

STUDY 200: Study Evaluating Bosutinib in Philadelphia Chromosome Positive Leukemia

INTRODUCTION	<ul style="list-style-type: none"> Chronic myeloid leukemia (CML), one of the four main types of leukemia, is a slow-growing blood cancer that starts in the blood-forming cells of bone marrow, the soft inner part of some bones.¹ Once these cells are affected by leukemia, they do not go through their normal process of maturing.² An abnormal chromosome, the Philadelphia chromosome, is a hallmark of CML. The Philadelphia chromosome initiates a series of events leading to the development of Bcr-Abl, a tyrosine kinase that causes CML cells to reproduce rapidly.³ Therapies such as imatinib,⁴ dasatinib⁵ and nilotinib⁶ target the inhibition of the Abl tyrosine kinase. The Src family of nonreceptor tyrosine kinases has been identified as potential mediators of Bcr-Abl-induced leukemogenesis.³ Bosutinib is an investigational orally available dual Src and Abl kinase inhibitor with minimal inhibitory activity against c-kit and PDGFR.⁷
RATIONALE	<ul style="list-style-type: none"> In some cases, CML develops resistance to currently available treatments.³ When this occurs, patients will stop responding to therapy or will progress to an advanced phase of disease while on treatment.^{3,8} Overexpression of the Src family of tyrosine kinases has been implicated in imatinib resistance and CML progression.³ There remains a need for additional options for relapsed CML patients, given challenges with treatment-related toxicities and resistance in this patient population.⁸
OBJECTIVES	<ul style="list-style-type: none"> The primary objective of the trial is to determine the major cytogenetic response (MCyR) rate in subjects with imatinib-resistant chronic phase CML.⁹
STUDY DESIGN	<ul style="list-style-type: none"> The Phase 1/2 study is a two-part, open-label trial of single-agent bosutinib in Philadelphia positive (Ph+) leukemias.⁹ In part one, chronic phase CML patients resistant to imatinib received bosutinib daily in order to determine the maximum tolerated dose.⁹ In part two, the study was expanded to determine the efficacy and safety of bosutinib in patients in other phases of Ph+ CML, including patients who were resistant or intolerant to imatinib therapy alone, or resistant or intolerant to imatinib and second generation tyrosine kinase inhibitors.⁹
SELECTED ELIGIBILITY CRITERIA	<ul style="list-style-type: none"> Selected Inclusion Criteria: <ul style="list-style-type: none"> Ph+ CML or Ph+ ALL patients who are primarily refractory to full-dose imatinib (600 mg), have disease progression/relapse while on full-dose imatinib, or are intolerant of any dose of imatinib. At least three months post stem cell transplantation.⁹ Selected Exclusion Criteria: <ul style="list-style-type: none"> Subjects with Ph+, and Bcr-Abl negative CML Overt leptomeningeal leukemia Subjects without evidence of leukemia in bone marrow⁹
NUMBER OF PATIENTS	<ul style="list-style-type: none"> The trial enrolled 571 patients from research sites in the United States and ex-U.S.⁹ This study is currently ongoing, but is closed to enrollment.
RESULTS	<ul style="list-style-type: none"> Initial results from a cohort of Study 200 that consists of more than 100 patients with chronic phase Ph+ CML who have failed prior imatinib therapy and were resistant or intolerant to dasatinib or resistant to nilotinib were previously presented at the American Society of Hematology 2010 annual meeting.

¹ American Cancer Society. What is Chronic Myeloid Leukemia? Available at: <http://www.cancer.org/Cancer/Leukemia-ChronicMyeloidCML/DetailedGuide/leukemia-chronic-myeloid-myelogenous-what-is-c-m-l>. Accessed April 25, 2011.

² National Cancer Institute. General Information About Chronic Myelogenous Leukemia. 2011. Available at: <http://www.cancer.gov/cancertopics/pdq/treatment/CML/patient>. Accessed April 26, 2011

³ Konig H et al. Effects of Dasatinib on Src Kinase Activity and Downstream Intracellular Signaling in Primitive Chronic Myelogenous Leukemia Hematopoietic Cells. *Cancer Research*. 2008; 68: 9624-9633.

⁴ CenterWatch. Drug Information: Imatinib. CenterWatch. Available at: <http://www.centerwatch.com/drug-information/fda-approvals/drug-details.aspx?DrugID=699>. Accessed April 20, 2010.

⁵ CenterWatch. Drug Information: Dasatinib. CenterWatch. Available at: <http://www.centerwatch.com/drug-information/fda-approvals/drug-details.aspx?DrugID=903>. Accessed April 20, 2010.

⁶ CenterWatch. Drug Information: Nilotinib. CenterWatch. Available at: <http://www.centerwatch.com/drug-information/fda-approvals/drug-details.aspx?DrugID=970>. Accessed April 20, 2010.

⁷ Gambacorti-Passerini C et al. Bosutinib (SKI-606) Demonstrates Clinical Activity and is Well Tolerated in Patients with AP and BP CML and Ph+ ALL. Poster Presented at the American Society of Hematology Meeting, December 6-9, 2008, San Francisco, CA. Wyeth.

⁸ O'Hare T et al. Toward a Cure for Chronic Myeloid Leukemia. *Clinical Cancer Research*. 2008; 14: 7971-7974.

⁹ ClinicalTrials. Study Evaluating SKI-606 in Philadelphia Chromosome Positive Leukemias. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00261846?term=bosutinib&phase=1&rank=7>. Accessed April 26, 2011.