Nilotinib Treatment-free Remission Study in CML (Chronic Myeloid Leukemia) Patients (ENESTFreedom)

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2015 by Novartis

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT01784068

First received: January 30, 2013
Last updated: August 14, 2015
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History of Changes

Purpose

The main purpose of the study is to investigate w hether nilotinib treatment can be safely suspended w ith no recurrence of CML in selected patients w ho responded optimally on this treatment

Condition	Intervention	Phase
Chronic Myelogenous Leukemia	Drug: Nilotinib follow ed by treatment-free	Phase 2

Study Type: Interventional
Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label

Official Title: A Single-arm, Multicenter, Nilotinib Treatment-free Remission Study in Patients With BCR-ABL1 Positive Chronic Myelogenous Leukemia in Chronic Phase Who Have Achieved Durable Minimal Residual Disease (MRD) Status on First Line Nilotinib Treatment.

Resource links provided by NLM:

MedlinePlus related topics: Chronic Myeloid Leukemia Leukemia

Drug Information available for: Nilotinib

Genetic and Rare Diseases Information Center resources: Chronic Myeloid Leukemia Chronic Myeloproliferative Disorders Myeloid Leukemia

U.S. FDA Resources

Further study details as provided by Novartis:

Primary Outcome Measures:

- Percentage of patients w ho are in MMR (major molecular response) at 48 w eeks after starting the treatment-free remission (TFR) phase [Time Frame: 48 w eeks] [Designated as safety issue: No]

  Primary endpoint is the proportion of patients w ho are in MMR at 48 w eeks after starting the TFR phase and is calculated by dividing the number of patients w ith MMR at 48 w eeks after starting the TFR phase w ith no loss of MMR and no re-initiation of nilotinib therapy in the first 48 w eeks after starting the TFR phase by the number of patients entered the TFR phase. Patients w ho required re-initiation of treatment w ill be considered as non-responders

Secondary Outcome Measures:

- Percentage of patients w ho are in MR4.5 (BCR-ABL ≤ 0.0032% IS) at 48 w eeks after starting the TFR phase [Time Frame: 48 w eeks] [Designated as safety issue: No]

  Proportion of patients w ho are in MR4.5 at 48 w eeks after starting the TFR phase is calculated by dividing the number of patients w ith MR4.5 at 48 w eeks after starting the TFR phase w ith no loss of MR4.5 and no re-initiation of nilotinib therapy in the first 48 w eeks after starting the TFR phase by the number of patients w ho entered the TFR phase. Patients w ho required re-initiation of treatment w ill be considered as non-responders. MR4.5 = log reductions of the BCR-ABR transcript load in blood as a measurement of deep molecular response of the CML clone to treatment.

- Percentage of patients w ho are in MMR at 96, 144 and 192 w eeks after starting the TFR phase [Time Frame: 96, 144 and 192 w eeks] [Designated as safety issue: No]

  Proportion of patients w ho are in MMR at 96, 144 and 192 w eeks after starting the TFR phase is calculated by dividing the number of patients w ith MMR at 96, 144 and 192 w eeks after starting the TFR phase w ith no loss of MMR and no re-initiation of nilotinib therapy in the first 96, 144 and 192 w eeks after starting the TFR phase by the number of patients w ho entered the TFR phase. Patients w ho required re-initiation of treatment w ill be considered as non-responders

- Percentage of patients w ho are in MR4.5 at 96, 144 and 192 w eeks after starting the TFR phase [Time Frame: 96, 144 and 192 w eeks] [Designated as safety issue: No]

  Proportion of patients w ho are in MR4.5 at 96, 144 and 192 w eeks after starting the TFR phase is calculated by dividing the number of patients w ith MR4.5 at 96, 144 and 192 w eeks after starting the TFR phase w ith no loss of MR4.5 and no re-initiation of nilotinib therapy in the first 96, 144 and 192 w eeks after starting the TFR phase by the number of patients w ho entered the TFR phase. Patients w ho required re-initiation of treatment w ill be considered as non-responders

- Percentage of patients in MMR at 48, 96, 144 and 192 w eeks after starting the TFR phase of nilotinib [Time Frame: 48, 96, 144 and 192 w eeks] [Designated as safety issue: No]

  Proportion of patients w ho are in MMR at 48, 96, 144 and 192 w eeks after starting the TFR phase is calculated by dividing the number of patients w ith MMR at 48, 96, 144 and 192 w eeks after starting the TFR phase by the number of patients w ho entered the TFR phase. Patients w ho are re-initiated w ith nilotinib but have less than 12 w eeks of re-initiation of treatment w ill be excluded from the analysis

- Percentage of patients in MR4.5 at 48, 96, 144 and 192 w eeks after starting the TFR phase of nilotinib [Time Frame: 48, 96, 144 and 192 w eeks] [Designated as safety issue: No]

  Proportion of patients w ho are in MR4.5 at 48, 96, 144 and 192 w eeks after starting the TFR phase is calculated by dividing the number of patients w ith MR4.5 at 48, 96, 144 and 192 w eeks after starting the TFR phase by the number of patients w ho entered the TFR phase. Patients w ho are re-initiated w ith nilotinib but have less than 12 w eeks of re-initiation of treatment w ill be excluded from the analysis

- Percentage of patients w ho achieve MMR w ithin 12 w eeks of re-treatment w ith nilotinib [Time Frame: 12 w eeks] [Designated as safety issue: No]

  Proportion of patients w ho achieve MMR w ithin 12 w eeks of re-initiation of nilotinib is calculated by dividing the number of patients w ho are in MMR at least at one assessment w ithin 12 w eeks after re-start of nilotinib treatment by the number of patients w ho are re-initiated for at least 12 w eeks

- Kinetics of BCR-ABL transcript after re-start of nilotinib therapy [Time Frame: Every 4 w eeks up to w eek 24 and every 12 w eeks thereafter up to 192 after last patient has entered the TFR] [Designated as safety issue: No]

  Descriptive statistics of BCR-ABL levels (IS) over time after re-start of nilotinib therapy up to 192 w eks after the last patient has entered TFR

- Duration of re-initiated treatment required to regain MMR after loss of MMR [Time Frame: Every 4 w eeks up to w eek 24 and every 12 w eeks therefater up to 192 w eks after the last patient has entered TFR] [Designated as safety issue: No]

  Defined as time from date of start of re-initiation of treatment after loss of MMR to the date of first achievement of MMR. Patients w ho do not regain MMR after re-initiation of treatment on or before the cut-off date, duration w ill be censored at the date of last PCR assessment

- Duration of re-initiated treatment required to regain MR4.5 after loss of MMR [Time Frame: Every 4 w eeks up to w eek 24 and every 12 w eeks thereafter up to 192 w eks after the last patient has entered TFR] [Designated as safety issue: No]

  Defined as the time from start of re-initiation of treatment after loss of MMR to the first achievement of MR4. Patients w ho do not regain MR4.5 after re-initiation of treatment on or before the cut-off date, duration w ill be censored at the date of last PCR assessment

- Treatment-free survival (TFS) after the start of the TFR phase [Time Frame: Every 4 w eeks in the first period of 48 w eeks of the TFR, every 6 w eeks in the second period of 48 w eeks in TFR and every 12 w eeks in the last period of 96 w eeks of the TFR]

[Designated as safety issue: No]

TFS is defined as the time from the start of the TFR phase to the earliest occurrence of loss of MMR, re-initiation of treatment due to any cause, progression of AP/BC or death due to any cause. For patients without any event on or before the cut-off date, survival time will be censored at the date of their last assessment (PCR, cytogenetic, hematologic or extramedullary)

- Progression-free survival (PFS) after the start of the TFR phase [Time Frame: Every 4 weeks in the first period of 48 weeks of the TFR, every 6 weeks in the second period of 48 weeks of TFR and every 12 weeks in the last period of 96 weeks of the TFR]
  [Designated as safety issue: No]

  PFS is defined as the time from the start of the TFR phase to the earliest occurrence of progression to AP/BC or death due to any cause. For patients without any event on or before the cut-off date, survival time will be censored at the date of their last assessment (cytogenetic, hematologic or extramedullary) for patients who are still on study and at the date of last contact for patients who are in follow-up

- Overall survival (OS) after the start of the TFR phase [Time Frame: Every 4 weeks in the first period of 48 weeks of the TFR, every 6 weeks in the second period of 48 weeks of TFR and every 12 weeks in the last period of 96 weeks of the TFR]
  [Designated as safety issue: No]

  OS is defined as the time from start of the TFR phase to death due to any cause. For patients without any event on or before the cut-off date, survival time will be censored at the date of their last assessment for patients who are still on study and at the date of last contact for patients who are in follow-up

- Safety profile during the nilotinib treatment consolidation phase, during the TFR phase and during re-initiation treatment with nilotinib [Time Frame: Every 4 weeks in the treatment consolidation and during the first 24 weeks of the re-initaion phase, every 12 weeks thereafter. Every 4, 6 and 12 weeks respectively in the first and second period of 48 weeks and in the last period of 96 weeks of the TFR] [Designated as safety issue: Yes]

  Safety profile includes type, frequency and severity of adverse events, laboratory abnormalities and clinically notable ECG and other safety parameters during the nilotinib treatment consolidation phase, during the TFR phase and during re-initiation of treatment with nilotinib

- Proportion of patients who develop T3151, E255K/V, Y253H, F359V/C/I mutations on study or any other BCR-ABL mutations in patients who lost MMR after nilotinib suspension [Time Frame: Every 3 months in patients who lost MMR until the result is negative or up to 192 weeks after the last patient entered TFR. On average 3 analyses (every 3 months or up to 192 weeks after the last patient has entered TFR.)] [Designated as safety issue: No]

  Proportion will be calculated by dividing the number of patients who developT315I, E255K/V, Y253H, F359V/C/I mutations after nilotinib suspension by the number of patients who lost MMR

Estimated Enrollment:	175
Study Start Date:	March 2013
Estimated Study Completion Date:	November 2018
Estimated Primary Completion Date:	November 2018 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Nilotinib followed by treatment-free Patients who have received a minimum of 2 years of first line nilotinib treatment and with pre-screen PCR results in ≥ MR4.5 will enter the consolidation phase of the study (52 weeks - nilotinib 300 mg BID). Patients with Minimal Residual Disease (MRD) at the end of this phase will enter the Treatment-Free Remission (TFR) phase where no treatment is given. Non eligible patients will enter the continuation phase of the study. Patients with MRD at the end of the continuation phase will enter the TFR-2 phase of the study where no treatment is given. Non eligible patients will enter the prolonged continuation phase of the study. If at any time during TFR or TFR-2 the patient loses MMR, nilotinib treatment will be immediately re-initiated (nilotinib 300 mg BID).	Drug: Nilotinib followed by treatment-free Nilotinib will be used as commercial available capsules (except in Japan where clinical supplies is used) of 150 mg and 200 mg strength. treatment occurs during consolidation, continuation, prolonged continuation, re-initiation and re-initiation-2 phases of the study.

Eligibility

Ages Eligible for Study:	18 Years and older
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Minimum of 2 calendar years of nilotinib treatment w ith at least the last 12 months of nilotinib treatment prior to pre-screening at approved total dialy dose of 600 mg BID or at a reduced dose of 400 mg QD if required from the perspective of tolerance for BCR-ABL positive CML in documented chronic phase at the time of diagnosis
- Evidence of typical BCR-ABL transcripts (b3a2 and/or b2a2) at the time of CML-CP diagnosis i.e. prior to first start of TKI treatment w hich are amenable to standardized RT-PCR quantification"
- Patient in MR4.5 at prescreening at Novartis designated lab
- ECOG performance status of 0-2
- Adequate end organ function as defined by:
  - Direct bilirubin ≤ 1.5 x ULN except for i) patients w ith documented Gilbert's syndrome for w hom any bilirubin value is allow ed and ii) for patients w ith asymptomatic hyperbilirubinemia (liver transaminases and alkaline phosphatase w ithin normal range).
  - SGOT(AST) and SGPT(ALT) ≤ 3 x ULN i.e. equivalent to ≤ Grade 1 NCI-CTCAE v.4.03
  - Serum lipase ≤ 2 x ULN i.e. equivalent to ≤ Grade 2 NCI-CTCAE v.4.03
  - Alkaline phosphatase ≤ 2.5 x ULN
  - Serum creatinine < 1.5 x ULN
- Patients must have the follow ing electrolyte values w ithin normal limits or corrected to be w ithin normal limits w ith supplements prior to first dose of study medication:
  - Potassium (suggested keep to prevent issues w ith QT and/or rhythm abnormalities)
  - Magnesium (suggested keep to prevent issues w ith QT and/or rhythm abnormalities)
  - Total calcium (corrected for serum albumin)
- Patients must have normal marrow function as defined:
  - Absolute Neutrophil Count (ANC) ≥ 1.5 x 10E9/L
  - Hemoglobin ≥ 9.0 g/dL
  - Platelets ≥ 100 x 10E9/L

Exclusion Criteria:

- Previous treatment w ith BCR-ABL inhibitors other than nilotinib for more than a total cumulative duration of 4 w eeks
- Previous treatment w ith alpha-interferon of any duration
- Previous anticancer agents for CML other than nilotinib except for cytoreduction after CML diagnosis until up to 4 w eeks after first dose of nilotinib
- Know n second chronic phase of CML after previous progression to AP/BC
- Poorly controlled diabetes mellitus (defined as HbA1c > 9%)
- Impaired cardiac function including any one of the follow ing:
  - LVEF < 45% or below the institutional low er limit of the normal range (w hichever is higher)
  - Inability to determine the QT interval on ECG, except for patients w ith evidence of measurable QT interval at the time of CML diagnosis (e.g. prior to first start of TKI treatment) and w ho have no documented clinical signs of cardiovascular disease and/or clinical signs of conduction abnormality.
  - Complete left bundle branch block
  - Right bundle branch block plus left anterior or posterior hemiblock
  - Use of a ventricular-paced pacemaker
  - Congenital long QT syndrome or a know n family history of long QT syndrome
  - History of or presence of clinically significant ventricular or atrial tachyarrhythmias
  - Clinically significant resting bradycardia
  - QTc > 450 msec on the average of three serial baseline ECG (using the QTcF formula). If QTcF > 450 msec and electrolytes are not w ithin normal ranges, electrolytes should be corrected and then the patient re-tested for QTc.This exclusion criterion is not applicable for patients w ith non-measurable QT interval w ho have evidence of measurable QT interval at the time of CML diagnosis (e.g. prior to first start of TKI treatment) and w ho have no documented clinical signs of cardiovascular disease and/or clinical signs of conduction abnormality.
  - History or clinical signs of myocardial infarction w ithin 1 year of study entry
  - History of unstable angina w ithin 1 year of study entry
  - Other clinically significant heart disease (e.g. congestive heart failure, cardiomyopathy or uncontrolled hypertension)
- History of acute pancreatitis w ithin 1 year of study entry or past medical history of chronic pancreatitis
- Know n presence of significant congenital or acquired bleeding disorder unrelated to cancer
- History of another active malignancy w ithin 5 years prior to study entry w ith the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively
- Treatment w ith other investigational agents (defined as not used in accordance w ith the approved indication) w ithin 4 w eeks 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 starting study drug. See Appendix 1 for a list of these medications. This list may not be exhaustive.
- 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 starting study drug. 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 starting study drug. (Please see http://www.torsades.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 highly effective methods of contraception during the study and for 14 days after the final dose of nilotinib. Highly effective contraception is defined as either:
    - 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
    - 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 by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to enrolling). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - Use of a combination of any two of the following:
        a. 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.
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel /film/cream/vaginal suppository 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) 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 suspects 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.

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: NCT01784068

Contacts

Contact: Novartis Pharmaceuticals 1-888-669-6682

Contact: Novartis Pharmaceuticals

Show 175 Study Locations

Sponsors and Collaborators

Novartis Pharmaceuticals

Investigators

Study Director: Novartis Pharmaceuticals Novartis Pharmaceuticals

More Information

No publications provided

Responsible Party:	Novartis (Novartis Pharmaceuticals)
ClinicalTrials.gov Identifier:	NCT01784068 History of Changes
Other Study ID Numbers:	**CAMN107I2201**
Study First Received:	January 30, 2013
Last Updated:	August 14, 2015
Health Authority:	Argentina: Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica Austria: Federal Office for Safety in Health Care Belgium: Federal Agency for Medicinal Products and Health Products China: Food and Drug Administration Colombia: INVIMA Instituto Nacional de Vigilancia de Medicamentos y Alimentos Denmark: Danish Medicines Agency France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) Germany: Federal Institute for Drugs and Medical Devices Greece: National Organization of Medicines Hungary: National Institute of Pharmacy Ireland: Irish Medicines Board Italy: The Italian Medicines Agency Japan: Ministry of Health, Labor and Welfare Netherlands: The Central Committee on Research Involving Human Subjects (CCMO) Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products Spain: Spanish Agency of Medicines Sw eden: Medical Products Agency United Kingdom: Medicines and Healthcare Products Regulatory Agency United States: Food and Drug Administration Bulgaria: Bulgarian Drug Agency

Keyw ords provided by Novartis:

Ph+ CML-CP
chronic phase
nilotinib treatment
2 years treatment
MR 4.5
Loss of MR 4
Loss of MMR

Additional relevant MeSH terms:

Leukemia
Leukemia, Myelogenous, Chronic, BCR-ABL Positive
Leukemia, Myeloid
Neoplasm, Residual
Bone Marrow Diseases
Hematologic Diseases
Myeloproliferative Disorders
Neoplasms
Neoplasms by Histologic Type
Neoplastic Processes
Pathologic Processes

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