### STUDY 200: Study Evaluating bosutinib in Philadelphia Chromosome Positive Leukemias

**INTRODUCTION**
- 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. Once these cells are affected by leukemia, they do not go through their normal process of maturing.
- 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.
- Therapies such as imatinib, dasatinib and nilotinib 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.
- Bosutinib is an investigational orally available dual Src and Abl kinase inhibitor with minimal inhibitory activity against c-kit and PDGFR.

**RATIONALE**
- In some cases, CML develops resistance to currently available treatments. This occurs when a patient stops responding to therapy or progresses to an advanced phase of disease while on treatment.
- Overexpression of the Src family of tyrosine kinases has been implicated in imatinib resistance and CML progression.
- There remains a need for additional options for relapsed CML patients, given challenges with treatment-related toxicities and resistance in this patient population.

**OBJECTIVES**
- The primary objective of the trial is to determine major cytogenetic response (MCyR) rate in subjects with imatinib-resistant chronic phase CML.

**STUDY DESIGN**
- The Phase 1/2 study is a two part, open-label trial of single agent bosutinib in Philadelphia positive (Ph+) leukemias.
- In part one, chronic phase CML patients resistant to imatinib received bosutinib daily in order to determine the maximum tolerated dose.
- 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.

**SELECTED ELIGIBILITY CRITERIA**
- Selected Inclusion Criteria:
  - 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.
- Selected Exclusion Criteria:
  - Subjects with Ph+, and Bcr-Abl negative CML
  - Overt leptomeningeal leukemia
  - Subjects without evidence of leukemia in bone marrow

**NUMBER OF PATIENTS**
- The trial planned to enroll approximately 450 patients from research sites in the United States and ex-U.S.