A Phase 4 Safety and Efficacy Study of Bosutinib (Bosulif®) in Patients with Philadelphia Chromosome Positive Chronic Myeloid Leukemia Previously Treated with One or More Tyrosine Kinase Inhibitors

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON41126

Source
ToetsingOnline

Brief title
B1871039 (9002/0235)

Condition

- Leukaemias

Synonym
Ph+ Chronic Myeloid Leukemia; Leukemia

Research involving

Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: industry; Pfizer

Intervention

Keyword: Bosutinib, Chronic myeloid leukemia, Phase 4, Tyrosine Kinase Inhibitors

Outcome measures

Primary outcome

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

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

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

Secondary outcome

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

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

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

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

* To estimate the probability of confirmed OHR at 3, 6, 9, 12, 18, and 24

months in the AP and BP Ph+ CML patient populations.

* To estimate the probability of cumulative confirmed Complete Hematological

Response (CHR) in the CP, AP and BP Ph+ CML patient populations.

* To estimate the probability of cumulative major molecular response (MMR) in

the CP, AP and BP Ph+ CML patient populations.

* To evaluate the overall safety profile of bosutinib in the study population.

Study description

Background summary

Bosutinib (Bosulif®) is an orally bioavailable, potent, multi-targeted, dual Src-Abl tyrosine kinase inhibitor (TKI) that has been approved for the treatment of adult patients with Philadelphia chromosome positive (Ph+) chronic phase chronic myelogenous leukemia previously treated with other TKI therapy. Chronic myelogenous leukemia (CML) is the fourth most commonly occurring adult leukemia. CML traditionally follows a triphasic course with most patients being diagnosed in an initial oligosymptomatic chronic phase (CP) which eventually progresses into a more advanced accelerated phase (AP) and culminates in a blastic phase (BP), which resembles a highly treatment-refractory form of acute leukemia that generally shows either a myeloid or a lymphoid phenotype. The transformation of CML from a deadly cancer to a chronic illness that took place over the last decade has been due to the development of TKIs, small-molecule inhibitors of the kinase activity of BCR-ABL1, including imatinib, bosutinib, dasatinib, nilotinib, and ponatinib. The transition of patients with CML from CP to BP with an intermediate AP is becoming less standard with the chief determinants of survival being
disease stage and TKI responsiveness.
On September 4, 2012, bosutinib was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy (United States Prescribing Information BOSULIF®). More recently, on March 27, 2013, the European Medicines Agency (EMA) granted conditional marketing authorization in the European Union (EU), for the treatment of adult patients with CP, AP and BP Ph+ CML previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options (EMA Summary of Product Characteristics).

The FDA and EMA approvals were granted based on the results obtained from the singlearm, Phase 1/2 study (3160A4-200-WW, *Study-200*) in adult patients with Ph+ leukemias who had failed prior TKI therapy, and with the support of the safety results obtained from the Phase 3 study (3160A4-3000-WW) comparing bosutinib with imatinib in newly diagnosed CP Ph+ CML patients. In addition, the EMA was provided with descriptive narrative information from the bosutinib compassionate use program in patients with Ph+CML who had received at least one prior TKI treatment and had progressed or were intolerant, and otherwise not considered suitable for other TKI therapy, as well as efficacy and safety analyses from a subset of Study-200 patients whose disease had failed prior imatinib and/or dasatinib or nilotinib and were contraindicated for treatment with dasatinib or nilotinib, as
well as 4th-line CML patients on the study.
The purpose of this phase 4 study is to fulfill the post-authorization commitment made by Pfizer to the EMA in providing additional safety and efficacy data in approximately 150 Ph+ CML patients with high unmet medical need, including 75 CP, AP or BP patients in the 4th or later line treatment setting (i.e., after treatment with at least 3 other TKIs). The EMA conditional approval requires completion of this post-authorization study in order to convert the conditional approval to a full marketing authorization approval.

Study objective

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

Study design

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

with continued benefit may be switched to commercially available therapy at that time.
During the first 3 months of study, disease assessments will be performed weekly during the first month, then approximately every 4 weeks until Week 13. Assessments will then be performed every 3 months until Week 52, then at 6 month intervals during year 2, 3, and 4 of
treatment. Complete blood counts should be performed weekly for the first month and then monthly thereafter, and as clinically indicated. Hematologic, cytogenetic and extramedullary disease assessments will be done locally, while molecular and mutation analysis will be
carried out by independent central analysis. Copies of the cytogenetic assessment (karyotype photograph or other relevant image) will be submitted and stored centrally for independent analysis. Patient participation will conclude not more than 4 years after the first dose.

Intervention

Patients will receive bosutinib 500 mg orally once daily, preferably in the morning with food. Bosutinib commercial formulation of 100 mg and 500 mg tablets will be provided.

Study burden and risks

See section E9 of this form.

Contacts

Public
Pfizer

East 42nd Street 235
New York NY 10017
US
Scientific
Pfizer

East 42nd Street 235
New York NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Cytogenetic or PCR-based diagnosis of Ph+ CML or BCR-ABL1+ if Ph- (from initial diagnosis). NOTE: Ph- subjects will not count towards the 150 patients for primary and secondary analyses, which include Ph+ patients only.;2. Prior treatment with 1 or more TKIs for CML.;3. Any CML phase, as long as the patient is resistant to, intolerant of, or otherwise not appropriate for treatment with imatinib, dasatinib and/or nilotinib.;4. ECOG Performance Status of 0 or 1 for CP patients, or 0, 1, 2, or 3 for 4th line CP (and beyond) and AP/ BP patients.;5. Adequate bone marrow function:
For 2nd and 3rd line CP CML patients:
(1) Absolute neutrophil count >1000/mm3 (>1 x109/L).
(2) Platelets *75,000/mm3 (*75 x109/L) absent any platelet transfusions during the preceding 14 days.;For 4th line CP and AP/BP CML patients:
(1) Absolute neutrophil count >500/mm3 (>0.5 x109/L).
(2) Platelets *50,000/mm3 (*50 x109/L) absent any platelet transfusions during the preceding 14 days.;6. Adequate hepatic and renal function:;(a) AST/ALT *2.5 x ULN or ALT/AST *5 x ULN if attributable to liver involvement of leukaemia.
(b) Total direct bilirubin *1.5 x ULN.
(c) Creatinine *1.5 x ULN.;7. Able to take daily oral tablets.;8. Age *18 years.;9. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study.;10. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.;11. Male and female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

Exclusion criteria

1. Participation in other studies involving investigational drug(s) (Phase 1-4) within 14 days or 3 half-lives (whichever is longer) prior to the first dose of bosutinib.;2. Prior bosutinib exposure.;3. Prior ponatinib exposure. ;4. Known T315I or V299L mutation in BCR-ABL1.;5.

Clinically active leptomeningeal leukemia. Patients must be free of central nervous system (CNS) involvement for a minimum of 2 months.;6. Hypersensitivity to the active substance or to any of the following excipients:
Microcrystalline cellulose (E460), Croscarmellose sodium (E468), Poloxamer 188, Povidone (E1201), Magnesium stearate (E470b), Polyvinyl alcohol, Titanium dioxide (E171), Macrogol 3350, Talc (E553b), Iron oxide red (E172).;7. Pregnant or breastfeeding females.;8. Males and females of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after last dose of investigational product.;9. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior) or laboratory.;abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.;10. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are Pfizer employees directly involved in the conduct of the trial.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Bosulif
Generic name:	Bosutinib

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-06-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-11-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-10-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-003250-25-NL
CCMO	NL48222.056.14