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
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Date of last version of protocol	Non Applicable
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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

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Marketing Authorisation Holder

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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
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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

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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