A Randomized, Open-label, Phase 2 Trial of Ponatinib in Patients with Resistant Chronic Phase Chronic Myeloid Leukemia to Characterize the Efficacy and Safety of a Range of Doses

Published: 08-09-2015
Last updated: 20-04-2024

Primary Objective:To characterize the efficacy of ponatinib administered in 3 starting doses (45 mg, 30 mg, and 15 mg daily) in patients with CP-CML who are resistant to at least 2 TKIs, as measured by MCyR by 12 months.Key Secondary Objectives:* To...

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

Summary

ID

NL-OMON43934

Source
ToetsingOnline

Brief title
OPTIC

Condition

- Leukaemias

Synonym
Chronic Phase Chronic Myeloid Leukemia; blood cancer

Research involving
Human

Sponsors and support

Primary sponsor: ARIAD Pharmaceuticals, Inc.
Source(s) of monetary or material Support: ARIAD Pharmaceuticals;Inc.

Intervention

Keyword: Iclusig, Ponatinib, Resistant Chronic Phase Chronic Myeloid Leukemia

Outcome measures

Primary outcome

MCyR by 12 months for each starting dose cohort. MCyR is defined as PCyR, CCyR,

or *1% BCR ABLIS (ie, MR2), which is equivalent to CCyR

Secondary outcome

Key Secondary Endpoints:

* Safety

a. Rate of VOEs in each dose cohort

b. Rate of AEs in each dose cohort

c. Rate of SAEs in each dose cohort

* Exposure-response and exposure-toxicity relationships of AUC and Cmax at

steady state on efficacy outcomes (including MCyR, MR2, and MMR) and safety

outcomes, including VOEs

Other Secondary Endpoints:

* Cytogenetic response rate: CCyR by and at 12 months

* Molecular response rates: MR2, MR3/MMR, MR4, and MR4.5 at 3-month intervals

and MR1 (* 10% BCR-ABLIS) at 3 months

* Hematologic response rates: Complete hematologic response (CHR) at 3 months

* Tolerability:

a. Rate of discontinuation due to AEs in each dose cohort

b. Dose reductions due to AEs in each dose cohort

c. Dose interruptions in each dose cohort

* Duration of response:

a. Rates of MR2 and MMR at 12, 18, and 24 months

b. Rate of MCyR at 12, 18, and 24 months

* Duration of response in responders

* Time to response

* Rate of progression to accelerated phase (AP-) or blast phase (BP-) CML

* PFS

* OS

Exploratory Endpoints:

* Correlation of tumor cell and plasma biomarkers with ponatinib efficacy and

safety

* QoL and health outcomes as measured by EuroQuol (EQ)-5D-5L and Functional

Assessment of Cancer Therapy * Leukemia (FACT-Leu)

Study description

Background summary

Ponatinib is a novel, synthetic, orally active tyrosine kinase inhibitor (TKI) specifically designed to optimally inhibit native BCR-ABL. It is also active against mutated forms of the protein that can arise during treatment with other TKIs and cause resistance, including the T315I gatekeeper mutant. The latter confers uniform resistance to all other available BCR-ABL inhibitors (eg, imatinib, nilotinib, dasatinib, and bosutinib). Ponatinib (Iclusig®, ARIAD Pharmaceuticals, Inc.) is approved in the United States (US) for the treatment of adult patients with CML (all phases) and Philadelphia chromosome-positive

(Ph+) acute lymphoblastic leukemia (ALL) that is T315I-positive (T315I+) or for whom no other TKI therapy is indicated (Iclusig®, ARIAD Pharmaceuticals, Inc.). In the European Union (EU), ponatinib is approved for the treatment of adult patients with CML (all phases) and Ph+ ALL who are resistant to dasatinib (or nilotinib for CML), who are intolerant to dasatinib (or nilotinib for CML), and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.

Preclinical studies have demonstrated that ponatinib potently inhibits the kinase enzymatic activity of native ABL and mutant versions of the protein, including T315I, with IC50s between 0.4 and 2.0 nM. Using an in vitro mutagenesis screen approach, which has successfully predicted mutations that confer clinical resistance to approved TKIs, 40 nM ponatinib was found to suppress the emergence of any resistant BCR-ABL mutation.

Clinical trial data, particularly from the phase 1 dose escalation study and the pivotal phase 2 PACE study, support the preclinical findings and have established the safety and efficacy of ponatinib. In the phase 1 trial, the inhibitory activity of ponatinib was observed in heavily pretreated patients with Ph+ leukemias with resistance to TKIs. Data from the pivotal phase 2 PACE trial demonstrate the efficacy of ponatinib in patients with CML and Ph+ ALL whose disease is resistant or who exhibit intolerance to prior therapy.

Multivariate analyses performed on data from the phase 2 PACE trial found significant relationships between dose intensity and the occurrence of * grade 3 adverse events (AEs), including vascular occlusion; thrombocytopenia; pancreatitis; neutropenia; rash; increases in ALT, AST, and lipase; and myelosuppression in CML patients treated with ponatinib. In the phase 2 PACE trial, the 45-mg dose provided rapid responses, and the data demonstrate that patients generally are able to maintain responses despite reductions in dose intensity later in the trial. Taken together, these data support the use of a 45-mg dose to achieve a response in patients with few good treatment options, and then to reduce the dose to maintain the response while lowering the risk of long-term AEs. Meaningful responses have been achieved at doses as low as 15 mg in the phase 1 trial, which provides support for testing lower starting doses.

Continuing analyses of the phase 2 PACE trial have demonstrated a cumulative incidence of arterial thrombosis (including cardiovascular, cerebrovascular, and peripheral vascular events) that has continued to increase with longer follow-up. Arterial and venous thrombosis and occlusions*including fatal myocardial infarction (MI), stroke, severe peripheral vascular disease, and the need for urgent revascularization procedures*have been reported in ponatinib-treated patients.

Current data suggest that a dose-effect relationship exists with the occurrence of vascular occlusive events (VOEs), and that a lower daily dose may reduce the incidence of those events. This clinical study will test 2 methods for assessing the relationships among exposure, efficacy, and safety: patients will receive a range of initial doses and at defined time points, patients in response will undergo a dose reduction. The goal of the study will thus be to understand responses, maintenance of responses, safety, and exposure-response

as consequences of these dosing strategies.
The primary endpoint of major cytogenetic response (MCyR) by 12 months is defined according to standard criteria as * 35% Ph+-containing metaphases (typically < 7/20 involved metaphases); that is, as either a partial cytogenetic response (PCyR) or a complete cytogenetic response (CCyR). Increasingly, patient monitoring is being performed by quantitation of BCR-ABL transcripts from a standard established by the international scale (IS). Using such monitoring, * 1% BCR-ABL1/ABL1IS (also denoted as Molecular Response [MR]2) is taken to be equivalent to CCyR. In this protocol, to facilitate patient convenience and to incorporate what are standard CML approaches to patient care, the achievement of MR2 will also qualify as MCyR (except at the 12-month time point, when bone marrow cytogenetics is required to assess primary endpoint response); when the term MCyR is used, it includes MR2.This trial is being conducted in fulfillment of an FDA post-marketing requirement (PMR2113-6).

Study objective

Primary Objective:
To characterize the efficacy of ponatinib administered in 3 starting doses (45 mg, 30 mg, and 15 mg daily) in patients with CP-CML who are resistant to at least 2 TKIs, as measured by MCyR by 12 months.

Key Secondary Objectives:
* To characterize, according to ponatinib starting dose, the rates of VOEs, AEs, and serious AEs (SAEs).
* To evaluate safety differences according to ponatinib starting dose among the 3 starting dose cohorts, particularly for VOEs.
* To characterize the exposure-response and exposure-toxicity relationships between PK parameters and selected safety and efficacy measures.

Other Secondary Objectives:
* To characterize, according to ponatinib starting dose, the rates of cytogenetic responses and molecular responses; durability will be assessed by evaluating molecular response (MR)2 and major molecular response (MMR) at 12, 18, and 24 months.
* To characterize, according to ponatinib starting dose, the rate of discontinuation, dose reductions, and interruptions.
* To characterize, according to ponatinib starting dose, the rates of hematologic responses.
* To evaluate, according to ponatinib starting dose, time to response, duration of response, and survival outcomes.

Exploratory Objectives:
* Correlation of tumor cell and plasma biomarkers with ponatinib efficacy and safety

* Quality of life (QoL) and health outcomes

Study design

This is a multi-center, randomized phase 2 trial to characterize the safety and efficacy of ponatinib over a range of 3 starting doses. Eligible patients must have CP-CML and be resistant to at least 2 TKIs.
Patients will be randomized to receive once-daily oral administration of 1 of 3 starting doses of ponatinib: 45 mg (Cohort A), 30 mg (Cohort B), or 15 mg (Cohort C). Patients starting at 45 mg or 30 mg will have their daily dose reduced to 15 mg upon achievement of MCyR, as defined in Section 14.1.3.

Intervention

Patients will be randomized to receive once-daily oral administration of 1 of 3 starting doses of ponatinib: 45 mg (Cohort A), 30 mg (Cohort B), or 15 mg (Cohort C). Patients starting at 45 mg or 30 mg will have their daily dose reduced to 15 mg upon achievement of MCyR (as defined within the protocol). Dose interruptions or reductions should be implemented for patients who experience treatment-related AEs (TRAEs) upon clinical judgment of the investigator. Guidelines for management of TRAEs are described in Section 14.2.2.

Study burden and risks

Patients are asked to undergo procedures described in the flowchart on pages 45 - 46 of the study protocol. These procedures include physical examination, ECOG performance score, eye examination, vital signs, urine pregnancy tests (female; chidbearing patients), ECG, ECHO, bone marrow aspiration, blood draw, completing questionnaire, diaries and administration of study drug (oral). Additionally, fertile patients who are sexually active must agree to use an effective form of contraception with their sexual partners throughout participation in the study. Patients are also asked to inform their study doctor on their medication use and change in health status.
The following are the most serious/frequent risks of ponatinib; blood vessel blockage, heart failure, liver problems, high blood pressure, inflammation of the pancreas, bleeding, low blood cell counts, low blood counts including white blood cells, platelets, or red blood; Increased lipase; nausea, fever, increased enzymes from the liver in the blood, skin rash, pain in the belly, fatigue, headache, dry skin, constipation, high blood pressure, vomiting, diarrhea, decreased appetite, seakness, Shortness of breath, dizziness, cough, abnormal buildup of fluid (which may cause swelling in the hands, feet, ankles, face or all over the body), an upper respiratory infection like the common cold, pain that may occur in the joints, muscles, bone, back or limbs, trouble getting adequate amount or quality of sleep, muscle cramps and pain. Patients may have pain, swelling, or bruising or possible infection during blood draws

and/or bone marrow aspiration. Additionally, the adhesive used for the electrodes from ECG the may irritate patient's skin

Contacts

Public
ARIAD Pharmaceuticals, Inc.

Landsdowne Street 26
Cambridge MA 02139
US
Scientific
ARIAD Pharmaceuticals, Inc.

Landsdowne Street 26
Cambridge MA 02139
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Have CP-CML and are resistant to at least two prior TKIs.
a.The diagnosis of CML will be made using standard hematopathologic and cytogenetic criteria; CP-CML will be defined by all of the following:
i < 15% blasts in bone marrow
ii < 30% blasts plus promyelocytes in bone marrow
iii < 20% basophils in peripheral blood
iv * 100 × 109/L platelets (* 100,000/mm3)
v No evidence of extramedullary disease except hepatosplenomegaly

vi No prior diagnosis of AP- or BP-CML
b. Cytogenetic assessment at screening must demonstrate the BCR-ABL fusion by presence of the t(9;22) Philadelphia chromosome
i Variant translocations are only allowed provided they are assessable for cytogenetic response utilizing conventional cytogenetic techniques
ii Conventional chromosome banding must be performed
iii A minimum of 20 metaphases must be assessable at entry
c. Resistance to prior TKI therapy is defined as follows (patients must meet at least 1 criterion):
i Three months after the initiation of prior TKI therapy: No cytogenetic response (> 95% Ph+) or failure to achieve CHR or new mutation
ii Six months after the initiation of prior TKI therapy: BCR-ABLIS >10% and/or Ph+ >65% or new mutation
iii Twelve months after the initiation of prior TKI therapy: BCR-ABLIS >10% and/or Ph+ >35% or new mutation
iv At any time after the initiation of prior TKI therapy: The development of new BCR-ABL kinase domain mutations in the absence of CCyR or PCyR
v At any time after the initiation of prior TKI therapy: The development of new clonal evolution in the absence of CCyR or PCyR
vi At any time after the initiation of prior TKI therapy, the loss CHR, the loss of CCyR or PCyR, or confirmed loss of MMR in 2 consecutive tests, one of which has a BCR-ABLIS transcript level of ><= 1% or new mutation
2. Be male or female patients * 18 years old.
3. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
4. Have adequate renal function as defined by the following criterion:
a. Serum creatinine * 1.5 × upper limit of normal (ULN) for institution
5. Have adequate hepatic function as defined by the following criteria:
a. Total serum bilirubin * 1.5 × ULN, unless due to Gilbert*s syndrome
b. Alanine aminotransferase (ALT) * 2.5 × ULN, or * 5 × ULN if leukemic infiltration of the liver is present
c. Aspartate aminotransferase (AST) * 2.5 × ULN, or * 5 × ULN if leukemic infiltration of the liver is present
6. Have normal pancreatic status as defined by the following criterion:
a. Serum lipase and amylase * 1.5 × ULN
7. Have normal QT interval corrected (Frederica) (QTcF) interval on screening electrocardiogram (ECG) evaluation, defined as QTcF of * 450 ms in males or * 470 ms in females.
8. Have a negative pregnancy test documented prior to enrollment (for females of childbearing potential).
9. Agree to use a highly effective form of contraception with sexual partners from randomization through at least 4 months after the end of treatment (for female and male patients who are fertile).
10. Provide written informed consent.
11. Be willing and able to comply with scheduled visits and study procedures.
12. Have fully recovered (* grade 1, returned to baseline, or deemed irreversible) from the acute effects of prior cancer therapy before initiation of study drug.

Exclusion criteria

1. Have used any approved TKIs or investigational agents within 2 weeks or 6 half lives of the agent, whichever is longer, prior to receiving study drug.
2. Received interferon or cytarabine within 14 days; immunotherapy within 14 days; or any other cytotoxic chemotherapy, radiotherapy, or investigational therapy within 28 days prior to receiving the first dose of ponatinib, or have not recovered (> grade 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], v4.0) from AEs (except alopecia) due to agents previously administered.
3. Have undergone autologous or allogeneic stem cell transplant (SCT) < 60 days prior to receiving the first dose of ponatinib; have any evidence of ongoing graft versus-host disease (GVHD) or GVHD requiring immunosuppressive therapy.
4. Are being considered for hematopoietic SCT (HSCT) within 6-12 months of enrollment (note: ponatinib is not to be used as a bridge to HSCT in this trial).
5. Are taking medications with a known risk of Torsades de Pointes (APPENDIX A).
6. Have previously been treated with ponatinib.
7. Are in MCyR (defined as CCyR, PCyR, or MR2, which is * 1% BCR-ABLIS).
8. Have active central nervous system (CNS) disease as evidenced by cytology or pathology; in the absence of clinical CNS disease, lumbar puncture is not required. History itself of CNS involvement is not exclusionary if CNS has been cleared with a documented negative lumbar puncture.
9. Have clinically significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:
a. Any history of myocardial infarction (MI), unstable angina, cerebrovascular accident, or transient ischemic attack (TIA)
b. Any history of peripheral vascular infarction, including visceral infarction
c. Any revascularization procedure, including the placement of a stent
d. Congestive heart failure (CHF) (New York Heart Association [NYHA] class III or IV) within 6 months prior to enrollment, or left ventricular ejection fraction (LVEF) less than lower limit of normal, per local institutional standards, within 6 months prior to enrollment
e. History of clinically significant (as determined by the treating physician) atrial arrhythmia or any history of ventricular arrhythmia
f. Venous thromboembolism, including deep venous thrombosis or pulmonary embolism, within 6 months prior to enrollment
10. Have uncontrolled hypertension (diastolic blood pressure > 90 mmHg; systolic > 150 mmHg). Patients with hypertension should be under treatment on study entry to effect blood pressure control.
11. Have poorly controlled diabetes, defined as HbA1c values over the previous year of > 7.5% (59 mmol/mol) on more than 3 occasions. Patients with preexisting, well-controlled diabetes are not excluded.
12. Have a significant bleeding disorder unrelated to CML.
13. Have a history of alcohol abuse.
14. Have a history of either acute pancreatitis within 1 year of study or of chronic pancreatitis.
15. Have malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of study drug.

16. Have a history of another malignancy, other than cervical cancer in situ or basal cell or squamous cell carcinoma of the skin; the exception is if patients have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy.
17. Are pregnant or lactating.
18. Have undergone major surgery (with the exception of minor surgical procedures, such as catheter placement or BM biopsy) within 14 days prior to first dose of ponatinib.
19. Have an ongoing or active infection; this includes but is not limited to the requirement for intravenous antibiotics.
20. Have a known history of human immunodeficiency virus infection; testing is not required in the absence of prior documentation or known history.
21. Have any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of the drug.
22. Have hypersensitivity to the ponatinib active substance or to any of its inactive ingredients listed in Section 14.7.1.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Iclusig
Generic name:	Ponatinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-09-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2014-001617-12-NL
ClinicalTrials.gov	NCT02467270
CCMO	NL54318.029.15