A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia

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Primary Objective:To determine the efficacy of ponatinib in patients with CML in CP, AP or BP or with Ph+ ALL who either:are resistant or intolerant to either dasatinib or nilotinib,Or:have the T315I mutation.Secondary Objectives:* To further...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON39645

Source
ToetsingOnline

Brief title
PACE

Condition

- Leukaemias

Synonym
Bloodcancer, bone marrow cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Chronic Myeloid Leukemia, Ph+ Acute Lymphoblastic Leukemia, Ponatinib, Tyrosine kinase inhibitor

Outcome measures

Primary outcome

Primary Endpoint:

- For CML patients in CP at study entry: major cytogenetic response (MCyR),

defined as complete cytogenetic response (CCyR) or partial cytogenetic response

(PCyR). CP patients in CCyR are not eligible for this study.

- For CML patients in AP at study entry: major hematologic response (MaHR),

defined as complete hematologic response (CHR) or no evidence of leukemia

(NEL). AP patients in MaHR are not eligible for this study.

- For CML patients in BP at study entry or Ph+ ALL patients: MaHR, consisting

of CHR or NEL. BP and Ph+ ALL patients in MaHR are not eligible for this

study.

Secondary outcome

Secondary Endpoints:

* For CML patients in CP:

- Hematologic responses: CHR;

- Cytogenetic responses: confirmed MCyR; and

- Molecular responses: major molecular response (MMR).

* For CML patients in AP or BP or Ph+ ALL patients:

- Cytogenetic responses: CCyR, PCyR, confirmed MCyR; and

- Molecular responses: MMR.

* For all patients: time to response, duration of response, progression-free

survival, and overall survival.

* For all patients: safety and tolerability.

Exploratory Endpoints:

* For all patients: BCR-ABL sequence;

* For all patients: allele-specific oligonucleotide (ASO) polymerase chain

reaction (PCR) for T315I; and

* For all patients: molecular genetic analyses.

Study description

Background summary

Approved therapies for Ph+ disease represent substantial progress, however they fail in a significant proportion of patients because of either the development of resistance or intolerance. Thus, the need for new therapies is evident.

Ponatinib (AP24534) is a novel synthetic orally-active tyrosine kinase inhibitor (TKI). Ponatinib was specifically developed to inhibit BCR ABL, the fusion protein that is the product of the Philadelphia chromosome (Ph) in chronic myeloid leukemia (CML) and in a subset of acute lymphoblastic leukemia (ALL). It potently inhibits the BCR-ABL protein, as well as mutated forms of the protein that arise in patients resistant to prior therapies with TKIs; for this reason, it is a pan-BCR-ABL inhibitor.

The AP24534-10-201 trial is a pivotal phae II trial in patients with refractory CML in CP, AP or BP or with Ph+ ALL to determine the efficacy of ponatinib .

Study objective

Primary Objective:
To determine the efficacy of ponatinib in patients with CML in CP, AP or BP or with Ph+ ALL who either:
are resistant or intolerant to either dasatinib or nilotinib,
Or:
have the T315I mutation.

Secondary Objectives:
* To further characterize the anti-leukemia activity of ponatinib in these patients as evidenced by clinical responses, molecular responses, and clinical outcomes,
* To characterize the molecular genetic status of patients, and
* To examine the safety of ponatinib in these patients.

Study design

This is a multi-center, international, phase 2, single-arm, open-label trial of oral ponatinib in patients with Ph+ disease. Eligible patients will have CML in CP, AP, or BP as defined below, or Ph+ ALL. Patients will either 1) have disease resistant to, or be intolerant to, therapy with either dasatinib or nilotinib; or 2) have the T315I mutation of BCR-ABL. Patients will receive once daily oral administration of ponatinib at a dose of 45 mg. Patients will be assessed for hematologic response, cytogenetic response, and molecular response. Molecular genetic analyses will also be performed. Adverse events will be assessed throughout and categorized by the United States of America (USA) National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v.4.0). Patients will be evaluated according to the Schedule of Events in Section 8 of the protocol. Assessments will be according to standard international criteria. Patients will remain on treatment until disease progression or intolerance develops or if they meet one or more criteria listed in Section 13.8. Progression-free survival and overall survival data will also be collected and analyzed. Progression-free survival and overall survival data will also be collected and analyzed. Patients will be grouped in the following cohorts:
- Cohort A: resistant or intolerant to dasatinib or nilotinib and in chronic phase (CP)
- Cohort B: T315I-mutation and in chronic phase (CP)
- Cohort C: resistant or intolerant to dasatinib or nilotinib and in advanced phase (AP)
- Cohort D: T315I-mutation and in advanced phase (AP)
- Cohort E: resistant or intolerant to dasatinib or nilotinib and in blast phase (BP)/Ph+ ALL
- Cohort F: T315I-mutation and in blast phase (BP)/Ph+ ALL
Each of the 6 cohorts proposed in this trial are representative of distinct patient populations with different primary endpoints. Each cohort of patients will be analyzed separately for efficacy. The safety data from all cohorts will be pooled for the purpose of describing the safety of all treated patients

as a whole. These cohorts can be viewed as 6 separate studies that are enrolled through this single *umbrella* protocol; therefore, no adjustments for multiplicity are planned.

Intervention

At study start ponatinib will be administered orally once daily at a dose of 45 mg per day.

Dose delays and/or reductions will be implemented for patients who experience adverse drug reactions as indicated in section 14-4 and 14-5 of the protocol.

Study burden and risks

For all details, please refer to schedule of events on pages 28-31of the protocol.

Also see E4, E6 en E9 for burden and possible risks.

Contacts

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients must have CML in any phase (CP, AP, or BP of any phenotype) or Ph+ ALL (defined in Sections 12.3 and 12.4).
a. All patients must have screening bone marrow (BM) cytogenetics with conventional banding performed within 42 days prior to beginning treatment
b. Examination of at least 20 metaphases is required. If less than 20 metaphases are examined, the BM aspirate should be repeated.
Patients must either meet criterion 2 or 3:
2. Be previously treated with and resistant, or intolerant, to either dasatinib or nilotinib:
2.1 Resistance is defined for CML CP patients (CP at the time of initiation of dasatinib or nilotinib therapy) as follows. Patients must meet at least 1 criterion.
a. Three months after the initiation of therapy: No cytogenetic response (>95% Ph+) or failure to achieve CHR.
b. Six months after the initiation of therapy: Less than a minor cytogenetic response (>65% Ph+).
c. Twelve months after the initiation of therapy: Less than a PCyR (>35% Ph+).
d. At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of CCyR.
e. At any time after the initiation of therapy, the development of new clonal evolution in the absence of CCyR.
f. At any time after the initiation of therapy, the loss of any cytogenetic response [from complete (0%), partial (1% to 35%), minor (36% to 65%), or minimal (66% to 95%) to a response at least 1 grade worse], confirmed in at least 2 consecutive analyses separated by at least 4 weeks.
g. At any time after the initiation of therapy, progression of disease (to AP or BP).
2.2 Resistance is defined for CML AP patients (AP at the time of initiation of dasatinib or nilotinib therapy) as follows. Patients must meet at least 1 criterion.
a. Three months after the initiation of therapy: failure to achieve a MaHR.
b. At any time after the initiation of therapy, the loss of a MaHR, confirmed in at least 2 consecutive analyses separated by at least 4 weeks.
c. At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of a MaHR.
2.3 Resistance is defined for CML BP patients (BP at the time of initiation of dasatinib or nilotinib therapy) and Ph+ ALL patients as follows. Patients must meet at least 1 criterion.
a. One month after the initiation of therapy: failure to achieve a MaHR.
b. At any time after the initiation of therapy, the loss of a MaHR, confirmed in at least 2 consecutive analyses separated by at least 1 week.
c. At any time after the initiation of therapy, the development of new BCR-ABL kinase domain

mutations in the absence of a MaHR.
2.4 Intolerance to dasatinib or nilotinib is defined as: a. Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal) in the absence of a CCyR for CP patients or MaHR for AP, BP or Ph+ ALL patients.
b. Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer (80 mg daily [QD] for dasatinib; 400 mg QD for nilotinib) in the absence of a CCyR for CP patients or MaHR for AP, BP or Ph+ ALL patients.
NOTE: Although, the above criteria define failure after dasatinib or nilotinib (mostly according to Baccarani et al., 2009), patients who have gone on to later line therapy are eligible having failed dasatinib or nilotinib.
OR
3. Develop the T315I mutation after any TKI therapy.
3.1 Patients with T315I mutation after any TKI need not have been treated with dasatinib or nilotinib.
3.2 Patients with T315I in CP must have less than a CCyR (>0% Ph+).
3.3 Patients with T315I in AP, BP, or Ph+ ALL must have less than a MaHR.
3.4 Patients with any history of T315I mutation will be eligible for study participation. However, only those patients who carry a T315I mutation that is detected by direct sequencing in a pre-treatment blood sample using the study*s central laboratory will be analyzed in the T315I subset.
Details are provided in Section 12.5 of the protocol.
Patients must meet all of the remaining criteria to be eligible for the study:
4. Must be *18 years old.
5. Provide written informed consent.
6. Eastern Cooperative Oncology Group (ECOG) performance status *2.
7. Minimum life expectancy of 3 months or more.
8. Adequate renal function defined as serum creatinine < 1.5 × upper limit of normal (ULN) for institution.
9. Adequate hepatic function defined as:
a. Total bilirubin < 1.5 × ULN,
b. Alanine aminotransferase (ALT [SGPT]) and aspartate aminotransferase (AST [SGOT]) < 2.5 × ULN for institution (<5 × ULN if liver involvement with leukemia),
c. Prothrombin time (PT) < 1.5 × ULN.
10. Normal pancreatic status defined as:
a. Lipase *1.5 × ULN for institution,
b. Amylase *1.5 × ULN for institution.
11. Normal QTcF interval on screening electrocardiogram (ECG) evaluation, defined as QTcF of *450 ms in males or *470 ms in females.
12. For females of childbearing potential, a negative pregnancy test must be documented prior to enrollment.
13. Female and male patients who are of childbearing potential must agree to use an effective form of contraception with their sexual partners throughout participation in this study.

14. Ability to comply with study procedures, in the Investigator*s opinion.

Exclusion criteria

Patients are not eligible for participation in the study if they meet any of the following exclusion criteria:
1. Received TKI therapy within 7 days prior to receiving the first dose of onatinib, or have not recovered (> grade 1 by NCI CTCAE, v. 4.0) from AEs except alopecia) due to agents previously administered.
2. Received other therapies as follows:
a. For CP and AP patients, received hydroxyurea or anagrelide within 24 hours prior to receiving the first dose of ponatinib, interferon, cytarabine, or immunotherapy within 14 days, or any other cytotoxic chemotherapy, radiotherapy, or investigational therapy within 28 days prior to receiving the first dose of ponatinib.
b. For BP patients, received chemotherapy within 14 days prior to the first dose of ponatinib. Otherwise 2a applies.
c. For Ph+ ALL patients, received corticosteroids within 24 hours before the first dose of ponatinib, or vincristine within 7 days prior to the first dose of ponatinib, or received other chemotherapy within 14 days prior to the first dose of ponatinib. Otherwise, 2a applies.
d. All patients are excluded if they have not recovered (> grade 1 by NCI CTCAE, v. 4.0) from AEs (except alopecia) due to agents previously administered.
3. Underwent autologous or allogeneic stem cell transplant < 60 days prior to receiving the first dose of ponatinib; any evidence of on-going graft versus-host disease (GVHD), or GVHD requiring immunosuppressive therapy.
4. Take medications that are known to be associated with Torsades de Pointes. These prohibited medications are listed in Attachment B.
5. Require concurrent treatment with immunosuppressive agents, other than corticosteroids prescribed for a short course of therapy.
6. Have previously been treated with ponatinib.
7. Patients with CML CP are excluded if they are in CCyR.
8. Patients with CML AP, CML BP, or Ph+ ALL are excluded if they are in MaHR.
9. 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.
10. Have significant or active cardiovascular disease, specifically including, but not restricted to:
a. Myocardial infarction within 3 months prior to first dose of ponatinib,
b. History of clinically significant atrial arrhythmia or any ventricular arrhythmia,
c. Unstable angina within 3 months prior to first dose of ponatinib,
d. Congestive heart failure within 3 months prior to first dose of ponatinib.
11. Have a significant bleeding disorder unrelated to CML or Ph+ ALL.
12. Have a history of pancreatitis or alcohol abuse.
13. Have uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
14. Have malabsorption syndrome or other gastrointestinal illness that could affect

absorption of orally administered ponatinib.
15. Have been diagnosed with another primary malignancy within the past 3 years (except for non-melanoma skin cancer or cervical cancer in situ, or controlled prostate cancer, which are allowed within 3 years).
16. Are pregnant or lactating. Women of childbearing potential must agree to effective contraception from the time of signing informed consent through the Follow-up Visit, approximately 30 days after last dose of ponatinib.
17. Underwent 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.
18. Have ongoing or active infection (including known history of human immunodeficiency virus [HIV], hepatitis B virus [HBV], or hepatitis C virus [HCV]). Testing for these viruses is not required in the absence of history.
19. Suffer from any condition or illness that, in the opinion of the Investigator or the medical monitor, would compromise patient safety or interfere with the evaluation of the safety of the study drug.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-02-2011
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Iclusig
Generic name:	Ponatinb

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-01-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-01-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-08-2015
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	EUCTR2010-020414-28-NL
ClinicalTrials.gov	NCT01207440
CCMO	NL34342.029.10