European LeukemiaNet
SHORTPROTOCOL
ENESTop

Public Title	Study of Treatment-free Remission After Achieving Sustained MR4.5 on Nilotinib
Scientific Title	A Phase II, Single Arm, Open Label Study of Treatment-free Remission After Achieving Sustained MR4.5 on Nilotinib (ENESTop)
Short Title	ENESTop
Id KN/ELN	LN_NN_2012_535
Trialgoup	NN
Type of Trial	multicentric, single-group, prospective, open-label
Phase	Phase II
Disease	Chronic myeloid leukemia(CML) All subtypes
Stage of Disease	.
Outcomes	- No documented confirmed loss of MR4, no documented loss of MMR and no re-starting of nilotinib therapy [Time Frame: First 12 months following nilotinib cessation.] (Primary Outcome) - No documented confirmed loss of MR4, no documented loss of MMR and no re-starting of nilotinib therapy in the first 24, 36, and 48 months following nilotinib cessation. [Time Frame: 24, 36 and 48 months following nilotinib cessation] - Progression to AP/BC or death where the "failure" event is the earliest occurrence of the following event: progression to AP/BC or death from any cause. [Time Frame: study duration] - Treatment free survival (TFS) defined as lack any of the following events: loss of MMR, confirmed loss of MR4, re-start of Nilotinib treatment, progression to AP/BC or death from any cause. [Time Frame: study duration] - Overall survival (OS) defined as the time from the date of cessation of nilotinib therapy to the date of death from any cause. [Time Frame: study duration] - BCR-ABL transcript changes within 12 months after re-start of nilotinib therapy [Time Frame: within 12 months after re-start of nilotinib therapy]
Inclusion Criteria	- Male or female patients >= 18 years of age - ECOG Performance Status of 0, 1, or 2 - Patient with diagnosis of BCR-ABL positive CML - Patient has received a minimum of 3 years of tyrosine kinase inhibitor treatment (first with imatinib and then switched to nilotinib) since initial diagnosis - Patient has at least 2 years of nilotinib treatment prior to study entry. - Patient has achieved MR4.5 (local laboratory assessment) during nilotinib treatment, and determined by a Novartis designated central PCR lab assessment at screening - Adequate end organ function as defined by: a) Direct bilirubin =< 15umol/L; b) SGOT(AST) and SGPT(ALT) < 3 x ULN (upper limit of normal); c) Serum lipase =< 2 x ULN; d) Alkaline phosphatase =< 2.5 x ULN; e) Serum creatinine < 1.5 x ULN - Patients must have the following electrolyte values >= LLN (lower limit of normal) limits or corrected to within normal limits with supplements prior to the first dose of study medication: a) Potassium; b) Magnesium; c) Total calcium (corrected for serum albumin) - Patients must have normal marrow function as defined below: a) Absolute Neutrophil Count (ANC) => 1.5 x 10^9/L; b) Platelets => 100 x 10^9/L; c) Hemoglobin => 9.0 g/dL - Written informed consent obtained prior to any screening procedures
Exclusion Criteria	- Prior AP, BC or allo-transplant - Patient has documented MR4.5 at the time when switched from imatinib to nilotinib - Patients with known atypical transcript

- Mutation(s) detected if a testing was done in the past (there is no requirement to perform mutation testing at study entry if it was not done in the past)
- Dose reductions due to neutropenia or thrombocytopenia in the past 6 months
- Patient ever attempted to permanently discontinue imatinib or nilotinib treatment
- Known impaired cardiac function including any one of the following: a) Inability to determine the QT interval on ECG; b) Complete left bundle branch block; c) Long QT syndrome or a known family history of long QT syndrome; d) History of or presence of clinically significant ventricular or atrial tachyarrhythmias; e) Clinically significant resting bradycardia; f) QTcF > 480 msec; g) History or clinical signs of myocardial infarction within 1 year prior to study entry; h) History of unstable angina within 1 year prior to study entry; i) Other clinically significant heart disease (e.g. uncontrolled congestive heart failure or uncontrolled hypertension)
- 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 (defined as HbA1c > 9%), uncontrolled infection)
- History of acute pancreatitis within 1 year prior to study entry or past medical history of chronic pancreatitis
- Known presence of a significant congenital or acquired bleeding disorder unrelated to cancer
- History of other active malignancy within 5 years prior to study entry with the exception of previous or concomitant basal cell skin cancer, previous cervical carcinoma in situ treated curatively
- Patients who have not recovered from prior surgery
- Treatment with other investigational agents (defined as not used in accordance with the approved indication) within 4 weeks of Day 1
- Patients actively receiving therapy with strong CYP3A4 inhibitors and/or inducers, and the treatment cannot be either discontinued or switched to a different medication prior to study entry. See Appendix 14.1 for a list of these medications. This list may not be comprehensive.
- Patients actively receiving therapy with herbal medicines that are strong CYP3A4 inhibitors and/or inducers, and the treatment cannot be either discontinued or switched to a different medication prior to study entry. These herbal medicines may include Echinacea, (including E. purpurea, E. angustifolia and E. pallida), Piperine, Artemisinin, St. John's Wort, and Ginkgo.
- Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval and the treatment cannot be either safely discontinued or switched to a different medication prior to study entry. (Please see www.azcert.org/medical-pros/drug-lists/printable-drug-list.cfm for a list of agents that prolong the QT interval.)
- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery)
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include: a) Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception; b) Female sterilization (have had surgical bilateral oophorectomy with or without 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 and documented by follow up hormone level assessment; c) Male sterilization (at least 6 months prior to screening). For female patients on the study, study participation assumes the vasectomized male partner is the sole partner for that patient; d) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository; e) Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception; f) Placement of an intrauterine device (IUD) or intrauterine system (IUS) 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) or tubal ligation at least six weeks prior to enrolling. 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.
- If a study patient becomes pregnant or is suspected of being pregnant during the study or within 30 days after the final dose of nilotinib, the Study Doctor needs to be informed immediately and ongoing study treatment with nilotinib has to be stopped immediately.

Age	>= 18 years
Status	Closed
start of Recruitment	01.12.2012
Recruiting countries	Germany France U.K. Brazil Belgium Spain Russian Federation Greece The Netherlands U.S.A Poland
Leader	Le Coutre, Dr. med., Phillipp Charité Universitätsmedizin Berlin, Campus Virchow Department of Oncology and Hematology Augustenburger Platz 1 13553 Berlin Tel: +49 (0)30 450-553065 Email: philipp.lecoutre@charite.de
Sponsors	Novartis Pharma AG (Main Sponsor)

Supporters	Novartis Pharma AG Homepage: www.novartispharma.de/index.shtml
Other Registers	ClinicalTrials.govNCT01698905