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Phase II Study Testing the Tolerability and the Efficacy of Bosutinib in Chronic Phase CML Patients (BODO)

ClinicalTrials.gov Identifier: NCT03205267

Recruitment Status: Recruiting
First Posted: July 2, 2017
Last Update Posted: July 2, 2017

See **Contacts and Locations**

Sponsor:
University of Bonn

Collaborators:
RWTH Aachen University
Ludwig-Maximilians - University of Munich
University of Jena
Heidelberg University
Pfizer

Information provided by (Responsible Party):
Prof. Dr. Dominik Wolf, University of Bonn

Study Details | **Tabular View** | **No Results Posted** | Disclaimer | How to Read a Study Record

Study Description

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Brief Summary:
Bosutinib is a 2nd generation tyrosine kinase inhibitor that has shown promising results from first up to fourth line treatment in patients with in chronic phase of chronic myelogenous leukaemia. Most patients discontinuing the treatment with Bosutinib do so because of side effects occuring early after starting the treatment. A step in dosing scheme could improve these early toxicities. The aim of this study therefore is to demonstrate that temporary lowering of the Bosutinib dose during early treatment may help to reduce or prevent side effects while preserving efficacy.

Condition or disease	Intervention/treatment	Phase
Chronic Myelogenous Leukaemia	Drug: Bosulif	Phase 2

Detailed Description:

Objectives:

The objective of the BODO trial is to assess the tolerability and efficacy of a step-in dosing concept of the dual SRC-ABL kinase inhibitor Bosutinib in CP-CML patients who either developed intolerance or treatment failure to previous Imatinib, Dasatinib or Nilotinib as 1st line therapy.

Primary endpoint:

• Rate of GI-Toxicity (i.e. incidence and severity of grade 2 to 4 toxicities) within the first 6 months of treatment

Secondary endpoints:

- Tolerability (i.e. all grade, grade 2 to 4 and grade 3 and 4 toxicities) at month 6, 12 and 24
- Efficacy parameters: CCyR, MMR, MR4 and MR4.5 rate at month 3, 6, 12, 18 and 24
- Patient-reported outcome measures (QoL)
- Progression-free survival (PFS)
- Overall survival (OS)
- The rate of emerging mutations during Bosutinib treatment

Exploratory endpoints linked to substudies:

Vascular biology substudy:

- Effects of previous therapy on the baseline vascular risk profile (i.e. Nilotinib- vs. Dasatinib-pre-treatment)
- Biological and clinical surrogates for vascular alterations during Bosutinib therapy at baseline, months 6, 12, and 24

Pharmacokinetic (PK), pharmacodynamic (PD) and immunology sub- study:

- Correlation of PK with response and toxicity
- Correlation of PK with PD (i.e. phosphoproteomic changes) in immune cell populations
- Correlation of PD changes in immune cell populations with response
- Evaluation of the effects of Bosutinib on frequency and phenotype of immune cells
- Evaluation whether Bosutinib-induced changes of immune cells correlate to response

Ultra-deep next-generation sequencing (UD-NGS) and telomere substudy:

- Documentation of subclone evolution or elimination during Bosutinib treatment
- Evaluation of telomere length in leukemic and non-leukemic cells as a prognostic indicator for depth and kinetics of response to and tolerability of Bosutinib

Study Design

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Study Type:	Interventional (Clinical Trial)
Estimated Enrollment:	127 participants
Intervention Model:	Single Group Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Multicenter, Open-label Single Arm Phase II Study Testing the Tolerability and the Efficacy of Bosutinib step-in Dosing in Chronic Phase CML Patients Intolerant or Refractory to Previous Imatinib, Nilotinib or Dasatinib Therapy
Study Start Date:	March 2016
Estimated Primary Completion Date:	October 2019
Estimated Study Completion Date:	October 2019

Resource links provided by the National Library of Medicine

Genetics Home Reference related topics:
Chronic myeloid leukemia

Drug Information available for: Bosutinib

Genetic and Rare Diseases Information Center resources:
Chronic Myeloid Leukemia Myeloid Leukemia
Chronic Myeloproliferative Disorders

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Experimental: Bosutinib Drug: Bosulif 100 mg or 500 mg tablets step in dosing scheme	Drug: Bosulif Patients will start with dose-level 1 (300 mg once daily) Bosutinib. If patients do not experience any toxicity or only G1 toxicity, they will be dose-increased first to dose-level 2 (400 mg once daily) and then to dose-level 3 (500 mg once daily). Dose will not be escalated above 500 mg which is the dose recommended by the summary of product information. If patients experience G2 toxicity, the study drug will be further continued at the same dose-level. In patients with G3 or G4 toxicities, therapy will be withheld until toxicity resolved to <G2. Other Name: Bosutinib

Outcome Measures

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Primary Outcome Measures:

1. Rate of GI-Toxicity (i.e. incidence and severity of grade 2 to 4 toxicities) [Time Frame: within the first 6 months of treatment]

   calculation of the incidence rate of grade 2 to 4 GI toxicity with and without regard to causality

Secondary Outcome Measures:

1. overall Tolerability (i.e. all grade, grade 2 to 4 and grade 3 and 4 toxicities) [Time Frame: at month 6, 12 and 24]

   Apart from grade 2 to 4 GI toxicity, the occurrence of toxicity will be analyzed in general. This regards all grade toxicity, 2 to 4 grade and 3 to 4 grade toxicity (NCI CTCAE v4.0).

2. Molecular response mesured by efficacy parametern [Time Frame: at month 3, 6, 12, 18 and 24]

   Rating of CCyR, MMR, MR4 and MR4.5 after bone marrow aspiration and biopsy

3. Patient-reported outcome measures (QoL) [Time Frame: at month 3 and 6]

   The EORTC QLQ-CML30 will be scored according to the respective user's guides.

4. Progression-free survival (PFS) [Time Frame: at month 3, 6, 9, 12, 15, 18, 21 and 24]

   Progression will be assessed according to the visit schedule at any visit.

5. Overall Survival (OS) [Time Frame: at month 3, 6, 9, 12, 15, 18, 21 and 24]

   Survival will be assessed according to the visit schedule at any visit.

6. The rate of emerging mutations during Bosutinib treatment [Time Frame: at month 3, 6, 9, 12, 15, 18, 21 and 24]

   The rate and type of mutations will be described. The rate will be given as percentage of patients developing mutations.

Other Outcome Measures:

1. Vascular biology substudy: analysis of clinical and laboratory vascular and metabolic risk factors [Time Frame: baseline, at months 6, 12 and 24]

   Ankle Brachial Index (ABI) will be prospectively evaluated followed by analysis of various biomarkers for vascular damage

2. Pharmacokinetic (PK), pharmacodynamic (PD) substudy [Time Frame: at day 1, months 1, 2, 3, 12, 18, 24]

   It is planned to analyze PK parameters sequentially by taking serum from PB and subsequent HPLC-MS/MS technology. Pharmacodynamics in different compartments will be analyzed by means of flow-cytometry of PB and BM samples.

3. Telomere substudy [Time Frame: at months 1, 2, 3, 12 and 24]

   Assessment of telomere length in normal and leukemic cells as potential new biomarker for prognosis, prediction of response under Bosutinib

4. Ultra-deep next-generation sequencing (UD-NGS) [Time Frame: at months 1, 2, 3, 12 and 24]

   Documentation of subclone evolution or elimination during Bosutinib treatment

5. Assessment of patients comorbidities and correlation to individual patient´s adverse side effect profile substudy [Time Frame: through study completion, an average of 2 years]

   Documentation of patient´s comorbidity profile using 3 different comorbidity scales

6. Transport mechanisms of Bosutinib and mechanisms of diarrhea substudy [Time Frame: every 14 days month 1-3]

   Investigation the role of the 5-HT pathway in directing bosutinib induced diarrhea by assessment of 5-HT and certain cytokine levels and genetic analysis including SNP and GWAS

Eligibility Criteria Go to

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Signed written informed consent
- Male or female patients aged ≥18 years
- ECOG performance status of 0 to 2
- CML in 1st or late chronic phase
- Intolerant or resistant to pretreatment with one of the approved 1st line TKIs (Imatinib, Nilotinib or Dasatinib). Imatinib therapy prior to 2nd generation TKI therapy for a maximum of 6 weeks is allowed.
- Patients must have a serum creatinine of ≤ 2 x ULN, SGOT/SGPT ≤ 3 x ULN, total bilirubin ≤ 2 x ULN (except known Gilbert's syndrome), and Lipase ≤ 1.5 x ULN
- Female patients of childbearing potential must have a negative pregnancy test performed during screening period
- Male and female patients of reproductive potential must currently use a highly effective contraceptive method and be willing to keep on using it throughout the study and for 6 months following discontinuation of study drug.

Exclusion Criteria:

- Hypersensitivity against Bosutinib or other ingredients of the medicinal product
- Evidence of features of accelerated (AP) or blast phase (BC) at any time before inclusion
- Patients with BCR-ABL negative CML
- Patients having received Imatinib for more than 6 weeks prior to initiation of 2nd generation TKI (either Nilotinib or Dasatinib)
- Patients with known T315I or V299L mutation
- Concomitant medications known to be strong inducers or inhibitors of P450 isoenzyme CYP3A4
- History of pancreatitis, inflammatory bowel disease requiring systemic or topical immunosuppressive therapy within the last 12 months
- Impaired cardiac function, including any of the following:
    1. History of or presence of complete left bundle branch block, right bundle branch block plus left anterior hemiblock, bifascicular block in screening ECG
    2. ST depression of >1mm in 2 or more leads and/or T wave inversions in 2 or more contiguous leads in screening ECG
    3. Congenital long QT syndrome
    4. QTc> 450 msec in the screening ECG
    5. QT-prolonging concomitant medication
    6. History of or presence of significant ventricular or atrial tachyarrhythmias in screening ECG

7. History of or presence of clinically significant resting bradycardia (< 50 beats per minute)
8. Myocardial infarction within 6 months prior to inclusion
9. Unstable angina diagnosed or treated during the past 12 months
10. Uncontrolled hypertension, history of labile hypertension

- Known HIV and/or active viral hepatitis (hepatitis B or C). Hepatitis B screening will be performed at screening. Patients with history of hepatitis B with negative HBV DNA may be included when using antiviral prophylaxis
- Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinoma of the skin
- Treatment with another investigational product during this study or during the last 30 days prior to study start, except treatment with Interferon alpha within the TIGER (CML V) protocol, which must be stopped at least 7 days prior to study entry
- Any circumstance at the time of study entry that would preclude completion of the study or the required follow-up prohibits inclusion into this study
- Patient must not have any active bacterial, viral or fungal infection at screening
- Patient must not have severe cerebral dysfunction and/or legal incapacity
- Conditions which interfere with the study treatment at the discretion of the investigator
- Women who are pregnant or breast feeding

Contacts and Locations

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Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT03205267***

Contacts

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Locations

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Ludwig-Maximilians - University of Munich

University of Jena

Heidelberg University

Pfizer

Investigators

Principal Investigator:	Dominik GF Wolf, Prof. Dr.	University of Bonn Medical Faculty
Study Chair:	Brümmendorf H Tim, Prof. Dr.	University of Aachen Medical Faculty

More Information

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Responsible Party:	Prof. Dr. Dominik Wolf, Principal Investigator Prof. Dr. med. D. Wolf, University of Bonn
ClinicalTrials.gov Identifier:	NCT03205267 History of Changes
Other Study ID Numbers:	MED3-201401-**BODO** 2014-005531-13 (EudraCT Number)
First Posted:	July 2, 2017 Key Record Dates
Last Update Posted:	July 2, 2017
Last Verified:	June 2017

Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD: No

Additional relevant MeSH terms:

Leukemia, Myeloid	Neoplasms
Leukemia, Myelogenous, Chronic, BCR-ABL Positive	Myeloproliferative Disorders
Leukemia, Myeloid, Chronic-Phase	Bone Marrow Diseases
Leukemia	Hematologic Diseases
Neoplasms by Histologic Type	