KURZPROTOKOLL
CABL001A2301

Öffentlicher Titel	Phase III Studie zu ABL001 bei TKI-vorbehandelten CML-Patienten
Wissenschaftl. Titel	A Phase 3, Multi-center, Open-label, Randomized Study of Oral ABL001 Versus Bosutinib in Patients With Chronic Myelogenous Leukemia in Chronic Phase (CML-CP), Previously Treated With 2 or More Tyrosine Kinase Inhibitors
Kurztitel	CABL001A2301
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, offen/unverblindet, Pharma-Studie, zweiarmig
Studienphase	Phase III
Erkrankung	Blut: Myeloische Neoplasien/Dysplasien: Chronische myeloische Leukämie (CML)
Einschlusskriterien	- Male or female patients with a diagnosis of CML-CP >= 18 years of age - Patients must meet all of the following laboratory values at the screening visit: a) < 15% blasts in peripheral blood and bone marrow; b) < 30% blasts plus promyelocytes in peripheral blood and bone marrow; c) < 20% basophils in the peripheral blood; d) => 50 x 109/L (=>50,000/mm3) platelets; d) Transient prior therapy related thrombocytopenia (< 50,000/mm3 for => 30 days prior to screening) is acceptable; e) No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly - BCR-ABL ratio >= 1% IS according to central laboratory at the screening examination - Prior treatment with a minimum of 2 prior ATP-binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib) - Failure or intolerance to the last previous TKI therapy at the time of screening (adapted from the 2013 ELN Guidelines Bacarrani 2013) - Failure is defined for CML-CP patients (CP at the time of initiation of last therapy) as follows. Patients must meet at least 1 of the following criteria: - Three months after the initiation of therapy: No CHR or > 95% Ph+ metaphases - Six months after the initiation of therapy: BCR-ABL ratio > 10% IS and/or > 65% Ph+ metaphases - Twelve months after initiation of therapy: BCR-ABL ratio > 10% IS and/or > 35% Ph+ metaphases - At any time after the initiation of therapy, loss of CHR, CCyR or PCyR - At any time after the initiation of therapy, the development of new BCR-ABL mutations - At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests, of which one must have a BCR-ABL ratio 1% IS - At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+ - Intolerance 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); 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
Ausschlusskriterien	- Known presence of the T315I or V299L mutation at any time prior to study entry - Known second chronic phase of CML after previous progression to AP/BC Previous treatment with a hematopoietic stem-cell transplantation Patient planning to undergo allogeneic hematopoietic stem cell transplantation - Cardiac or cardiac repolarization abnormality, including any of the following: - History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG)

- Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
- QTcF at screening =>450 ms (male patients), =>460 ms (female patients)
- Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
- Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
- Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointes that cannot be discontinued or replaced 7 days prior to starting study drug by safe alternative medication.
- Inability to determine the QTcF interval
- Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, active or uncontrolled infection, pulmonary hypertension)
- History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis
- History of acute or chronic liver disease
- Treatment with medications that meet one of the following criteria and that cannot be discontinued at least one week prior to the start of treatment with study treatment
- Moderate or strong inducers of CYP3A
- Moderate or strong inhibitors of CYP3A and/or P-gp
- Substrates of CYP3A4/5, CYP2C8, or CYP2C9 with narrow therapeutic index
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 days after last dose of ABL001. Highly effective contraception methods include:
- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

	- Sexually active males unless they use a condom during intercourse while taking the drug during treatment and for 3 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen.
Alter	18 Jahre und älter
Molekularer Marker	BCR-ABL1
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Sponsor	Novartis Pharma
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT03106779 EudraCT 2016-002461-66
Links	Studiendokumente zum Download (roXtra)