian ☐ Other
Please specify:	

Primary Diagnostic Testing

Chronic Myelogenous Leukemia (CML)

Date of Diagnosis: *(For partial dates use UN for missing day and month. Example: UN/MAR/2013)*	
CML Phase at Initial Diagnosis:	Chronic Accelerated Blast

Primary diagnostic testing was based on:

Was bone marrow cytogenetics performed at the time of primary diagnosis?	Yes No
Percentage of Ph+ metaphases? (%)	
Was FISH (fluorescence in situ hybridization) test performed at the time of Primary Diagnosis?	Yes No Unknown
Please specify the source:	Bone Marrow Peripheral Blood
Percentage of positive nuclei: (%)	
Was Quantitative RT-PCR test performed at the time of Primary Diagnosis?	Yes No Unknown
On international scale?	Yes No Unknown
BCR/ABL (%):	
ABL (control gene):	
Was SOKAL status known at primary diagnosis?	Yes No
Please specify SOKAL status:	Low Intermediate High
Since primary diagnosis was made, has the phase of CML changed?	Yes No
Please specify date: *(For partial dates use UN for missing day and month. Example: UN/MAR/2013)*	
	Chronic

Indicate to which phase: CML phase:	Accelerated Blast	
Has the patient had a stem cell transplant?	Yes No	
Type:	Allogeneic Autologous	
Please specify:	Related Not Related	
Source:	Bone marrow Peripheral Blood	
Transplant date *(For partial dates use UN for missing day and month. Example: UN/MAR/2013)*		

ECOG Performance Status at Diagnosis

Was ECOG performance status known at diagnosis?	Yes No
Was ECOG performance status known at baseline?	Yes No
Please specify:	Fully active, able to carry on all pre-disease performance without restriction. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Trial Name: A Non-Interventional Study of Bosutinib Site Name: Casebook Version MSC002
Subject ID: Visit Name: Baseline

BCR-ABL Mutation Analysis Before Baseline

Was the mutation analysis done prior to the baseline visit?	Yes / No
Date of Collection: *(For partial dates use UN for missing day and month. Example: UN/MAR/2013)*	
Was a mutation identified?	Yes / No

Please specify identified mutations:

Mutation History	Yes/No
	Yes No
	Yes No
	Yes No
	Yes No
	Yes No
	Yes No
	Yes No
	Yes No
	Yes No
	Yes No
	Yes No
	Yes No
	Yes No
	Yes No
	Yes No

Medical History

Was Medical History collected?	○ Yes ○ No

Has patient experienced:	Yes/No/Unknown	If Yes, is condition ongoing?	If Yes, is condition related to previous Tyrosine Kinase Inhibitor (TKI)?
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		

Medical History (Part II)

Has patient experienced:	Yes/No/Unknown	If Yes, is condition ongoing?	If Yes, is condition related to previous Tyrosine Kinase Inhibitor (TKI)?
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		
	Yes No Unknown		

Prior CML Therapy

Prior CML Therapy	Gleevec (imatinib) Sprycel (dasatinib) Tasigna (nilotinib) Ponatinib Other CML Treatment
Please specify	
Frequency	QD BID Other
Please specify:	
Dose	
Please specify:	
Start Date *(For partial dates use UN for missing day and month. Example: UN/MAR/2013)*	
Stop Date *(For partial dates use UN for missing day and month. Example: UN/MAR/2013)*	
Reason for discontinuation	Intolerance Lack of response Loss of response Other
Please specify	
Was mutation testing done?	Yes No
Please specify mutation testing	
Please specify	

Please specify

Hematological	
Anemia	☐
Thrombocytopenia	☐
Neutropenia	☐
Non-Hematologic	
Rash	☐

Gastrointestinal		
Diarrhea	☐	⊕
Nausea	☐	⊕
Abdominal Pain	☐	⊕
Vomiting	☐	⊕
Hepatotoxicity		
ALT Increased	☐	⊕
AST Increased	☐	⊕
Vascular Toxicity		
Cardiovascular	☐	⊕
Cerebrovascular	☐	⊕
Peripheral Vascular	☐	⊕
Cardiotoxicity		
QTc Prolongation	☐	⊕
Fluid Retention	☐	⊕
Cardiac failure/decreased LVEF	☐	⊕
Musculoskeletal		
Arthralgia	☐	⊕
Back Pain	☐	⊕
Myalgias/Muscle cramps	☐	⊕
Other		
Fatigue	☐	⊕
Pleural effusion	☐	⊕
Edema	☐	⊕
Pancreatitis	☐	⊕
Myalgias/Muscle cramps	☐	⊕
Please specify other	☐	⊕
Specify		⊕

Best response	
Best response for the specified treatment	Unknown Hematologic Cytogenetic Molecular
Hematologic	Complete Partial
Cytogenetic	Complete Partial Major Minor
Molecular	Complete Major

SOKAL Assessment at Baseline

Was Sokal Score assessed at this visit?	Yes No
Please specify:	Low Intermediate High

Investigator Assessment of CML at Baseline

Date of Assessment:

CML Phase at Baseline:
- Chronic
- Accelerated
- Blast

ECOG Performance Status at Baseline

Was ECOG performance status known at diagnosis?	Yes No
Was ECOG performance status known at baseline?	Yes No
Please specify:	Fully active, able to carry on all pre-disease performance without restriction. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Chemistry

Was a lab test performed?	Yes / No
Date of Collection:	
Laboratory Name:	

Not Done	Lab Test Name	Lab Test Result	Units	Clinically Significant	Lower Range	Upper Range	Export Unit
☐	ALT			Yes No			
☐	AST			Yes No			
☐	Alkaline Phosphatase			Yes No			
☐	Bilirubin, total			Yes No			
☐	Bilirubin, direct			Yes No			
☐	LDH			Yes No			
☐	Albumin			Yes No			
☐	Amylase			Yes No			

☐	Lipase			Yes No			
☐	Serum Creatinine			Yes No			
☐	Glucose, fasting			Yes No			
☐	Glucose, non-fasting			Yes No			
☐	Magnesium			Yes No			
☐	Calcium			Yes No			
☐	T3			Yes No			
☐	TSH			Yes No			
☐	T4			Yes No			
☐	Blood Urea			Yes No			
☐	Uric Acid			Yes No			
☐	INR			Yes No			
☐	Pregnancy Test (Blood)			Yes No			

Pregnancy Test (Urine)

Not done: ☐	Result: Negative / Positive

Other Lab Test(s)

Lab Test Name	Lab Test Result	Units	Clinically Significant
			Yes No

Hematology

Did the patient receive a blood transfusion since their last visit?	Yes No Unknown
What type of blood transfusion?	RBC Platelets
Was a lab test performed?	Yes No
Date of Collection:	
Laboratory Name:	

Not Done	Lab Test Name	Lab Test Result	Units	Clinically Significant	Lower Range	Upper Range	Export Unit
☐	Hemoglobin			Yes No			
☐	Hematocrit			Yes No			
☐	WBC			Yes No			
☐	RBC			Yes No			
☐	Platelets			Yes No			
☐	Peripheral blood blasts			Yes No			
☐	Basophils			Yes No			
☐	Eosinophils			Yes No			
☐	Neutrophils			Yes No			
☐	Monocytes			Yes No			
☐	Lymphocytes			Yes No			
☐	Band Cells			Yes No			

Did the Investigator assess Hematological Response?	Yes No
Was a complete hematological response achieved?	Yes No

CML Laboratory Assessments

CYTOGENETIC:

Was bone marrow cytogenetics performed?	Yes / No / Unknown
Date of Collection:	
Percentage of Ph+ metaphases (%):	

FISH:

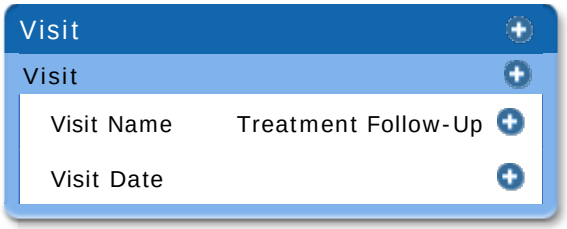
Was FISH (fluorescence in situ hybridization) test performed?	Yes / No / Unknown
Please specify the source:	Bone Marrow / Peripheral Blood
Percentage of positive nuclei (%):	
Date of Collection:	

MOLECULAR:

Was Quantitative RT-PCR test performed?	Yes / No / Unknown
On international scale?	Yes / No / Unknown
BCR/ABL (%):	
ABL (control gene):	
Date of Collection:	

INVESTIGATOR ASSESSMENT:

CYTOGENETIC:
MOLECULAR:


Visit
Visit
Visit Name
Treatment Follow-Up
Visit Date

Chemistry

Was a lab test performed?	Yes / No
Date of Collection:	
Laboratory Name:	

Not Done	Lab Test Name	Lab Test Result	Units	Clinically Significant	Lower Range	Upper Range	Export Unit
☐	ALT			Yes No			
☐	AST			Yes No			
☐	Alkaline Phosphatase			Yes No			
☐	Bilirubin, total			Yes No			
☐	Bilirubin, direct			Yes No			
☐	LDH			Yes No			
☐	Albumin			Yes No			
☐	Amylase			Yes No			

☐	Lipase			Yes No			
☐	Serum Creatinine			Yes No			
☐	Glucose, fasting			Yes No			
☐	Glucose, non-fasting			Yes No			
☐	Magnesium			Yes No			
☐	Calcium			Yes No			
☐	T3			Yes No			
☐	TSH			Yes No			
☐	T4			Yes No			
☐	Blood Urea			Yes No			
☐	Uric Acid			Yes No			
☐	INR			Yes No			
☐	Pregnancy Test (Blood)			Yes No			

Pregnancy Test (Urine)

Not done: ☐	Result: Negative / Positive

Other Lab Test(s)

Lab Test Name	Lab Test Result	Units	Clinically Significant
			Yes No

Hematology

Did the patient receive a blood transfusion since their last visit?	Yes No Unknown
What type of blood transfusion?	RBC Platelets
Was a lab test performed?	Yes No
Date of Collection:	
Laboratory Name:	

Not Done	Lab Test Name	Lab Test Result	Units	Clinically Significant	Lower Range	Upper Range	Export Unit
☐	Hemoglobin			Yes No			
☐	Hematocrit			Yes No			
☐	WBC			Yes No			
☐	RBC			Yes No			
☐	Platelets			Yes No			
☐	Peripheral blood blasts			Yes No			
☐	Basophils			Yes No			
☐	Eosinophils			Yes No			
☐	Neutrophils			Yes No			
☐	Monocytes			Yes No			
☐	Lymphocytes			Yes No			
☐	Band Cells			Yes No			

Did the Investigator assess Hematological Response?	Yes No
Was a complete hematological response achieved?	Yes No

CML Laboratory Assessments

CYTOGENETIC:

Was bone marrow cytogenetics performed?	Yes / No / Unknown
Date of Collection:	
Percentage of Ph+ metaphases (%):	

FISH:

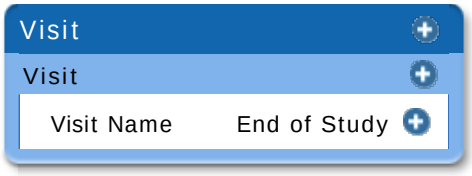
Was FISH (fluorescence in situ hybridization) test performed?	Yes / No / Unknown
Please specify the source:	Bone Marrow / Peripheral Blood
Percentage of positive nuclei (%):	
Date of Collection:	

MOLECULAR:

Was Quantitative RT-PCR test performed?	Yes / No / Unknown
On international scale?	Yes / No / Unknown
BCR/ABL (%):	
ABL (control gene):	
Date of Collection:	

INVESTIGATOR ASSESSMENT OF RESPONSE:

- CYTOGENETIC:
- MOLECULAR:


Visit
Visit
Visit Name
End of Study

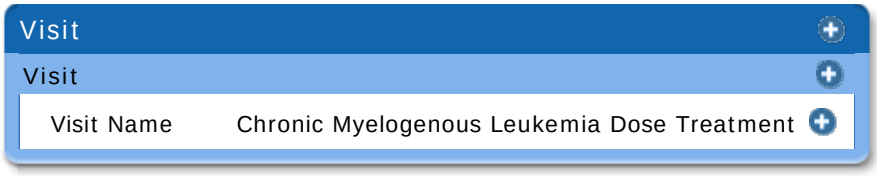
Investigator Assessment of Best Response During Treatment

Was Investigator Assessment of Best Response performed?	Yes / No
Date of Assessment:	
Best Response (check all that apply)	
Hematologic	☐
Cytogenetic	☐
Molecular	☐
No Response	☐
Unknown	☐
Please specify Hematologic response:	Complete / Partial
Please specify Cytogenetic response:	Complete / Partial / Minor
Please specify Molecular response:	Complete / Major
Did CML status change to Accelerated or Blast phase during treatment?	Yes / No
Please provide date:	

Trial Name: A Non-Interventional Study of Bosutinib Site Name: Casebook Version MSC002
Subject ID: Visit Name: End of Study

Subject Summary

Subject:	¦ Completed Follow up Period ¦ Withdrawn without taking treatment ¦ Withdrawn during Follow up Period
Date subject withdrawn:	
Please indicate ONE primary Reason for withdrawal :	¦ No response ¦ Loss of response ¦ Intolerance - Adverse event(s) (As Noted in the CRF adverse event page) ¦ Patient died ¦ Lost to follow-up (Patient could not be contacted by telephone or other means) ¦ Investigator no longer willing to participate study ¦ Patient no longer willing to participate in study ¦ Withdrawn due to pregnancy ¦ Study terminated by sponsor ¦ Other
Date of death: *(For partial dates use UN for missing day and month. Example: UN/MAR/2013)*	
Cause of Death:	
Date of last contact:	
Please specify:	
Please specify:	
Please specify:	

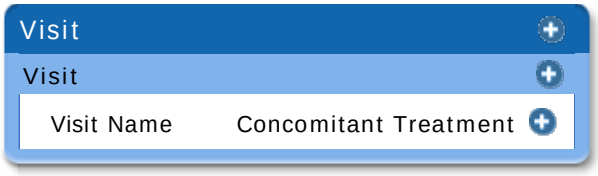

Visit
Visit
Visit Name
Chronic Myelogenous Leukemia Dose Treatment

Chronic Myelogenous Leukemia Dose Treatment

Drug Name	
Start Date:	
Stop Date:	
Ongoing	☐
Was patient compliance assessed?	Yes No
Was patient compliant with Bosutinib?	Yes No
Percentage of compliance (%):	
Dose:	
Please specify:	
Frequency:	Once a day Twice a day Other
Please specify:	

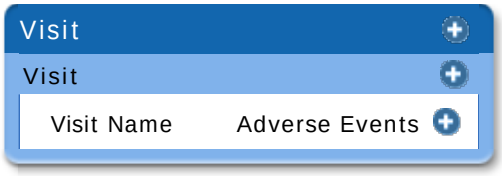
If there is any dose changed since the previous visit, please record a stop date and log a new dosing page and clarify the reason for dose changed below

Reason for dose change:	Lack of Response to Treatment Loss of Response to Treatment Intolerance Social Preference Other
Please specify:	


Visit
Visit
Visit Name
Concomitant Treatment

Concomitant Treatment

CM Number:	
Drug Name (Generic preferred but use brand name for combination product):	
Dose:	
Dose Unit:	
Please specify:	
Reason for use:	Adverse Event Medical History Overall Health Maintenance Not specified Other
Please specify:	
Please specify AE: *If the reason for use for the concomitant medication is AE, then enter the corresponding AE on the AE form prior to completing the CM form.*	
Please specify MH:	
Start Date: *(For partial dates use UN for missing day and month. Example: UN/MAR/2013)*	
Stop Date: *(For partial dates use UN for missing day and month. Example: UN/MAR/2013)*	
Ongoing	☐


Visit
Visit
Visit Name
Adverse Events

Trial Name: A Non-Interventional Study of Bosutinib Site Name: Casebook Version MSC002
Subject ID: Visit Name: Adverse Events

Adverse Event(s)

Visit

Did the patient experience an adverse event?

- Yes
- No

If any adverse events have occurred, this page must be completed. Adverse events that are present through more than one visit should be recorded only once. Please document all adverse events regardless of causal relationship to Bosutinib.

Adverse Event Report

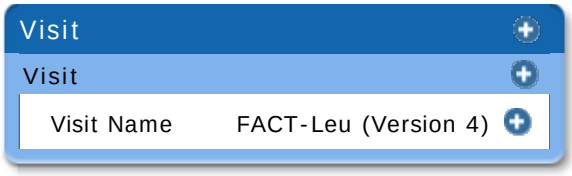
AE Number:		
Adverse Event (if possible, specify diagnosis not individual symptoms):		
Date of onset (Approximate date if actual not known):		
Severity:		
Action Taken with Bosutinib Dose:		
Action Taken (Check all relevant options)		
No action	☐	
Withdrawn from the study	☐	
Concomitant treatment given	☐	
Other	☐	
Please specify:		
Do serious criteria apply?	○ Yes ○ No	
FOR PFIZER USE ONLY - CASE ID #:		

Check all relevant criteria

Resulted in death	☐	
Life-Threatening	☐	
Hospitalization/Prolongation of hospitalization	☐	
Persistent/Significant disability/Incapacity	☐	
Congenital anomaly/Birth defect	☐	
Important medical event	☐	

Complete the following section when causality is determined, when the event resolved or at the end of the study, whichever occurs first

Outcome of AE to date: Still present?	Yes No - resolved Unknown
Was outcome resolved with sequelae?	Yes No
Date Resolved:	
Causality: Is there a reasonable possibility the adverse event is related to study treatment?	Yes No
What was the most likely cause of the AE?	Disease under study Other illness Concomitant medication Other
Please specify:	
Please specify:	


Visit
Visit
Visit Name
FACT-Leu (Version 4)

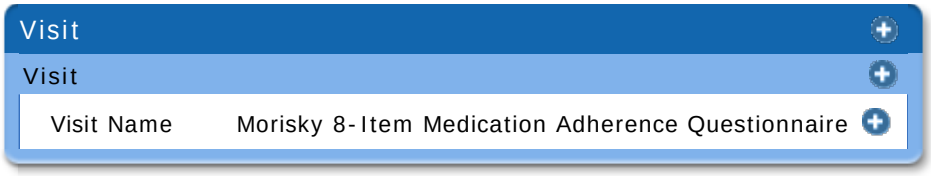
FACT-Leu (Version 4)

	Please tick if Questionnaire is filled on paper	☐
	Date of Questionnaire	

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days

	PHYSICAL WELL-BEING	
GP1.	I have a lack of energy	
GP2.	I have nausea	
GP3.	Because of my physical condition, I have trouble meeting the needs of my family	
GP4.	I have pain	
GP5.	I am bothered by side effects of treatment	
GP6.	I feel ill	
GP7.	I am forced to spend time in bed	
	SOCIAL/FAMILY WELL-BEING	
GS1.	I feel close to my friends	
GS2.	I get emotional support from my family	
GS3.	I get support from my friends	
GS4.	My family has accepted my illness	
GS5.	I am satisfied with family communication about my illness	
GS6.	I feel close to my partner (or the person who is my main support)	
Q1.	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*	☐
GS7.	I am satisfied with my sex life	
	EMOTIONAL WELL-BEING	
GE1.	I feel sad	
GE2.	I am satisfied with how I am coping with my illness	
GE3.	I am losing hope in the fight against my illness	
GE4.	I feel nervous	
GE5.	I worry about dying	
GE6.	I worry that my condition will get worse	
	FUNCTIONAL WELL-BEING	
GF1.	I am able to work (include work at home)	
GF2.	My work (include work at home) is fulfilling	

GF3.	I am able to enjoy life
GF4.	I have accepted my illness
GF5.	I am sleeping well
GF6.	I am enjoying the things I usually do for fun
GF7.	I am content with the quality of my life right now
	ADDITIONAL CONCERNS
BRM3.	I am bothered by fevers (episodes of high body temperature)
P2.	I have certain parts of my body where I experience pain
BRM2.	I am bothered by the chills
ES3.	I have night sweats
LEU1.	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)
TH1.	I bleed easily
TH2.	I bruise easily
HI12.	I feel weak all over
BMT6.	I get tired easily
C2.	I am losing weight
C6.	I have a good appetite
An7.	I am able to do my usual activities
N3.	I worry about getting infections
LEU5.	I feel uncertain about my future health
LEU6.	I worry that I might get new symptoms of my illness
BRM9.	I have emotional ups and downs
LEU7.	I feel isolated from others because of my illness or treatment


Visit
Visit
Visit Name
Morisky 8-Item Medication Adherence Questionnaire

Morisky 8-Item Medication Adherence Questionnaire

Please select 'Add Form' at Visit level to add an additional Questionnaire.

Please tick if Questionnaire is filled on paper	☐	
Date of Questionnaire		

1. Do you sometimes forget to take your medicine?	Yes	No
2. People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?	Yes	No
3. Have you ever cut back or stopped taking your medicine without telling your doctor, because you felt worse when you took it?	Yes	No
4. When you travel or leave home, do you sometimes forget to bring along your medicine?	Yes	No
5. Did you take all your medicines yesterday?	Yes	No
6. When you feel like your symptoms are under control, do you sometimes stop taking your medicine?	Yes	No
7. Taking medicine everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	Yes	No
8. How often do you have difficulty remembering to take all your medicine?		

CONSENT TO TAKE PART IN A NON-INTERVENTIONAL RESEARCH STUDY

Name of Research Study: **A Non-Interventional Study of Bosutinib in Patients with Previously Treated Chronic Phase Chronic Myelogenous Leukemia (CML)**

Protocol Number: **B1871042**

Name of Company Sponsoring the Research Study: **Pfizer, Inc.**

Name of Principal Investigator (Study Doctor):

Address of Research Site:

Daytime Phone Number:

24-Hour Phone Number:

This consent document is for use in a research study that will involve research participants who may or may not have the capacity to consent to their participation. In this consent document, "you" refers to the research participant. If you are a legal representative, please remember that "you" refers to the research participant.

This consent document gives you important information about the non-interventional research study you have been asked to participate in. A non-interventional study collects information only. Your doctor will manage your care no differently than if you were not part of this study.

Please read this information carefully before deciding to take part. No one can make you take part and you can stop at any time. If you choose to take part in this research study, you will need to sign this consent document and you will receive a copy of the signed document for your records.

This research study is being conducted for Pfizer. Pfizer is sponsoring the study and will be paying [study doctor/Institution] to conduct the study.

The following sections describe the research study. Before you decide to take part, please take as much time as you need to ask questions of the site staff, with family and friends, or with your personal physician or other healthcare professional. The site staff will fully answer any questions you have before you make a decision.

1. WHAT IS THE PURPOSE OF THE STUDY?

You are being asked to take part in this research study because you been prescribed bosutinib treatment for the treatment of previously treated Chronic Phase Chronic Myelogenous Leukemia and are 18 years or older. There is a need to learn more about the use of Bosutinib (BOSULIF®) in clinical practice. For this reason, Pfizer is conducting a prospective, observational, non-interventional study to collect additional information on the good and bad effects of the drug, Bosutinib, which has been prescribed to you by your doctor.

2. HOW MANY OTHER PEOPLE WILL BE IN THE STUDY AND HOW LONG WILL PARTICIPATION IN THE STUDY LAST?

There will be about 170 people enrolled in this study. This study is being done at about 30 different research sites in the United States. Approximately 4 people will be enrolled at this site.

3. HOW LONG WILL PARTICIPATION IN THE STUDY LAST?

Your participation in this study will last for 12 months. You will visit the study site during your regular clinic visits to your doctor.

4. WHAT WILL HAPPEN DURING THE STUDY?

Before starting the study, you should know that your doctor will provide usual routine medical care as he/she normally would do for any patient with CML. The routine medical care will not be changed in any way by your decision to take part in this study. You and your doctor will decide what treatment(s) you receive. Your doctor will also give you a prescription as he/she normally would do when you get new or added medications. If you agree to take part in this study, you will see your doctor as you normally would for all of your office visits. While in this study the doctor will replace your name with a special code or subject number that identifies you.

It is important to take your medications as the doctor tells you. Tell your doctor about all medications you are taking, and if you have stopped taking any medications. This includes prescription drugs, over-the-counter medicines, including herbal treatments, and vitamins. You should contact your doctor about unusual symptoms that you may be feeling. Your doctor will help you as he/she should in your normal routine care.

To be included in this study, you will need to sign the consent form. After signing the consent form, your routine and follow-up office visits will not change. In addition to coming in for your regular office visits, your study doctor will collect information about you, such as your medical history and personal information such as your age, date of birth, race, gender and your height and weight. You will also be asked to complete

two questionnaires called the Morisky 8-Item Medication Adherence Questionnaire and FACT-Leu (Version 4) called Patient Reported Outcomes (PROs).

Patient Reported Outcomes Questionnaires (PROs):

If you agree to take part in this study, you should know that you will be asked to answer some questions in the form of questionnaires. These are called Patient Reported Outcomes (PRO). These questionnaires will ask you questions about:

- your CML symptoms
- how you feel
- the quality of your life and work
- how satisfied you are with taking your medications

All of the questionnaires are easy to follow, and each one of them will take approximately 20 minutes of your time. Completing the PROs is optional and not a requirement to participate in the study. You will be asked to complete the questionnaires during the following times throughout your participation in the study:

Fact-Leu Version 4 questionnaire will be collected at the baseline visit. Morisky 8-Item Medication Adherence Questionnaire and Fact-Leu Version 4 questionnaires will be collected at least one time in Weeks 4, 8, 12, and every 12 weeks for 12 months.

You will be asked to complete internet and/or paper questionnaires during your baseline and routine follow up visits to your doctor. You will be asked to provide an email address to complete the questionnaire over the internet. The research staff will instruct you on how to complete the questionnaires.

The questionnaires will be used to collect information about you as a patient. They are not to be used to report unusual or serious medical symptoms or conditions. If you experience any unusual or serious signs or symptoms, contact your doctor. Your doctor can help you as he/she would in accordance with his/her medical practices.

Your participation in this study is voluntary and you can withdraw from the study at any time. The medical care you receive from your doctor will not be affected in any way, whether or not you decide to stay in the study. The investigator has the right to stop your participation at any time. This could be because you have failed to follow instructions or because the entire study has been stopped, or for any other reason.

If you are pregnant or nursing a child you will not be allowed to participate in this study. If you plan to become pregnant, you should not take part in this study. If there is any possibility that you can become pregnant during the study, your doctor will discuss birth control methods with you. If you would like more information about birth control, ask your doctor. If you think you have become pregnant during the study,

contact your doctor immediately. The doctor or study staff may ask for information about the pregnancy and the birth of the baby. The doctor or study staff may share this information with the sponsor and the Institutional Review Board (a group of people who review research studies to protect the rights and welfare of research participants).

5. WHAT ARE THE RISKS AND POSSIBLE DISCOMFORTS OF BEING IN THIS STUDY?

Bosutinib may cause some side effects, as described in the information sheet accompanying your prescription. Any negative affects you experience should be reported to your doctor. If you experience a serious adverse event, such as any illness requiring you to be hospitalized, report that to your study doctor immediately or as soon as possible.

Because this is a non-interventional study and you are receiving treatment with Bosutinib as part of your standard medical care, an adverse reaction to Bosutinib would not be considered a research injury.

Completing the questionnaires could cause you to feel uncomfortable or upset. Please tell your doctor or his/her staff if you feel uncomfortable or upset while filling out the questionnaires.

If you, or your partner, become pregnant during the study, please tell the study doctor immediately. Please also tell the doctor who will be taking care of you/your partner during the pregnancy that you were taking Bosutinib. The study doctor will ask if you/your partner or your pregnancy doctor is willing to provide updates on the progress of the pregnancy and its outcome. If you/your partner agree, this information will be provided to the study sponsor for safety monitoring follow-up.

6. WHAT OPTIONS ARE AVAILABLE OTHER THAN BEING IN THIS STUDY?

This study is for research purposes only. The only alternative is to not take part in this study and continue with your routine care/treatment.

7. WHAT ARE POSSIBLE BENEFITS OF BEING IN THIS STUDY?

This study is for research purposes only. There is no direct benefit to you from your participation in the study since you will receive your routine care/treatment. However, information learned from the study may help other people in the future.

8. IS BEING IN THE STUDY VOLUNTARY?

Yes. Taking part in this study is up to you. You may choose not to take part or you can change your mind and withdraw (drop out) later. There will be no penalty, and you will not lose any benefits you receive now or have a right to receive.

You will be given any new information gained during the course of the study that may affect your willingness to continue your participation.

9. WHAT WILL I HAVE TO PAY FOR IF I TAKE PART IN THIS STUDY?

There is no additional cost burden to you for being in this study.

Because this study is collecting information only and there is no change to your usual medical care, the sponsor will not pay for any treatments or procedures that you may receive during your participation in this study, including Bosutinib.

10. WILL I BE PAID FOR TAKING PART IN THIS STUDY?

You will not receive any payment for taking part in this study.

11. IF I TAKE PART IN THIS RESEARCH STUDY, HOW WILL MY PRIVACY BE PROTECTED?

A federal regulation known as the Privacy Rule gives you certain rights concerning the privacy of your health information. The Privacy Rule was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Researchers covered by this regulation are required to get your authorization (permission) to use and disclose (share with others) any health information that could identify you.

If you sign this informed consent form, you are giving permission for the use and disclosure of your health information for purposes of this research study. You do not have to give this permission. However, if you do not, you will not be able to take part in the study.

Who Will Use and Disclose My Health Information?
The study team at [Name of Covered Entity] may use your health information to conduct, review, and determine the results of the study. The study team may also use your information to prepare reports or publications about the study. However, your name will not appear in any report or publication.

What Health Information will be Used and Disclosed?
During the study, the study team will use, collect, and record health information about you (your “records”). Your records will include any information about you that the study team needs to do the study, including information from the procedures

described above. Your records may include other health information about you and will include identifying information such as your name and address. The study team will record some of this information on "study forms" provided by the study sponsor. Your name or address will not appear on the study forms. Instead, you will be assigned a participant identification number. The study team will send the completed study forms to the study sponsor and may share this information with others, as described below.

Representatives from the groups identified below may also need to look at your records (which identify you) to make sure that the information on the study forms is correct or that the study was conducted properly. Reviews like that will take place at the research site or where the records are stored and can take place after the study is over.

Who Will Receive My Health Information?

Your study information may be shared with the following people or groups:

- The study sponsor (Pfizer Inc) or its representatives, including companies it hires to provide study-related services
- Researchers who are conducting this study at other research sites
- The institutional review board (ethics committee) that approved this study and any other committees responsible for overseeing the research
- Government health agencies (such as the Food and Drug Administration) in the US or other countries
- [Insert additional people or entities, as appropriate]

Will My Information be Protected by the Privacy Rule After it is Disclosed to Others?

[Name of Covered Entity] is required by the Privacy Rule to protect your health information. After your information is shared with others, such as the study sponsor, it may no longer be protected by the Privacy Rule. The people who receive this information could use it in ways not discussed in this form and could disclose it to others. The study sponsor will use and disclose your information only for research or regulatory purposes or to prepare research publications. In addition to using it for this study, the study sponsor may reanalyze the study data at a later date or combine your information with information from other studies for research purposes not directly related to this study. The goal of any such research would be to learn more about drugs or diseases or to help design better studies in the future. When using your information in these ways, the study sponsor may share it with regulatory authorities, other researchers, its business partners, or companies it hires to provide research-related services. This could result in transfer of your information outside the United States. However, your name will never appear in any study sponsor reports or publications, or in any future disclosures by the study sponsor.

What Happens if I Leave the Study Early?

If you stop participating in the study early for any reason, the study team will tell the study sponsor why. If the study team asks you to come to any more study visits and you agree, the study team will send the study sponsor information from those visits as well. All information collected about you may continue to be used and disclosed.

Will My Authorization Ever Expire?
This Authorization does not have an expiration date. The study team may need to correct or provide missing information about you even after your study participation is over. The review of your medical records (described above) may also take place after the study is over.

May I Take Back My Authorization?
You have the right to take back (revoke) your Authorization at any time by writing to [name and address].

If you revoke your Authorization, the study team will not collect any new health information about you. However, they can continue to use and disclose any already collected information if that is necessary for the reliability (the scientific value) of the study. The study sponsor can also still keep and use any information that it has already received. In addition, during and after your participation in the study your study doctor will be required to report to the sponsor information related to any serious adverse effect that you may experience due to your participation in the study. If you revoke your Authorization, you can no longer continue to participate in the study.

May I Look At My Study Information?
You have a right to see and make copies of your medical records. However, to ensure the reliability of the study, you will need to wait to see your study records until the study is completed.

Confidentiality language for main consent if study site is using a stand-alone HIPAA form:
You will not be directly identified in connection with this study unless required by applicable laws or regulations. However, absolute confidentiality cannot be guaranteed because of the need to share your study-related information with others. The study sponsor or groups working for the sponsor, government health agencies in the US and other countries, the institutional review board for this study, and others may receive study-related information about you. They may also need to review your medical records to make sure the information on the study forms is correct and that the study was conducted properly. The sponsor will use and disclose your information only for research or regulatory purposes or to prepare research publications. In addition to using it for this study, the sponsor may reanalyze the study data at a later date or combine your information with information from other studies for research purposes not directly related to this study. The goal of any such

research would be to learn more about drugs or diseases or to help design better studies in the future. Your name will never appear in any sponsor reports or publications, or in any future disclosures by the sponsor.

The ways your study doctor will use your study-related health information and the people who may receive it are identified in a separate form entitled [Insert Title of Authorization form.] You will be asked to sign that form to show that you give permission for these uses and sharing of your information. You do not have to sign the authorization form. However, if you do not, you will not be able to participate in the study.

12. WHERE CAN I FIND ADDITIONAL INFORMATION ABOUT THIS RESEARCH STUDY OR THE RESEARCH RESULTS?

A description of this study will be available on the European Union (EU) post-authorization study (PAS) register ***http://www.encepp.eu/encepp/studiesDatabase.jsp***. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. It may be many years; however, before research results are posted.

If you need assistance understanding the content on this Web site, please ask your study doctor.

13. WHO SHOULD I CONTACT ABOUT MY RIGHTS OR IF I HAVE QUESTIONS?

Before you sign this document, you should ask questions about anything that you do not understand. The site staff will answer questions before, during, and after the study. If you do not think your question was fully answered or do not understand the answer, please continue to ask until you are satisfied.

If you have any concerns or complaints about this study or how it is being run, please discuss your concerns with the site staff. The phone numbers to reach the site staff are on the first page of this document. If you do not feel comfortable discussing your complaint with the site staff, please contact the [IRB, Patient Rights Advocate, Institutional Contact, or Bioethicist] listed below.

If you have any questions about your rights as a research participant, or you would like to obtain information or offer input, or you wish to speak with someone **not** directly involved with the study, you should contact:

Provide name, phone number and address of any of the following: (1) Institutional Review Board/Independent Ethics Committee (IRB/IEC); (2) Patient rights advocate; (3) Institutional contact; and/or, (4) Bioethicist.

14. CONSENT

I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given enough time and opportunity to ask about the details of the study and to decide whether or not to participate in the study. I voluntarily agree to take part in this study. I do not give up any of my legal rights by signing this consent document.

I have been told that I will receive a signed and dated copy of this document.

_____
Printed name of study participant

_____ _____ _____
Signature of study participant Date of signature Time (if needed)*

_____ _____ _____
Signature of legal representative Date of signature Time (if needed)*

_____
Printed name of legal representative and relationship

PERSON OBTAINING CONSENT

_____
Printed Name of the Person Conducting the Consent Discussion

_____ _____ _____
Signature of the Person Conducting the Consent Discussion Date of signature Time (if needed)*

A Non-Interventional Study of Bosutinib: B1871042
Demographic Characteristics

Subject ID	Age (Years)	Sex	Race	Weight (lbs)	Height (inch)
1002 10021001	40	Male	White	174	71
1012 10121001	61	Female	Black	295	64
1016 10161001	47	Female	Other	169	65

Treatment Group: Bosutinib

System Organ Class	Prefered Term/ INVESTIGATOR ENTRY	Dose**	Adverse Event: study start day+ /study end day	SEVERITY/ Outcome	ACTION/ Causality	SAE
10021001 (Male/ 40 (Years)/ White/ 174 (lbs)						
Gastrointestinal disorders	Diarrhoea / DIARRHEA	500 mg	140/ [>174]	Grade 1 (Mild) / Still Present	STUDY DRUG ACTION: Dose not changed SUBJECT ACTION: No action	No
10161001 (Female/ 47 (Years)/ Other/ 169 (lbs)						
Gastrointestinal disorders	Abdominal pain / ABDOMINAL PAIN	500 mg	32 /33	Grade 4 (Life threatening disabling) / Resolved (11NOV2014)	STUDY DRUG ACTION: Dose not changed SUBJECT ACTION: No action	Yes
	Diarrhoea / DIARRHEA	500 mg	32 /33	Grade 2 (Moderate) / Resolved (11NOV2014)	STUDY DRUG ACTION: Dose not changed SUBJECT ACTION: Concomitant treatment given	No

Age and weight are at screening
** Dose at onset of adverse event.
+ Day relative to start of study treatment. First day of study treatment = day 1
[] Values in brackets are imputed from incomplete dates and times.
SAE = Serious Adverse Event (according to Investigators assessment).
MedDRA (v17.0) coding dictionary applied.
PFIZER CONFIDENTIAL, Date of Reporting Dataset Creation 13MAY2015, Source is project database (PD),
Date of Table Generation 11JUN2015 16:06:08

Treatment Group: Bosutinib

System Organ Class	Prefered Term/ INVESTIGATOR ENTRY	Dose**	Adverse Event: study start day+ /study end day	SEVERITY/ Outcome	ACTION/ Causality	SAE
Gastrointestinal disorders	Gastrooesophageal reflux disease / WORSENING OF GERD	500 mg		Grade 2 (Moderate) / Unknown	STUDY DRUG ACTION: Dose not changed SUBJECT ACTION: Concomitant treatment given	No
	Vomiting / VOMITING	500 mg	32 /33	Grade 2 (Moderate) / Resolved (11NOV2014)	STUDY DRUG ACTION: Dose not changed SUBJECT ACTION: No action	No
General disorders and administration site conditions	Pyrexia / FEVER (INTERMITTENT)	500 mg	44/ [>1]	Grade 2 (Moderate) / Still Present	STUDY DRUG ACTION: Dose not changed SUBJECT ACTION: No action	No
Musculoskeletal and connective tissue disorders	Back pain / BACK PAIN	500 mg	44/ [>1]	Grade 2 (Moderate) / Still Present	STUDY DRUG ACTION: Dose not changed SUBJECT ACTION: Concomitant treatment given	No

Age and weight are at screening
** Dose at onset of adverse event.
+ Day relative to start of study treatment. First day of study treatment = day 1
[] Values in brackets are imputed from incomplete dates and times.
SAE = Serious Adverse Event (according to Investigators assessment).
MedDRA (v17.0) coding dictionary applied.
PFIZER CONFIDENTIAL, Date of Reporting Dataset Creation 13MAY2015, Source is project database (PD),
Date of Table Generation 11JUN2015 16:06:08

Treatment Group: Bosutinib

System Organ Class	Prefered Term/ INVESTIGATOR ENTRY	Dose**	Adverse Event: study start day+ /study end day	SEVERITY/ Outcome	ACTION/ Causality	SAE
Musculoskeletal and connective tissue disorders	Pain in extremity / LEG PAIN (BILATERAL)	500 mg	44/ [>1]	Grade 2 (Moderate) / Still Present	STUDY DRUG ACTION: Dose not changed SUBJECT ACTION: Concomitant treatment given	No

Age and weight are at screening
** Dose at onset of adverse event.
+ Day relative to start of study treatment. First day of study treatment = day 1
[] Values in brackets are imputed from incomplete dates and times.
SAE = Serious Adverse Event (according to Investigators assessment).
MedDRA (v17.0) coding dictionary applied.
PFIZER CONFIDENTIAL, Date of Reporting Dataset Creation 13MAY2015, Source is project database (PD),
Date of Table Generation 11JUN2015 16:06:08

A Non-Interventional Study of Bosutinib: B1871042
Serious Adverse Events

Actual Treatment Group: Bosutinib

Patient Identifier(Country/Sex/Age at Onset(a)/Race/Weight(Kg))

AER Number	Suspect Drug(s) Dose (b)	Action Taken (Drug level)	Therapy Stop Day(c)	Event Onset Day(d)	Event Stop Day(e)	Verbatim Term/ MedDRA Preferred Term	Investigator Causality/ Sponsor Causality	Clinical Outcome / Seriousness
10161001 (UNITED STATES /FEMALE /47 YEARS /HISPANIC /78.73 Kg)								
2014358134	BOSUTINIB / 500 mg DAILY	DOSE NOT CHANGED	UNK	32	33	abdominal pain ABDOMINAL PAIN	RELATED /RELATED	RECOVERED/RESOLVED WITH SEQUEL //SERIOUS

(a) Age at date of SAE onset.
(b) Source of Actual treatment Group or Sequence is project database (PD) and source of Suspect Drug is from SDW. Dose for treatment(s) at the earliest ONSET date.
(c) Therapy stop day is calculated as PD last active therapy date minus PD first active therapy date plus one.
(d) Onset study day is calculated as SDW onset date minus PD first active therapy date plus one.
(e) Event stop day is calculated as SDW SAE stop date minus PD first active therapy date plus one.
(f) Onset period day is calculated as SDW onset date minus PD treatment period start date plus one.
N/A = Not Available or Not Applicable UNK = Unknown
MedDRA v.18.0 coding dictionary applied