A Randomized, Open-label Study of Ponatinib Versus Nilotinib in Patients with Chronic Myeloid Leukemia in Chronic Phase Following Resistance to Imatinib

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To demonstrate the efficacy of ponatinib administered at 2 starting doses (30 and 15 mg QD) compared to nilotinib administered at 400 mg BID in patients with CP-CML who are resistant to imatinib, as measured by MMR by 12 months

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

Summary

ID

NL-OMON43611

Source
ToetsingOnline

Brief title
OPTIC 2L

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: Chronic Myeloid Leukemia in Chronic Phase, Iclusig, Nilotinib, Ponatinib

Outcome measures

Primary outcome

Major molecular response (MMR) by 12 months for each cohort

Secondary outcome

Cytogenetic response rates:

- Major cytogenetic response (MCyR) by 12 months

- Complete cytogenetic response (CCyR) by 12 months

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

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

Safety

- Vascular occlusive events in each cohort

- AEs in each cohort

- SAEs in each cohort

- Time to response

- Duration of response:

- MR2 and MMR at 3, 6, 9, and 12 months, and then at 3-month intervals until

completion of treatment

- MCyR at 12 months, by cytogenetic analysis

- Duration of response in responders

- Duration of therapy

- Progression-free survival

- Overall survival

Other Secondary Endpoints

- Hematologic response: complete hematologic response (CHR)

- Tolerability:

- Discontinuations due to AEs in each cohort

- Dose reductions due to toxicity (prior to response) in each cohort

Study description

Background summary

Most patients with newly diagnosed CML are initially treated with an imatinib regimen with good results. However, 30% to 50% of all newly diagnosed CP-CML patients who are treated in the first-line setting with imatinib are in need of another treatment, either because they become resistant to imatinib (20%-25%) or because they become intolerant of imatinib (15%-20%). A review of efficacy in the second-line setting demonstrates that there is potential for improvement. Among the available second-line therapies (nilotinib, dasatinib, or [in the US] bosutinib), major cytogenetic response (MCyR) rates in second-line CP-CML range from 51% with nilotinib therapy (n=321) to 62% in dasatinib treated patients (n=387) indicating that second-line therapy initially fails to achieve a response in a substantial fraction of patients. Additionally, none of the available second-line agents have activity against all of the known mutants and the T315I mutation is refractory to all TKIs with the exception of ponatinib. Thus, both with regard to response rates and activity against resistant mutants, an unmet need remains in many patients who fail first-line TKI therapy. Ponatinib is a novel, synthetic, orally active 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.
Pharmacokinetic analysis of samples from the ongoing phase 1 clinical study (AP24534-07-101) showed that the threshold for pan-BCR-ABL activity is surpassed with =15 mg once daily dosing (Cmax) and with =30 mg once daily (steady-state trough).
Clinical study data, particularly from the phase 1 dose escalation study and

the pivotal phase 2 PACE study, support the preclinical findings and have established the favorable benefit-risk profile of ponatinib. In the phase 1 study, the activity of ponatinib was observed in heavily pretreated patients with Ph+ leukemias with resistance to TKIs . Data from the pivotal phase 2 study demonstrated the efficacy of ponatinib 45 mg daily in patients with CML and Ph+ ALL whose disease is resistant or who exhibit intolerance to prior therapy. These data have formed the basis of regulatory approvals in the US, EU, Australia, Israel, and Canada.
The impact of ponatinib dose on achievement of MCyR in patients with CP-CML has been evaluated using a multivariate analysis of data from the phase 2 study adjusting for covariates and an analysis of response by dose tertile. Both analyses show that increasing dose intensity is associated with higher response rates in this predominantly fourth-line population of CP-CML patients. Nevertheless, response rates are still high in the lowest tertile, with the understanding that this is not a second-line patient population. Increasing dose intensity also correlated with an increased probability of experiencing AEs. Taken together, these data underpin the rationale for investigating lower doses of ponatinib in conjunction with dose reduction following response. This study will employ starting doses of 30 mg and 15 mg to achieve response and then reduce dosing to lower the risk of AEs while maintaining response.
Nilotinib is the second drug that was approved for the treatment of CML and Ph+ALL
that is resistant to imatinib therapy. It is approved in the US for chronic phase CML in adult patients who are resistant to or intolerant of prior therapy that included imatinib, and in the European Union for chronic phase CML with resistance or intolerance to prior therapy including imatinib. The approved dose in both the US and the EU is
400 mg twice daily for this indication. Both the National Comprehensive Cancer Network (NCCN) and the European Leukemia Net (ELN) recommend consideration of the use of nilotinib in patients initially treated with imatinib whose disease develops resistance to therapy. Like ponatinib, nilotinib-treated patients have experienced
peripheral vascular events. In both the ponatinib and nilotinib development programs, most of these patients had additional risk factors for cardiovascular disease. The use of nilotinib as a comparator thus offers the opportunity to compare these agents directly in a single patient population.
This protocol describes a phase 3, open-label, randomized study of ponatinib for the treatment of patients with refractory chronic myeloid leukemia (CML) in chronic phase (CP) whose imatinib therapy has failed. The goal of this study is to test the hypothesis that ponatinib will be efficacious and safe in treating second-line CP-CML
patients, that it will be superior to nilotinib, that each of the starting doses will demonstrate the continued efficacy of ponatinib, and that the dose reduction strategy will lessen arterial occlusive complications.

Study objective

To demonstrate the efficacy of ponatinib administered at 2 starting doses (30 and 15 mg QD) compared to nilotinib administered at 400 mg BID in patients with CP-CML who are resistant to imatinib, as measured by MMR by 12 months

Study design

This is a multi-center, randomized study to demonstrate the efficacy and safety of 2 starting doses of ponatinib as compared to nilotinib. Eligible patients must have CP-CML, be resistant to first-line imatinib treatment and have received no other TKIs.

Intervention

Patients will be randomized to receive once daily oral administration of either 30 mg ponatinib QD (once daily) (Cohort A), 15 mg ponatinib QD (Cohort B), or 400 mg nilotinib BID (twice daily) (Cohort C). They will be randomized in a ratio of 1:2:1, respectively. Upon achievement of major molecular response (MMR) as defined in the protocol, patients in Cohort A will have their daily dose of ponatinib reduced to 15 mg and patients in cohort B will have their daily dose of ponatinib reduced to 10 mg. The dose of nilotinib for patients in Cohort C will not be adjusted based on response. The primary endpoint of MMR by12 months is defined according to standard criteria as *0.1% BCR-ABL/ABL.

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 (which may increase the risk of infection), platelets (which may increase the risk of bleeding), or red blood cells (which can cause you to feel tired or short of breath); 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, Weakness, 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 first-line imatinib treatment.
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 must demonstrate the BCR-ABL fusion by presence of the t(9;22) Philadelphia chromosome.
i Conventional chromosome banding must be performed
ii A minimum of 20 metaphases must be assessable at entry
iii Variant translocations are not allowed
c. BCR-ABL transcript levels must be assessable using the International Scale.
i b2a2 or b3a2 transcript type
d. Resistance is defined as follows. Patients must meet at least 1 criterion.
i Three months after the initiation of therapy: No cytogenetic response (>95% Ph+) or failure to achieve CHR.
ii Six months after the initiation of therapy: BCR-ABLIS >10% and/or >35% Ph+.
iii Twelve months after the initiation of therapy: BCR-ABLIS >1% and/or Ph+ >0.
iv At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of MCyR.
v At any time after the initiation of therapy, the development of new clonal evolution in the absence of MCyR.
vi At any time after the initiation of therapy, the loss of CHR, the loss of CCyR, or the confirmed loss of MMR (in 2 consecutive tests, one of which has a BCR-ABLIS transcript level of <=1%.
2. Be male or female <=18 years old.
3. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
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 all of 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 a negative pregnancy test documented prior to enrollment (for females of childbearing potential).
8. Agree to use a highly effective form of contraception with sexual partners from the time of randomization through at least four (4) months after end of study treatment (for female and male patients who are fertile).
9. Provide written informed consent.
10. Be willing and able to comply with scheduled visits and study procedures.
11. Have fully recovered (<= grade 1 or returned to baseline or deemed irreversible) from the acute effects of prior cancer therapy (ie, hydroxyurea or imatinib) before initiation of study drug.

Exclusion criteria

1. Have previously been treated with any approved or investigational TKIs other than imatinib or treated with imatinib within 14 days prior to receiving study drug.
2. Have previously been treated with any anti-CML therapy other than hydroxyurea, including interferon, cytarabine, immunotherapy, or any cytotoxic chemotherapy, radiotherapy, or investigational therapy.
3. Underwent autologous or allogeneic stem cell transplant.
4. Are in CCyR or MMR.
5. 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 history of a revascularization procedure, including vascular surgery or the placement of a stent
d. History of venous thromboembolism, including deep venous thrombosis, superficial venous thrombosis, or pulmonary embolism, within 6 months prior to enrollment
e. Congestive heart failure (New York Heart Association [NYHA] class III or IV) within 6 months prior to enrollment or left ventricular ejection fraction (LVEF) less than 45% or less than the institutional lower limit of normal (whichever is higher) within 6 months prior to enrollment
6. Have cardiac conduction abnormalities as follows:
a. QTcF >450 msec on the average of 3 serial baseline ECGs (using the QTcF formula); congenital long QT syndrome, or a known family history of long QT syndrome; or inability to determine the QTcF
b. Presence of a complete left bundle branch block
c. Use of a ventricular pacemaker
d. History of clinically significant (as determined by the treating physician) atrial arrhythmia
e. Resting bradycardia <50 beats per minute
f. Any history of ventricular arrhythmia
7. Are taking medications with a known risk of Torsades de Pointes or that have the potential to prolong the QT interval (Appendix A), unless the medication can be discontinued or be substituted by another without the risk.
8. Are taking medicines that are strong CYP3A4 inhibitors, unless the medication can be discontinued or be substituted by another that is not an inhibitor (Appendix B)
9. Are taking medicines that are strong CYP3A4 inducers, unless the medication can be discontinued or be substituted by another that is not an inducer (Appendix B)
10. Have uncontrolled hypertension (diastolic blood pressure >90 mmHg and/or systolic >150 mmHg). Patients with hypertension should be under treatment at 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/mL) on more than 3 occasions. Patients with preexisting, well-controlled, diabetes are not excluded.
12. Have uncorrected hypokalemia or hypomagnesemia.
13. 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. A history of CNS

involvement itself is not an exclusion if the CNS has been cleared of disease with a documented negative lumbar puncture.
14. Have a significant bleeding disorder unrelated to CML.
15. Have a history of thrombophilia (eg, Protein C deficiency)
16. Have a history of alcohol abuse.
17. Have a history of acute pancreatitis within 1 year of study entry or history of chronic pancreatitis.
18. Have history of malabsorption syndrome or other gastrointestinal condition that could affect oral absorption of study drug.
19. Have a history of a different malignancy, other than cervical cancer in situ or basal cell or squamous cell carcinoma of the skin, except if patient has been disease-free for at least 5 years, and are deemed by the investigator to be at low risk for recurrence of that malignancy.
20. Are pregnant or lactating.
21. Have undergone major surgery within 14 days prior to first dose of study treatment. Minor surgical procedures, such as catheter placement or bone marrow biopsy are allowed.
22. Have an ongoing or active infection. This includes but is not limited to the requirement for intravenous antibiotics.
23. Have any surgical or medical condition / illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of the study drug
24. Have hypersensitivity to the active substance in ponatinib and nilotinib or to any of the inactive ingredients listed in Section 14.9.1.1 for ponatinib and in Section 14.9.1.2 for nilotinib

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	6

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:	28-10-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-12-2016

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2015-001318-92-NL
ClinicalTrials.gov	NCT02627677
CCMO	NL55013.078.15