A Phase I Study of Oral ABL001 in Patients With CML or Ph+ ALL

This study is currently recruiting participants. (see Contacts and Locations)

Verified October 2016 by Novartis

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT02081378

First received: February 28, 2014
Last updated: October 12, 2016
Last verified: October 2016
History of Changes

Purpose

The design of a phase I, open label, dose finding study was chosen in order to establish a safe and tolerated dose of single agent ABL001 in CML and Ph+ ALL patients who are relapsed or refractory to or are intolerant of TKIs, and of ABL001+Nilotinib, ABL001+Imatinib and ABL001+Dasatinib in Ph positive CML patients who are relapsed or refractory to TKIs.

Condition	Intervention	Phase
Chronic Myelogenous Leukemia Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia	Drug: ABL001 Drug: ABL001 + Nilotinib Drug: ABL001+imatinib Drug: ABL001+dasatinib	Phase 1

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Endpoint Classification: Safety Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Health Services Research

Official Title: A Phase I, Multicenter, Open-label Study of Oral ABL001 in Patients With Chronic Myelogenous Leukemia (CML) or Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia (Ph+ ALL)

Resource links provided by NLM:

Genetics Home Reference related topics: chronic myeloid leukemia

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

U.S. FDA Resources

Further study details as provided by Novartis:

Primary Outcome Measures:

- Incidence of dose limiting toxicities (DLTs) during the first cycle of study treatment [Time Frame: First Cycle is 28 days]
  [Designated as safety issue: Yes]

  Determine the MTD and/or RDE of ABL001 as single agent in CML and Ph+ ALL, and in combination with either nilotinib or imatinib or dasatinib in CML patients

Secondary Outcome Measures:

- Hematologic Response [Time Frame: At screening and first day of cycle 2 and 3 and every 12 weeks afterwards]
  [Designated as safety issue: No]

- Cytogenetic response [Time Frame: at screening or when a patient's BCR-ABL ratio has risen to >1%] [Designated as safety issue: No]
- BCR-ABL transcript level [Time Frame: At screening and first day of cycle 2 and 3 and every 12 weeks afterwards] [Designated as safety issue: No]
- Cmax of ABL001 as measured in plasma [Time Frame: Cycle 1 days 1,2,8,15,16 and 22. Cycle 2 days 1 and 2, and subsequent cycles at the begining of each cycle up to cycle 6.] [Designated as safety issue: No]
- Cmin of ABL001 as measured in plasma [Time Frame: Cycle 1 days 1,2,8,15,16 and 22. Cycle 2 days 1 and 2, and subsequent cycles at the begining of each cycle up to cycle 6.] [Designated as safety issue: No]
- AUCinf of ABL001 as measured in plasma [Time Frame: Cycle 1 days 1,2,8,15,16 and 22. Cycle 2 days 1 and 2, and subsequent cycles at the begining of each cycle up to cycle 6.] [Designated as safety issue: No]
- AUClast of ABL001 as measured in plasma [Time Frame: Cycle 1 days 1,2,8,15,16 and 22. Cycle 2 days 1 and 2, and subsequent cycles at the begining of each cycle up to cycle 6.] [Designated as safety issue: No]
- AUCtau of ABL001 as measured in plasma [Time Frame: Cycle 1 days 1,2,8,15,16 and 22. Cycle 2 days 1 and 2, and subsequent cycles at the begining of each cycle up to cycle 6.] [Designated as safety issue: No]
- T1/2 of ABL001 as measured in plasma [Time Frame: Cycle 1 days 1,2,8,15,16 and 22. Cycle 2 days 1 and 2, and subsequent cycles at the begining of each cycle up to cycle 6.] [Designated as safety issue: No]
- Adverse events [Time Frame: Collected from screening visit through post-treatment follow-up period] [Designated as safety issue: No]

Estimated Enrollment:	250
Study Start Date:	April 2014
Estimated Study Completion Date:	August 2017
Estimated Primary Completion Date:	August 2017 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: ABL001 in CML patients Dose escalation study to estimate the MTD and/or RDE of ABL001 in adult patients with CML	Drug: ABL001 ABL001 will be administered orally in a dose escalation schedule.
Experimental: ABL001+Nilotinib in CML patients Dose escalation study to estimate the MTD and/or RDE of ABL001 in combination with Nilotinib in adult CML patients	Drug: ABL001 + Nilotinib ABL001 and Nilotinib will be administered orally in CML patients
Experimental: ABL001 in Ph+ ALL patients Dose escalation study to estimate the MTD and/or RDE of ABL001 in adult patients with Ph positive ALL patients	Drug: ABL001 ABL001 will be administered orally in Ph+ ALL patients
Experimental: ABL001+Imatinib in CML patients Dose escalation study to estimate the MTD and/or RDE of ABL001 in combination with imatinib in adult CML patients	Drug: ABL001+imatinib ABL001 and imatinib will be administered orally in CML patients
Experimental: ABL001+dasatinib in CML patients Dose escalation study to estimate the MTD and/or RDE of ABL001 in combination with dasatinib in adult CML patients	Drug: ABL001+dasatinib ABL001+dasatinib will be administered orally in CML patients

Detailed Description:

This first-in-human trial with ABL001 is a dose escalation study whose primary purpose is to estimate the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of single agent ABL001 in CML or Ph+ ALL patients, and in combination with either Nilotinib or Imatinib or Dasatinib in Ph positive CML patients. The safety, tolerability and pharmacokinetic (PK) profile of ABL001 and ABL001+Nilotinib, ABL001+Imatinib and ABL001+Dasatinib will be assessed together with an evaluation of pharmacodynamic (PD) changes in peripheral blood mononuclear cells (PBMC) and bone marrow aspirates and all data may contribute to the assessment of the RDE.

An understanding of the MTD/RDE, safety profile, PK/PD relationship, and preliminary evidence of anti-CML and ALL activity will be used to inform future development in adults with CML and Ph+ ALL. By virtue of its distinct pharmacological profile and by preclinical pharmacological studies demonstrating an additive effect, a combination of ABL001 and a tyrosine-kinase inhibitor (TKI) has the potential to achieve a deeper molecular response in a higher proportion of CML patients as compared to single agent TKI therapy. Such a combination has the added advantage of targeting the ABL kinase domain at two distinct locations, theoretically preventing single point mutation-associated treatment resistance. The prediction is that a nilotinib+ABL001, imatinib+ABL001 and/or dasatinib+ABL001 combination will increase the percentage of patients who achieve a complete molecular response (CMR) and decrease the time to CMR, thereby increasing the possibility of achieving sustained treatment-free remissions in these patients. In addition, some patients may be intolerant of therapy with TKIs or may develop mutations that promote resistance to TKI therapy. In these patients, ABL001 may provide a novel therapeutic option.

Eligibility

Ages Eligible for Study:	18 Years and older (Adult, Senior)
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

For CML patients either:

- a. Patients with Ph+ CML in chronic or accelerated phase who were previously treated with at least two different tyrosine kinase inhibitors prior to study entry and are relapsed, refractory to or intolerant of TKIs as determined by investigators or
- b. Patients with CML in chronic or accelerated phase who exhibit relapsed disease associated with the presence of the T315I "gatekeeper mutation" after at least one TKI are also eligible provided that no other effective therapy exists

For ALL and CML-BP patients:

- Patients with CML BP or Ph+ ALL who have a cytopathologically confirmed diagnosis and are relapsed or refractory to at least one prior TKI or intolerant of TKIs. TKI failure for Ph+ ALL and CML-BP patients is defined as at least the loss of Molecular Response (MR) 4.5 (BCR-ABL ≤ 0.0032%)
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
- Willingness and ability to comply with all study procedures
- Written informed consent obtained prior to any screening procedures

Exclusion Criteria:

Wash-out period:

- Systemic antineoplastic therapy (including cytotoxic chemotherapy, alfa-interferon and toxin immunoconjugates) or any experimental therapy within 14 days or 5 half-lives, whichever is shorter, before the first dose of study treatment
- Therapy with TKIs as single agent within 5 half-lives before the first dose of study treatment
- Unconjugated monoclonal antibody therapies within 28 days or 5 half-lives, whichever is shorter, before the first dose of study treatment
- For patients receiving ABL001 in combination with either nilotinib or imatinib or dasatinib, intolerance to nilotinib, imatinib or dasatinib, respectivelyRadiotherapy with a wide field of radiation within 4 weeks or radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment.
- CNS irradiation for meningeal leukemia, except if radiotherapy occurred > 3 months previously. At least four weeks must have elapsed since prophylactic CNS irradiation given as part of a front-line therapy regimen for ALL
- Major surgery within 2 weeks before the first dose of study treatment

Other protocol-defined inclusion/exclusion criteria may apply

Contacts and Locations

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, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02081378

Contacts

Contact: Novartis Pharmaceuticals 1-888-669-6682

Contact: Novartis Pharmaceuticals +41613241111

Locations

United States, Massachusetts

Dana Farber Cancer Institute Hematology / Oncology **Recruiting**
Boston, Massachusetts, United States, 02215
Contact: Shannon Mililo 617-632-6840 shannon_mililo@dfci.harvard.edu
Principal Investigator: Daniel J. DeAngelo

United States, Michigan

University of Michigan Comprehensive Cancer Center SC **Recruiting**
Ann Arbor, Michigan, United States, 48109-0944
Contact: Julio L. Garcia-Castro 734-232-0759 jgarciac@med.umich.edu
Principal Investigator: Moshe Talpaz

United States, New York

Memorial Sloan Kettering Cancer Center Memorial Sloan Kettering **Recruiting**
NY, New York, United States, 10065
Contact: Gerry J. O'Neill 212-639-3107 oneillg@mskcc.org
Principal Investigator: Michael J. Mauro

United States, Oregon

Oregon Health & Science University SC-6 **Recruiting**
Portland, Oregon, United States, 97239
Contact: Barbie Jackson 503-494-4603 jacksoba@ohsu.edu

Principal Investigator: Michael J. Heinrich

United States, Texas

University of Texas/MD Anderson Cancer Center UT MD Anderson — **Recruiting**
Houston, Texas, United States, 77030-4009
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Principal Investigator: Jorge E. Cortes

Australia, South Australia

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France

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Paris, Cedex 10, France, 75475

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Sponsors and Collaborators

Novartis Pharmaceuticals

Investigators

Study Director: Novartis Pharmaceuticals Novartis Pharmaceuticals

More Information

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Keywords provided by Novartis:
CML
Ph+ ALL

Additional relevant MeSH terms:

Leukemia
Precursor Cell Lymphoblastic Leukemia-Lymphoma
Leukemia, Lymphoid
Leukemia, Myeloid
Leukemia, Myelogenous, Chronic, BCR-ABL Positive
Philadelphia Chromosome
Neoplasms by Histologic Type
Neoplasms
Lymphoproliferative Disorders
Lymphatic Diseases
Immunoproliferative Disorders
Immune System Diseases
Myeloproliferative Disorders
Bone Marrow Diseases
Hematologic Diseases
Translocation, Genetic
Chromosome Aberrations
Pathologic Processes
Imatinib Mesylate
Dasatinib
Antineoplastic Agents
Protein Kinase Inhibitors
Enzyme Inhibitors
Molecular Mechanisms of Pharmacological Action

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