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

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

- Chronic Myelogenous Leukemia
- Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia

Intervention

- Drug: ABL001
- Drug: ABL001 + Nilotinib
- Drug: ABL001+imatinib
- Drug: ABL001+dasatinib

Phase

- 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)

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 Ph positive CML patients who are relapsed or refractory to TKIs

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 ]
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Estimated Primary Completion Date: August 2017 (Final data collection date for primary outcome measure)

Study Start Date: April 2014

Estimated Enrollment: 250

Estimated Study Completion Date: August 2017

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 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 aspirations 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 predicting 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.

Criteria

Ages Eligible for Study: 18 Years and older (Adult, Senior)

Genders Eligible for Study: Both

Accepts Healthy Volunteers: No

Eligibility

Arms Assigned Interventions

Experimental: ABL001 in CML patients Drug: ABL001

Dose escalation study to estimate the MTD and/or RDE of ABL001 in adult patients with CML

ABL001 will be administered orally in a dose escalation schedule.

Experimental: ABL001+Nilotinib in CML patients Drug: ABL001 + Nilotinib

Dose escalation study to estimate the MTD and/or RDE of ABL001 in combination with Nilotinib in adult CML patients

ABL001 and Nilotinib will be administered orally in CML patients

Experimental: ABL001 in Ph+ ALL patients Drug: ABL001

Dose escalation study to estimate the MTD and/or RDE of ABL001 in adult patients with Ph positive ALL patients

ABL001 will be administered orally in Ph+ ALL patients

Experimental: ABL001+Imatinib in CML patients Drug: ABL001+Imatinib

Dose escalation study to estimate the MTD and/or RDE of ABL001 in combination with imatinib in adult CML patients

ABL001 and imatinib will be administered orally in CML patients

Experimental: ABL001+dasatinib in CML patients Drug: ABL001+dasatinib

Dose escalation study to estimate the MTD and/or RDE of ABL001 in combination with dasatinib in adult CML patients

ABL001+dasatinib will be administered orally in CML patients

**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

Boston, Massachusetts, United States, 02215

Contact: Shannon Milillo 617-632-6840 shannon_milillo@dfci.harvard.edu

Principal Investigator: Daniel J. DeAngelo

**United States, Michigan**

University of Michigan Comprehensive Cancer Center SC

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

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

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
  - Contact: Nichole R Arb 713-794-5783 rrabramo@mdanderson.org
- Principal Investigator: Jorge E. Cortes

**Australia, South Australia**
- Novartis Investigative Site Recruiting
  - Adelaide, South Australia, Australia, 5000

**France**
- Novartis Investigative Site Recruiting
  - Paris, Codex 10, France, 75475
- Novartis Investigative Site Recruiting
  - Bordeaux, France, 33076

**Germany**
- Novartis Investigative Site Recruiting
  - Berlin, Germany, 13353
- Novartis Investigative Site Recruiting
  - Frankfurt, Germany, 60590
- Novartis Investigative Site Recruiting
  - Jena, Germany, 07740

**Italy**
- Novartis Investigative Site Recruiting
  - Roma, RM, Italy, 00161

**Japan**
- Novartis Investigative Site Recruiting
  - Kobe-city, Hyogo, Japan, 650-0017

**Korea, Republic of**
- Novartis Investigative Site Recruiting
  - Seoul, Korea, Korea, Republic of, 06591

**Netherlands**
- Novartis Investigative Site Recruiting
  - Amsterdam, Netherlands, 1081 HV

**Singapore**
- Novartis Investigative Site Recruiting
  - Singapore, Singapore, 169608

**Spain**
- Novartis Investigative Site Recruiting
  - Madrid, Spain, 28006

**Sponsors and Collaborators**
- Novartis Pharmaceuticals

**Investigators**
- Study Director: Novartis Pharmaceuticals

**More Information**

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- CML
- Ph+ ALL