



## Protocol Page

Therapy of Early Chronic Phase Chronic Myelogenous Leukemia (CML) with Oral Nilotinib  
2005-0048

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### Core Protocol Information

<b>Short Title</b>	Phase II nilotinib with newly diagnosed chronic phase CML
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#### Which Committee will review this protocol?

- The Clinical Research Committee - (CRC)

## Protocol Body

**Title:** Therapy of Early Chronic Phase Chronic Myelogenous Leukemia (CML)  
with Oral Nilotinib

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## Protocol Body

### 1.0 Objectives

#### Primary:

To determine the percentage of patients who achieve low levels of PCR ratios of Bcr-Abl/Abl (molecular CR) after 12 months of therapy with nilotinib.

#### Secondary:

- To determine the proportion of patients with Ph-positive early chronic phase CML achieving a complete cytogenetic response after nilotinib therapy, and the time to achieve the response.
- To evaluate the durations of PCR negativity, cytogenetic response, hematologic control, and survival.
- To analyze differences in response rates and in prognosis within different risk groups and patient characteristics.
- To evaluate symptom burden in patients with CML receiving nilotinib.

### 2.0 Background

#### 2.1 Purpose

The basic hypothesis underlying our therapeutic program in CML is to be able to achieve meaningful and long-lasting suppression of the Philadelphia chromosome and Bcr-Abl abnormalities. Such complete cytogenetic responses and complete/major molecular responses have been associated with survival prolongation in CML.

#### 2.2 Historical Experience

The prognosis of patients with chronic myelogenous leukemia is improving (1). Historically, the median survival of untreated patients with CML was 19 months from diagnosis. In our historical experience of 303 patients with a diagnosis of Philadelphia-positive early chronic-phase CML referred to our institution within 3 months of diagnosis with minimal or no prior therapy, the overall median survival was 39 months (2). Patients were divided into good, intermediate and poor risk groups with different hazard rates and median survivals (2).

Symptoms are subjective phenomena reported by patients that indicate a change in normal functioning, sensation, or appearance due to disease (30). Symptom burden is the combined impact of disease- and therapy-related symptoms on the ability of persons to function as they did prior to onset of their disease and/or therapy (31). The MD Anderson Symptom Inventory (MDASI) is a valid and reliable measure of symptom burden (32). Recently a CML-specific version of the MDASI, the MDASI-CML, has been validated. Common symptoms of chronic

myeloid leukemia (CML) and its treatment can significantly impair the daily functioning of patients (33). Symptoms such as fatigue, nausea and vomiting, diarrhea, muscle cramps, skin changes, and headache add to the burden of CML. Patients with serious illnesses often report that they would like to “return to a normal life” (34). Decreasing the symptom burden of CML and its treatments will allow patients to function as normally as possible. Currently, there is little research on symptoms and their impact on daily functioning experienced by patients with CML to direct interventions that may assist patients in returning to normal.

We have successfully developed IVR technology for the assessment of multiple symptoms using the MDASI in patients with cancer undergoing chemotherapy, radiation therapy, and surgery. We currently have one active study in a sample of patients with CML, many of whom are receiving kinase inhibitor therapies, using the MDASI-CML. Initial evaluation has shown this to be a feasible option for patient-reported symptom burden assessment in this group of patients and further evaluation is ongoing. The patient chooses the day and the time to receive the IVR system call; the system calls the patient three times if necessary to complete the assessment.

### **2.3 Interferon Therapy in CML**

At M.D. Anderson Cancer Center, 80% of patients with early chronic phase Philadelphia chromosome (Ph)-positive CML treated with interferon alpha (IFN- $\alpha$ ) alone or in combinations, achieved a complete hematologic response (CHR); 55% had a cytogenetic response, which was major and durable in 25% (3-5). Achieving a complete cytogenetic response was associated with estimated 10-year survival rates above 70% to 80%(5). In randomized studies and by meta-analysis, IFN- $\alpha$  was associated with significant survival prolongation compared with conventional chemotherapy (6-11). Similar associations of achieving minimal tumor burden and survival prolongation have been reported by these studies.

The addition of low-dose cytarabine to interferon-alpha may have improved outcome (12-14).

### **2.4 Imatinib Mesylate (STI571; Gleevec) in CML**

Imatinib is an inhibitor of the protein-tyrosine kinases associated with Bcr-Abl, the platelet-derived growth factor (PDGF) receptor and c-Kit. CML represents an ideal disease target for imatinib, given that the Bcr-Abl kinase plays a dominant role in the deregulated myeloid cell proliferation which is the hallmark of this disease.

Imatinib shows selectivity for the Abl protein tyrosine kinase at the *in vitro*, cellular and *in vivo* level (15). The compound specifically inhibits proliferation of Bcr-Abl expressing cells. In colony forming assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows selective inhibition of Bcr-Abl positive colonies from CML patients (16-18). In animal models, the compound shows

potent anti-tumor activity against Bcr-Abl and v-Abl expressing cells at tolerated doses (16).

In phase I studies, imatinib has demonstrated activity in all CML phases post IFN- $\alpha$  failure and in Ph-positive ALL (19,20).

Three large-scale pivotal trials of imatinib in CML chronic, accelerated and blastic phases have been completed (21-24). In chronic phase CML, 532 patients who had failed IFN- $\alpha$  therapy were treated with imatinib 400 mg orally daily. The CHR rate was above 90%. The major cytogenetic response rate (Ph-positive less than 35%) was 60%. Imatinib was well-tolerated. Side effects included nausea, vomiting, diarrhea, skin rashes, muscle cramps, bone and joint aches, and liver dysfunction. Grade 3-4 toxicities requiring discontinuation of therapy occurred in 2% or less of patients. Periorbital and leg edema and fluid retention were frequent at imatinib doses of 600 to 1000 mg orally daily.

An open-label, multicenter, randomized phase III study (International Randomized Interferon vs. STI571 [IRIS]) has been conducted in patients with newly diagnosed Ph+ CML. This study compared treatment with either single-agent Imatinib or a combination of IFN plus cytarabine (ara-C), and allowed for crossover for lack of response, loss of response, or toxicity. A total of 1106 patients have been randomized from 177 centers in 16 countries, 553 to each arm. The major cytogenetic response rate for patients treated with Imatinib was 83% (68% complete) compared to 20% with IFN and ara-C (7% complete). With the follow-up currently available, the 4-year estimated rate of free of progression to accelerated phase or blast crisis was above 90% with imatinib (25,26). High-dose imatinib 400 mg orally BID has improved the early incidences of complete cytogenetic and molecular remissions. Its impact on long-term prognosis remains to be determined (27,28).

## **2.5 Nilotinib**

Nilotinib is a selective Bcr-Abl kinase inhibitor 10 to 100 times more potent than imatinib. In a phase I study, nilotinib was given in a dose escalation schedule to patients with CML accelerated or blastic phase resistant to imatinib. Doses of nilotinib were 50, 100, 200, 400, 600, 800 and 1200 mg orally daily, then 400 mg BID and 600 mg BID. Ninety-five patients have so far been treated. Sustained responses have been observed at nilotinib doses 200 mg daily or above. The response rate was 50% in accelerated and blastic phases and the cytogenetic response rate 30+%. Side-effects included skin rashes, and transient elevations of indirect bilirubin. No MTD or DLT have yet been defined (29, and unpublished data 2005).

## **2.6 Proposed Therapy with Nilotinib**

In this study we propose to treat patients with nilotinib, a selective Bcr-Abl kinase inhibitor more potent than imatinib. We hypothesize that nilotinib may be very effective in achieving molecular remissions in a larger proportion of patients with

early chronic phase CML.

The endpoints of therapy in early chronic phase will be to achieve a PCR ratio of  $\leq 0.05\%$ , as well as evaluate the cumulative overall incidences of complete and major cytogenetic responses. In early chronic phase CML, PCR ratios  $\leq 0.05\%$  are unusual (less than 10%) after 12 months of therapy. We will treat 150 patients, 125 chronic phase and 25 accelerated phase, in a phase II study. Based on the current accrual rate of 50 patients/year with a minimum follow up of 1 year, the study will be completed in 3 years.

## 2.7 Other Biologic Endpoints

We have recently shown the value of interphase FISH analysis in the evaluation of cytogenetic response and in monitoring patients on therapy. In our long-term studies 50% of patients in complete cytogenetic response by regular cytogenetics were also PCR-negative for Bcr-Abl. More recently, PCR quantification has proven useful in monitoring and predicting outcome of patients with CML. Patients with CML on imatinib therapy who achieve a PCR value ratio of Bcr-Abl transcripts/Abl transcripts of 0.05% or less have an excellent long-term prognosis. These studies will help understand better the degree and quality of cytogenetic and molecular responses and their impact on prognosis.

## 3.0 Background Drug Information

Nilotinib is an ATP-competitive inhibitor of the protein tyrosine kinase activity of Bcr-Abl, which prevents the activation of Bcr-Abl dependent mitogenic and anti-apoptotic pathways (e.g. PI-3 kinase and STAT5), leading to the death of the Bcr-Abl phenotype. Following oral administration to animals, nilotinib is well absorbed, shows a good pharmacokinetic profile and is well tolerated. Therefore, nilotinib is expected to be an effective treatment for Bcr-Abl driven diseases (Ph+ ALL and CML). In proliferation assays nilotinib is more potent than imatinib against p210 Bcr-Abl expressing cell lines (IC<sub>50</sub>: 8-22 nM vs. 61-577nM). In a p190 Bcr-Abl-expressing cell line, the IC<sub>50</sub> for autophosphorylation for nilotinib was 31 nM. In addition, nilotinib is effective against the following nilotinib-resistant mutants that have been identified in some relapsed patients: Glu255Val, Phe317Leu, and Met351Thr, inhibiting Bcr-Abl dependent cell proliferation with IC<sub>50</sub> values: 313, 54, and 40 nM, respectively. It is believed that the increased potency and broader spectrum of activity of nilotinib against Bcr-Abl will result in clinical benefit for CML and Ph+ ALL patients.

### 3.1 Overview of Nilotinib

Nilotinib is a novel aminopyrimidine, available as an oral formulation that is an ATP-competitive inhibitor of Bcr-Abl, which prevents the activation of Bcr-Abl dependent mitogenic and anti-apoptotic pathways (e.g. PI-3 kinase and STAT5), leading to the death of the BCR-ABL phenotype. Phase I trials of nilotinib in patients with accelerated-blastic phase CML post imatinib failure have shown hematologic response rates of 50% in accelerated and blastic phases of CML post-imatinib failure, and cytogenetic response rates of 30%. In chronic phase



CML post imatinib failure, the results were better (Kantarjian. Preliminary data 2005).

## 3.2 Preclinical Pharmacology

### 3.2.1 In-vitro Pharmacology

The effects of nilotinib on Bcr-Abl autophosphorylation have been evaluated in K-562 and KU-812F human leukemia cell lines, which naturally express Bcr-Abl, as well as with p190 or p210-bcr-abl transfected murine hematopoietic 32D and p210-bcr-abl transfected Ba/F3 cells. In addition, the compound has been evaluated for effects on autophosphorylation in a panel of Ba/F3 cells, transfected murine hematopoietic cells, expressing different mutant forms of the Bcr-Abl kinase. Nilotinib potently inhibits the Bcr-Abl kinase in cell lines, derived from human leukemic CML cells and from transfected murine hematopoietic cells, with IC<sub>50</sub> values in the range of 20 to 60 nM. In addition, nilotinib inhibits the tyrosine kinase activity of certain Bcr-Abl kinase domain mutants (Glu255Val, Phe317Leu, and Met351Thr), at relevant concentrations (IC<sub>50</sub> values: 313 ± 75, 54 ± 8 and 40 ± 7 nM, respectively). Nilotinib also inhibits the tyrosine kinase activities of the PDGF-R (IC<sub>50</sub> value in A31 cells 79 ± 11 nM) and the stem cell factor receptor, c-kit (IC<sub>50</sub> value in GIST cells 190 ± 24 nM), determined by analogous cell-capture ELISA assays.

Like the Bcr-Abl expressing human cell lines K-562 and KU-812F, murine Ba/F3 cells transfected to express Bcr-Abl exhibit growth factor independent cell viability and proliferation. Similarly, Ba/F3 cells transfected to express other protein kinases exhibit growth factor independent cell viability and proliferation. The effect of drugs on the viability and proliferation of cells may be determined as total growth inhibition of cell cultures, using a luminescent ATP-detection assay kit. In all of the above cell lines, the inhibition of the protein kinase activity is generally well correlated with the effect on cell viability and proliferation. Nilotinib potently inhibits the proliferation of K-562, KU-812F and murine Ba/F3 cells expressing p210 Bcr-Abl kinase, with IC<sub>50</sub> values in the range of 8 to 22 nM. Consistent with the effects on mutant Bcr-Abl kinase activity, nilotinib inhibits Glu255Val, Phe317Leu, and Met351Thr Bcr-Abl dependent cell proliferation, with IC<sub>50</sub> values of 528 ± 112, 74 ± 11 and 27 ± 5 nM respectively. Nilotinib also inhibits PDGF-R $\alpha$  (IC<sub>50</sub> values in FIP-PDGF-R $\alpha$  Ba/F3 cells in the range of 2.5 - 11 nM) and PDGF-R $\beta$  (IC<sub>50</sub> value Tel-PDGF-R $\beta$  Ba/F3 cells of 63 ± 15 nM), as well as c-kit (IC<sub>50</sub> value in GIST cells 153 ± 13 nM) dependent cell proliferation, determined by analogous assays.

The selectivity of nilotinib as a protein kinase inhibitor has been demonstrated by its lack of appreciable activity (IC<sub>50</sub> value for inhibition of

cell proliferation > 3000 nM) against a panel of Ba/F3 cells transfected to express a variety of different kinases.

### **3.2.2 In-vivo Pharmacology**

Efficacy studies in murine models of Bcr-Abl dependent myeloproliferative disease models have been initiated. Preliminary data indicate nilotinib is capable of inhibiting disease progression, as measured either by the bioluminescence produced by luciferase-labeled bcr-abl.32D cells following 100 mg/kg/day, or by the effect on spleen weight following 75 mg/kg/day.

### **3.3 Animal Pharmacokinetics and Drug Metabolism**

Absorption was moderate with a moderate bioavailability (34%) in rats following a single oral dose of 20 mg/kg. The plasma clearance was low in the rat. The volume of distribution was high for the rat, moderate for the dog and monkey. Elimination half-lives of the biphasic plasma profile were 1.5 h (83% of AUC) and 116 h for the rat.

The distribution of nilotinib between plasma and red blood cells was independent of concentration and blood-to-plasma concentration ratios were less than one in rats (0.79), dogs (0.83), and humans (0.71). The binding of nilotinib to plasma proteins was high and there were no species differences in binding among the rat (97.3-99.5%), dog (96.6-99.0%), and human (97.0-99.4%). Serum protein binding was similar to plasma protein binding.

When radiolabeled nilotinib was administered intravenously to rats, drug-related radioactivity was widely distributed to most tissues, consistent with a large volume of distribution. The highest radioactivity levels were found in stomach glandular, adrenal, and liver and bile at 5 min post dose consistent with the in vivo finding where biliary excretion is a major elimination route. The radioactivity in bone marrow was similar to the blood (ratio = ~1). Drug-related radioactivity was highly bound to melanin. There was a minimal passage for drug-related radioactivity across the blood:brain and blood:testis barriers.

The parent compound was the major circulating drug-related material in rats. The other main metabolites in rat plasma were glucuronic acid conjugates of nilotinib-hydrolyzed metabolite, pyridine N-oxide-, and monohydroxy-nilotinib. Nilotinib was eliminated in the rats mainly via oxidative metabolism. All metabolites observed in the human liver slices incubate were also found in the animal species. The metabolism profiles of rat and monkey liver slices were most similar to that of human while the dog liver slice profile was most dissimilar to the other systems. Nilotinib was metabolized by oxidation of the methyl-imidazole ring, degradation of the oxidized imidazole, oxidation of the pyridinyl-pyrimidinyl-amino-methyl-benzamide moiety, amide hydrolysis, glucuronic acid formation of the primary metabolites, and various combinations of the above pathways.

Based on its inhibition ( $IC_{50} \leq 7.5 \mu M$ ) for CYP enzymes, 2C8, 2C9, 2C19, 2D6, and 3A4/5, nilotinib may inhibit the metabolic clearance of comedications

metabolized by these CYP enzymes, if sufficiently high concentrations of nilotinib are achieved in vivo.

### 3.4 Animal Toxicology

In 4-week toxicity studies with daily oral gavage dosing, the maximum tolerated dose (MTD) was 60 mg/kg in rats ( $AUC_{(0-24h)}$  120000 ng.h/mL in males and 187000 ng.h/mL in females) and 45 mg/kg in dogs ( $AUC_{(0-24h)}$  3880 ng.h/mL in males and 25700 ng.h/mL in females).

The main target organ in both species was the liver and findings were consistent with hepatocholestatic disease. In dogs, drug effects were observed at 15 and 45 mg/kg. These were more pronounced in females than males and included elevated liver enzymes (ALT and ALP), increased cholesterol, hyperbilirubinemia and bilirubinuria. Histopathologically this was associated with intrasinusoidal aggregates of hyperplastic and/or hypertrophic Kupffer cells, occasionally accompanied by bile duct proliferation, leading to a disturbance of the bile flow. Minor kidney findings were an increased number and severity of lipid containing vacuoles of tubular epithelium in female dogs at 45 mg/kg. These are not considered to be of toxicological significance, and the hyaline droplets seen at all dose levels in male rats are compatible with an exacerbation of hyaline droplet formation representing the initial phase of the inducible male rat  $\alpha_2\mu$  globulin nephropathy syndrome, a syndrome specific to male rats and of no relevance to other species including human. Clinically, female dogs showed emesis particularly during the last week of dosing. This finding correlates with the higher systemic exposure seen following multiple administration to female dogs at the high dose.

In vitro electrophysiology data from the hERG channel assay revealed an  $IC_{50}$  value of 0.13  $\mu$ M. Nilotinib induced a decrease in the coronary perfusion rate at concentrations of 0.9  $\mu$ M and higher and showed signs of prolonged action potential duration in the isolated rabbit heart at concentrations  $\geq 3$   $\mu$ M. No effects were seen in ECG measurements included into the 4-week toxicity study in dogs up to 45 mg/kg and no effects on cardiac electrophysiological changes were observed in a special telemetry study in dogs at single doses up to 300 mg/kg. Based on the low  $IC_{50}$  value seen in the hERG channel assay it is concluded that nilotinib showed a preclinical signal for QT prolongation.

Nilotinib did not show a genotoxic potential in the AMES test or Chromosome Aberration test in human peripheral lymphocytes.

The NOAEL in rats was 20 mg/kg ( $AUC_{(0-24h)}$  20900 ng.h/mL in males and 46100 ng.h/mL in females) and 5 mg/kg in dogs ( $AUC_{(0-24h)}$  1560 ng.h/mL in males and 1780 ng.h/mL in females).

Based on the findings observed in animals, kidney, liver and cardiac function should be monitored in humans. Emesis may also occur in patients. Following completion of a 4-week treatment, patients may continue treatment with nilotinib based upon the absence of unacceptable toxicity and/or disease progression.

### 3.5 Biomarkers

In Philadelphia-chromosome positive leukemias (CML-CP, CML-AP, CML-BC, Ph+ ALL), the following assays of Bcr-Abl activity will be performed to examine the ability of nilotinib to down-regulate Bcr-Abl and its downstream effectors: Bcr-Abl phosphorylation, STAT 1, STAT 5 signaling, AKT phosphorylation and Q-RT-PCR to detect the presence of Bcr-Abl transcripts. An attempt will be made to correlate the effects on the various biomarkers with plasma drug levels obtained at similar timepoints. Mutational analysis of Bcr-Abl will be conducted at baseline and at the time of disease progression.

### 3.6 Phase I Study of Nilotinib

The phase I study of nilotinib initially started as a single daily dose at 50 mg daily with dose escalation to 100, 200, 400, 600, 800 and 1200 mg orally daily. Patients with accelerated-blastic phase post imatinib failure were initially treated. Among the initial 65 patients, the CHR rate was 50% in accelerated and blastic phases, and the cytogenetic response rate 30+%. The PK studies showed saturation of levels at 400 to 1200 mg daily. The T<sub>1/2</sub> was 13 hours. Because of possible GI-hepatic absorption/metabolism saturation, patients were then treated at 400 mg orally BID. This showed a 50% increase of PK levels. Side-effects so far have included mild-moderate nausea and skin rashes, and transient elevations of indirect bilirubin which normalized after 2 to 7 days with combination therapy. The study is currently at a dose of 600 mg. P.O. BID, which maybe dose-limiting and PK saturating. At 600 mg P.O. BID, grade 3 thrombocytopenia was noted in 3 patients, grade 2 pancreatitis in 1 patient. Patients with chronic phase CML post imatinib failure are currently treated at 400 mg orally BID, showing good tolerance and favorable responses. A total of 17 patients in chronic phase have so far been treated. All had imatinib resistant disease. With a median follow up time of 3 months on therapy, 12 (70%) achieved CHR, and 7 (41%) have already had a cytogenetic response.

The onset of several cases of hyperbilirubinemia in the Phase I study prompted a pharmacogenetic analysis of UGT1A1 genotyping for all patients enrolled in this study who had signed an informed consent for pharmacogenetic testing and for whom a blood sample was available. This analysis was performed while the study was ongoing; to date 51 patients have been genotyped. A significant association between the susceptible genotype (7,7) and elevated bilirubin levels (> 1.5 x ULN) has been found. Analysis of the remaining patients is ongoing. This result is consistent with previous reports linking UGT1A1\*28 to Gilbert's Syndrome and elevated bilirubin levels (Bosma et al., 1995; Monaghan et al., 1996). While the role of glucuronidation by UGT1A1 of nilotinib remains to be defined, the onset of hyperbilirubinemia during the study might suggest inhibition of overall UGT1A1 activity by nilotinib, through direct interaction, competition or some other mechanism.

As part of the phase I study, we have performed over 3,000 EKGs so far on patients on nilotinib pretreatment and serially. None have revealed any safety issues in relation to QT interval changes or other abnormalities.

### **3.7 Physical, chemical and pharmaceutical properties (per Investigator's Brochure)**

#### **3.7.1 Drug Substance**

The nilotinib-AA drug substance exists as the monohydrate form of the hydrochloride salt.

**Chemical name:** 4-Methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide, monohydrochloride, monohydrate.

#### **3.7.2 Drug product**

##### **Clinical service form**

Novartis will supply nilotinib as 200 mg and 50 mg capsules or tablets. Dosage strengths correspond to the free base. The inactive ingredients are lactose monohydrate, crospovidone, poloxamer, colloidal silicon dioxide and magnesium stearate.

##### **Shelf-life and storage conditions**

Based on currently available stability data, the drug product should be protected from light – do not store above 25°C. The re-evaluation period is 12 months.

### **4.0 Patient Eligibility**

- 4.1 Diagnosis of Ph-positive or Bcr-positive CML in early chronic phase CML (i.e., time from diagnosis 12 months). Except for hydroxyurea, patients must have received no or minimal prior therapy, defined as <1 month (30 days) of prior interferon-alpha (with or without cytarabine) and/or an FDA-approved TKI. Patients with de novo accelerated phase will be treated but analyzed separately.
- 4.2 Age  $\geq$  16 years (Age > 18 years to participate in optional symptom burden assessment)
- 4.3 ECOG performance of 0-2.
- 4.4 Adequate end organ function, defined as the following: total bilirubin < 1.5 x ULN, SGPT < 2.5 x ULN, creatinine < 1.5 x ULN.
- 4.5 Patients must sign an informed consent indicating they are aware of the investigational nature of this study, in keeping with the policies of the hospital.
- 4.6 Reliable telephone access to receive calls from an interactive voice response system (IVR) (only applicable to patients who will participate in optional symptom burden assessment).

#### **4.7 Exclusions:**

- a. NYHA cardiac class 3-4 heart disease as well as impaired cardiac function defined as:
- LVEF < 45% as determined by MUGA scan or electrocardiogram
  - Complete left bundle branch block
  - Use of cardiac pacemaker
  - ST depression of > 1 mm in 2 or more leads and/or T wave inversions in 2 or more continuous leads
  - Congenital long QT syndrome
  - History of, or presence of significant ventricular or atrial tachyarrhythmia's
  - Clinically significant resting bradycardia (< 50 bpm)
  - QT<sub>c</sub> > 450 msec on screening ECG (using the QT<sub>cF</sub> formula)
  - Right bundle branch block plus left anterior hemiblock, bifascular block
  - Myocardial infarction within 12 months prior to starting nilotinib
  - Unstable angina diagnosed or treated within the past 12 months
  - Other clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen).
- b. Patients with active, uncontrolled psychiatric disorders including: psychosis, major depression, and bipolar disorders.
- c. Female patients of childbearing potential must have negative pregnancy test within 7 days before initiation of study drug dosing. Postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Surgical sterilization is considered non-childbearing potential. Female patients of reproductive potential must agree to employ an effective method of birth control (hormonal or barrier) throughout the study and for up to 3 months following discontinuation of study drug.
- d. Patients with severe and/or uncontrolled medial disease (i.e., uncontrolled diabetes, chronic renal disease, or active uncontrolled infection [persistent fever and worsening clinical condition]).
- e. Patient with known chronic liver disease (i.e., chronic active hepatitis, and cirrhosis).
- f. Patient with known diagnosis of human immunodeficiency virus (HIV) infection.
- 4.8** Patients in late chronic phase (i.e., time from diagnosis to treatment >12 months) or blastic phase are excluded.

The definitions of CML phases are as follows:

- a. Early chronic phase: time from diagnosis to therapy < 12 months  
Late chronic phase: time from diagnosis to therapy > 12 months
- b. Blastic phase: presence of 30% blasts or more in the peripheral blood or bone marrow.
- c. Accelerated phase CML: presence of any of the following features:
  - Peripheral or marrow blasts 15% or more
  - Peripheral or marrow basophils 20% or more
  - Thrombocytopenia < 100 x 10<sup>9</sup>/L unrelated to therapy
  - Documented extramedullary blastic disease outside liver or spleen due to past causes
- d. Clonal evolution defined as the presence of additional chromosomal abnormalities other than the Ph chromosome is part of accelerated phase CML. Ph chromosome variants or complex Ph chromosome translocations are not considered to indicate disease acceleration. We have recently found clonal evolution to have a variable prognostic impact and may be suppressed with interferon-alpha therapy. Hence these patients, like others with de novo accelerated phase, will be eligible, and analyzed separately.

## 5.0 Treatment Plan

### 5.1 General

All patients should be registered with the Data Management Office PDMS system.

### 5.2 Treatment Plan

Patients will receive nilotinib therapy according to the suggested guidelines below. Individual minor variations in the initiation of therapy, WBC count at start of therapy, are acceptable as indicated by patient condition and physician judgment.

**5.2.1 CML debulking:** patients may receive hydroxyurea for debulking before and during the first 6 weeks of therapy. Patients who cannot take hydroxyurea may receive other agents such as 6-mercaptopurine and 6-thioguanine.

**5.2.2 Therapy:** nilotinib 400 mg orally twice daily.

Patients must not drink grapefruit juice or eat grapefruit while taking nilotinib. Patients should avoid drinking caffeine within an hour of taking nilotinib. Patients should avoid alcohol while taking nilotinib.

**5.2.3 Dose adjustments:** Dose adjustments will be done as described below

using the following dose-levels:

Dose Level	Nilotinib
0	400 mg BID
-1	200 mg BID
-2	200 mg daily

**5.2.4** Ph studies including cytogenetics, interphase FISH, and PCR, to be done as follows, as a general guideline. Some may be omitted if judged not necessary.

- a) Cytogenetic (or FISH) pretreatment
- b) Cytogenetic (or FISH), and PCR quantification every 3-4 months as indicated in year one then every 6-12 months as indicated (e.g., PCR not mandated when patient not with major cytogenetic response)

### 5.3 Dose modifications of Nilotinib

General guidelines include the following:

a) Non-Hematologic Toxicity

- **Grade 2:** Patients with persistent grade 2 toxicity that is considered clinically significant, unresponsive to appropriate therapy, may have treatment held until the toxicity has resolved to grade  $\leq 1$ . Nilotinib may then be resumed at the same dose the patient was receiving at the time treatment was interrupted. If the grade  $\leq 2$  toxicity recurs, nilotinib may be held until the toxicity has resolved to grade 1. Treatment may then be resumed at a reduced dose of 400 mg daily or the next  $-1$  dose level.
- **Grade 3-4:** If a patient experiences Grade 3-4 toxicity, nilotinib must be withheld until the toxicity has resolved to Grade  $\leq 1$ . Nilotinib may then be resumed at a reduced dose of 400 mg daily, or the next  $-1$  dose level.
- Do not reduce dose for indirect hyperbilirubinemia without hemolysis, unless indirect bilirubin exceeds 5 mg/dL and lasts for more than 5-7 days.

b) Hematologic Toxicity

If granulocytes are  $< 0.5 \times 10^9/L$  or platelets are  $< 40 \times 10^9/L$ , hold therapy until granulocytes are above  $10^9/L$  and platelets are above  $60 \times 10^9/l$ , then resume therapy.

If recovery takes more than 2 weeks, resume nilotinib at 1 dose level reduction from the dose the patient was receiving at the time therapy was interrupted.



If recovery takes less than 2 weeks, resume nilotinib at the same dose the patient was receiving at the time treatment was interrupted.

If myelosuppression recurs, resume nilotinib at one dose level reduction from the dose the patient was receiving at the time the treatment was interrupted.

**If a similar degree of toxicity returns, a further dose reduction by one dose level can be performed, using the above procedures.**

c) Modifications of dose schedules other than the above will be allowed within the following guidelines:

- Intermediate dose levels are acceptable when judged to be in the best interest of the patient. Acceptable dose levels are the following: 300mg BID, 150mg BID, and 150mg QD.
- Further dose reductions can be made to keep toxicity grade  $\leq 2$ . However, the lowest acceptable dose is 150 mg/daily.
- Dose adjustments by more than 1 dose level at a time can be considered when judged in the best interest of the patient (e.g., neutropenia with sepsis, bleeding requiring platelet transfusions) when toxicity has resolved. The reason for this reduction will be discussed with the PI or Co-PI and documented.
- A patient who has had a dose reduction because of any of the reasons mentioned above may have their dose escalated provided the patient has remained free of toxicity requiring dose adjustments as defined above for at least 1 month. Escalation will be made to the previous dose-level, and not more frequent than every month.

### 5.3.1 Dose Escalations

Patients who do not achieve a molecular remission at 12 months and who had a prior dose reduction of nilotinib, and who have no toxicity after 2 months of therapy may increase the dose of nilotinib back to 800mg P.O. daily (400mg P.O. twice a day).

## 5.4 Duration of Therapy

Total duration of therapy will be 8-10 years. Subsequent changes of duration of treatment will depend on the earlier analyses of data with nilotinib to justify the safety of continued therapy versus treatment interruption.

Novartis will supply nilotinib as 200 mg, 150 mg and 50 mg capsules or tablets for the core trial period of 6 years. Continuing treatment beyond this time will be at the discretion of the investigator and may become the financial responsibility of the patient if nilotinib becomes commercially available, if no alternative method of obtaining or paying for the drug can be identified at that time. Medication labels will comply with the legal requirements of the US and will be printed in English. The storage conditions for nilotinib will be described on the medication label. The study medication must be stored in a safe, secure location.

## 5.5 Concomitant Medications

The use of hematopoietic growth factors (i.e., G-CSF, interleukin-11, erythropoietin) is allowed during the trial if clinically indicated for these patients.

The use of anagrelide is allowed for severe thrombocytosis  $> 600 \times 10^9/L$ .

- 5.5.1 In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed. Concomitant medications will be recorded in the patient records. The administration of any other anticancer agents including chemotherapy and biologic agents is NOT permitted except as mentioned above.
- 5.5.2 Concomitant administration of agents that prolong the QT interval and CYP 3A4 inhibitors while patients are receiving nilotinib is contraindicated unless determined to be absolutely necessary. In addition to medications, patients must be counseled not to consume grapefruit, grapefruit juice, star fruit or star fruit juice. Please see <http://www.torsades.org/medical-pros/drug-lists/printable-drug-list.cfm> for a comprehensive list of agents that prolong the QT interval as well as Appendix H. In cases where administration of a QT prolonging agent or a CYP 3A4 inhibitor cannot be avoided, it is strongly recommended that an ECG be obtained 24 to 48 hours and one week after initiating the concomitant therapy.
- 5.5.3 In in-vitro assays, nilotinib has been shown to interact with CYP 2C9, CYP 2C8, CYP 2 D6, and CYP 3A4. Because of the inherent risk of either reduced activity or enhanced toxicity of the concomitant medication and/or nilotinib, drugs known to interact with the same CYP450 isoenzymes (2D6 and 3A4) as nilotinib should be used with caution (Appendix G). Patients using concomitant medications known to be metabolized by these cytochrome p450 enzymes will not be excluded from the study. However, the patients must be carefully monitored for potentiation of toxicity due to individual concomitant medication. Consideration should be given to using alternative agents with less potential for interaction with nilotinib. Special care has to be given to the concomitant use of acetaminophen (e.g. Tylenol or Percocet) with nilotinib. Any use of concomitant medication will be captured in the patient's record.
- 5.5.4 Since warfarin is metabolized through the CYP450 system, anticoagulation with warfarin (e.g. Coumadin® or Coumadine®) should be avoided whenever possible in patients participating in this study. As an alternative, therapeutic anticoagulation may be accomplished using low-molecular weight heparin (e.g. Lovenox) or heparin. In general, the use of Coumadin® is discouraged on this protocol.
- 5.5.5 It is recommended that prophylactic anti-emetics be withheld until the patient has experienced grade 1 nausea or vomiting. Prophylactic use of loperamide (e.g. Imodium®, with suggested dosing as start: 4mg po. x 1, than 2mg po after each loose stool, max 16mg/d) is recommended for

patients experiencing grade 1 or 2 diarrhea, before dose interruption.

## **6.0 Pretreatment Evaluation (See Appendix B)**

- 6.1 A complete history and physical examination including performance status.
- 6.2 CBC, platelet count and differential, total bilirubin, SGPT (or SGOT), and creatinine. (Differential not required if  $WBC < 0.5 \times 10^9/L$ ).
- 6.3 Bone marrow aspirate for morphology; cytogenetics or FISH (if not done within 3 months).
- 6.4 Pregnancy test for female patients of childbearing potential within 7 days before initiation of study drug dosing
- 6.5 Peripheral blood and bone marrow for Abl mutations.
- 6.6 Pretreatment EKG. Patients with NYHA cardiac class I or II will have an echocardiogram or cardiac scan performed before start of therapy.
- 6.7 MDASI-CML and single item quality of life (QOL) rating completed by patient, and ECOG performance status (optional)
- 6.8 miRNA analysis (optional): one single blood sample (5cc) will be collected only by EDTA or citrate (Dr. Calin's lab at MD Anderson Cancer Center).

**\* Missed collection of any of the optional procedures will not be considered a protocol deviation or violation.**

## **7.0 Evaluation During Study (See Appendix B)**

- 7.1 Physical exam every 3-4 months. After the first year, physical exams will be recommended once every year. Toxicity will be assessed at every leukemia physician clinic visit. Patients will be instructed to notify the research nurse for any toxicities.
- 7.2 CBC, platelet, differential every 1-2 weeks for 4 weeks, every 4-8 weeks until 6 months from the start of therapy, then every 3-6 months until 2 years on therapy then at the discretion of the treating physician. (Differential not required if  $WBC \leq 0.5 \times 10^9/L$ ).
- 7.3 Bone marrow aspirate with cytogenetics or FISH every 3-4 months in year 1, then every 6-12 months in year 2, then every 2-3 years. For patients in complete cytogenetic remission, bone marrow will be at the discretion of the treating physician after year 2. Peripheral blood FISH for BCR/ABL may be substituted for bone marrow cytogenetic every 1-3 years.
- 7.4 Total bilirubin, SGPT or SGOT, and creatinine every 2-4 weeks for 1 month then every 4-8 weeks until 6 months from the start of therapy, then every 3-6 months until 2 years on therapy then at the discretion of the treating physician.

- 7.5 Diaries may be returned on every visit to MD Anderson Cancer Center for bone marrow aspiration. Compliance to the treatment schedule may also be verified verbally with the patient at the clinic visit.
- 7.6 Peripheral blood or bone marrow for quantitative PCR (QPCR) every 3-4 months for 1 year then every 6-12 months in year 2 then once per year (+/- 3 months).
- 7.7 EKG on day 5 +/- 3 days of therapy, then at 6 weeks +/- 2 weeks, and 3 months
- 7.8 miRNA analysis (optional): one single blood sample (5cc – only by EDTA or citrate) will be collected at the time of any or all scheduled blood collections when PCR is scheduled (Dr. Calin's lab at MD Anderson Cancer Center).
- 7.9 MDASI-CML weekly during the first three months of treatment, then every other week for the remainder of the study. MDASI-CML will be collected by paper, computer, or IVR system. Patients will be instructed during the first visit on the use of the Interactive Voice Response (IVR) system (optional\*).
- 7.10 Single item QOL at each clinic visit during study (optional\*).

\* Every effort will be made to collect optional procedures at all time points for all patients; however, missing collection in one or more of these time points in occasional patients will not be considered a protocol deviation/violation.

## 8.0 Criteria for Response

- 8.1 Complete Hematologic Remission (CHR) - normalization for at least 4 weeks of the bone marrow (less than 5% blasts) and peripheral blood with WBC < 10 x 10<sup>9</sup>/L and no peripheral blasts, promyelocytes or myelocytes. This is in addition to disappearance of all signs and symptoms of the disease.  
Partial Hematologic Response (PHR) = CHR except for persistence of immature cells (myelocytes, metamyelocytes), or splenomegaly < 50% of pretreatment, or thrombocytosis >450x10<sup>9</sup>/L but <50% of pretreatment.
- 8.2 Complete hematologic remission will further be classified according to suppression of the Philadelphia chromosome (Ph) by cytogenetics or i FISH
  - a) No cytogenetic response - Ph positive 100% of pretreatment value
  - b) Minor cytogenetic response - Ph positive 35-90% of pretreatment value
  - c) Partial cytogenetic response - Ph positive 1-34% of pretreatment value
  - d) Complete cytogenetic response - Ph positive 0%

\* Major cytogenetic response = complete + partial (Ph positive <35%)
- 8.3 Molecular response = PCR ratio ≤ 0.05%, or PCR negative

## 9.0 Criteria for Removal from the Study

- 9.1 Ph-positive disease still  $\geq 35\%$  after 6 months of nilotinib therapy. Patients should be changed to imatinib 400 – 800 mg orally daily.
- 9.2 Patients who develop accelerated disease features (but not clonal evolution) or blastic phase with no response to optimization of therapy as defined under 5.2 and 5.3.
- 9.3 Resistant hematologic disease on optimal therapy
- 9.4 Unacceptable severe (grade 3-4) toxicity despite dose optimization
- 9.5 Patient request

## 10.0 Statistical Considerations

- 10.1 This is a single-arm, phase II study of oral nilotinib to patients with Ph-positive or Bcr-positive CML in early chronic phase CML. The primary outcomes will be molecular response (MR) after 12 months of therapy (defined in protocol section 8.3) and grade 3-4 therapy related toxicity. Major cytogenetic response at 6 months is a secondary end point. A maximum of 125 patients, 100 chronic phase and 25 accelerated phase, will be recruited for the study. Patients are expected to be accrued to the trial at a rate of approximately 5 patients per month, 50 patients are anticipated to be enrolled in each of the first two years. Due to the long time to assess molecular response (12 months) and major cytogenetic response (6 months), only the first 50 patients can be used for interim analysis for molecular response, and the first 75 patients will be used in interim analysis for cytogenetic response. The study will be completed in 3 years.

### Sample Size and End Point Monitoring

Historical data on similar patients show molecular response rate of 19% at 12 months, major cytogenetic response rate of 50% at 6 months, and toxicity rate of 10%. The method of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998) will be used for monitoring efficacy and safety simultaneously. The stopping boundary tables are given below. Mathematical details are deferred to the end of this section.

The trial will be monitored according to the following stopping boundaries for the primary end point, molecular response (MR) at 12 months.

Recommend Stopping if $\leq$ # of MR Observed	Number of Patients Evaluated
0	7
1	19

2	29
3	39
4	48
5	50

The trial will be also be monitored according to the following stopping boundaries for major cytogenetic response (CyR) at 6 months.

Recommend Stopping if $\leq$ # of CyR Observed	Number of Patients Evaluated
0	5
1	6-7
2	8-10
3	11-12
4	13-14
5	15-16
6	17-19
7	20-21
8	22-23
9	24-25
10	26-28
11	29-30
12	31-32
13	33-34
14	35-36
15	37-39
16	40-41
17	42-43
18	44-45
19	46-47
20	48-49
21	50-51
22	52-53
23	54-55
24	56-57
25	58-59
26	60-61
27	62-63
28	64-65
29	66-67
30	68-69
31	70-71
32	72-73
33	74-75

At the same time, the trial will be monitored according to the following stopping boundaries for toxicity.

Recommend Stopping if $\geq$ # of Toxicity Observed	Among These Number of Patients
2	2-3
3	5-7
4	9-12
5	14-17
6	19-23
7	25-28
8	30-33
9	35-39
10	41-44
11	46-50

The operating characteristics are summarized in the following table.

True Toxicity Rate	True MR Rate	Probability of Stopping Early	Achieved Sample Size Quartiles*		
			25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>
0.05	0.2	0.26	79	100	100
	0.3	0.10	100	100	100
	0.4	0.04	100	100	100
	0.5	0.02	100	100	100
	0.6	0.01	100	100	100
0.1	0.2	0.31	62	100	100
	0.3	0.16	100	100	100
	0.4	0.11	100	100	100
	0.5	0.09	100	100	100
	0.6	0.08	100	100	100
0.15	0.2	0.46	57	100	100
	0.3	0.34	70	100	100
	0.4	0.30	80	100	100
	0.5	0.29	85	100	100
	0.6	0.28	87	100	100
0.2	0.2	0.69	57	70	100
	0.3	0.62	57	78	100
	0.4	0.59	61	83	100
	0.5	0.58	62	86	100
	0.6	0.58	62	87	100
0.25	0.2	0.87	57	61	78
	0.3	0.84	57	66	85

True Toxicity Rate	True MR Rate	Probability of Stopping Early	Achieved Sample Size Quartiles*		
			25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>
	0.4	0.83	57	67	87
	0.5	0.83	57	67	88
	0.6	0.83	57	67	88

\* Because MR can only be assessed after 12 months, all achieved quartiles are evaluable quartiles + 50.

When toxicity is equal to the historical rate 0.10, the operating characteristics for the stopping rule for secondary end point (major cytogenetic response) are summarized in the following table.

True Major Cytogenetic response Rate	Probability of Stopping Early	Achieved Sample Size Quartiles*		
		25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>
0.4	0.81	58	65	87
0.5	0.41	65	100	100
0.6	0.12	100	100	100
0.7	0.04	100	100	100
0.8	0.03	100	100	100

The stopping boundary tables are obtained using the following Bayesian rules. Let E correspond to the experimental regimen, H denote historical data, MR for molecular response, CyR for major cytogenetic response, and T for toxicity. The trial will be stopped if any of the following conditions is satisfied.

- 1)  $\text{Prob}\{p(\text{MR},\text{H}) + \delta_{\text{MR}} < p(\text{MR},\text{E}) \mid \text{data}\} < 0.05$ , where  $\delta_{\text{MR}} = 0.20$
- 2)  $\text{Prob}\{p(\text{CyR},\text{H}) + \delta_{\text{CyR}} < p(\text{CyR},\text{E}) \mid \text{data}\} < 0.06$ , where  $\delta_{\text{CyR}} = 0.10$
- 3) Stop if  $\text{Prob}\{p(\text{T},\text{H}) + \delta_{\text{T}} < p(\text{T},\text{E}) \mid \text{data}\} > 0.95$ , where  $\delta_{\text{T}} = 0.05$

## 10.2 Updated Statistical Design

To date, 94 patients have been treated with 400 mg BID nilotinib, with an observed 12-month MMR rate of 84%. Under the current design, which has target total sample size 100, 6 additional patients would be treated. Under the proposed design with target total sample size 125, an additional 31 patients would be treated. Assuming a non-informative beta(0.5, 0.5) prior on  $\text{Pr}(\text{MMR}_{12})$  = probability of major molecular response at 12 months, the trial's primary endpoint, and assuming that the currently observed rate of 84% for MMR<sub>12</sub> persists, under the current design if 84/100 (84%) MMR<sub>12</sub>'s were observed then a posterior 95% credible for  $\text{Pr}(\text{MMR}_{12})$  would be [0.760 – 0.902], which has a width of 0.142. Under the proposed design with



125 patients, if 105/125 (84%) MMR12's were observed then a posterior 95% credible for  $\text{Pr}(\text{MMR12})$  would be [0.768 – 0.896] which has a width of 0.128. Consequently, in terms of reliability of estimation, 25 additional patients would provide a 10% reduction in the width of a posterior 95% credible interval for  $\text{Pr}(\text{MMR12})$ . Similarly, substantial improvements in statistical reliability would be obtained for estimates all other parameters of interest, including the probability of complete cytogenetic response, distribution of response duration, Kaplan-Meier estimates of progression-free and overall survival time distributions, and toxicity rates.

There will be no change in the planned accrual for accelerated phase. This will remain at 25 patients.

### **10.3 Statistical Considerations for MDASI and QoL**

Continuous variables (e.g., age, hematology values) will be summarized using the mean (s.d.) or median (range). Frequency tables will be used to summarize categorical variables. Logistic regression will be used to assess the impact of patient characteristics on the molecular response rate and on symptom severity, interference, and QOL. The distribution of time-to-event endpoints (e.g., molecular response, overall survival) will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups of patients will be made using the log rank test. Cox (proportional hazards) regression will be used to evaluate multivariable predictive models of time-to-event outcomes. Correlations of symptom severity and therapy adherence (from research nurse records) will be determined.

## **11.0 Reporting Requirements**

11.1 Reporting requirements will be as per institutional guidelines. Exceptions will include:

- Grade 3-4 myelosuppression
- Grade 3 weight gain

### **11.2 Serious Adverse Event Reporting (SAE)**

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an

adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events**, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

### **Reporting to FDA:**

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

**It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.**

### **11.3 ADVERSE EVENT REPORTING POLICY FOR LEUKEMIA LATER PHASE II AND PHASE III STUDIES**

Recognizing the need to protect patients and the unique characteristics of leukemia, viz prolonged myelosuppression, consequent hospitalizations and potential for death, the following standards for reporting AEs in patients treated on later Phase II and Phase III Dept. of Leukemia protocols in which myelotoxic therapy is to be given will be followed.

1. All deaths with possible, probable or definite attribution to the study drug must have a written report submitted to the Institutional Review Board (IRB) via OPR within 24 hours (next working day) of knowledge of the event. All deaths not related to the study drug must have a written report submitted to the IRB within 5 working days.
2. Unexpected life-threatening events will be reported within 5 working days of notification, regardless of attribution to study drug. These events may include opportunistic infections e.g., CMV, pneumocystis, tuberculosis or other unusual organisms or their presentations. Other unexpected life-threatening events, specifically events prompting initiation of life support and organ failure known not to be due to leukemia, will be reported.

[Examples: a) Simple febrile neutropenia with hospitalization is not an expedited reportable event to the IRB but will be included in the annual report to the IRB whereas febrile neutropenia complicated by Gram-negative bacteremia with shock or its complications is to be reported within 5 working days of notification. b) Thrombocytopenic epistaxis or bleeding from mucosal surfaces easily managed with platelet support is not an expedited reportable event to the IRB but will be included in the annual report to the IRB whereas major gastrointestinal bleed will be reported within 5 working days of notification.]

- 3a. Prolonged myelosuppression following induction therapy defined as viz marrow cellularity 5% without evidence of leukemia 42 or more days from start of therapy and not due to use of additional anti-leukemia agents before day 42 will be reported within 30 days of notification.

- 3b. Myelosuppression following post remission therapy will be reported if at 30 days post-treatment marrow has not recovered to platelets >20,000 or granulocytes > 500.

Myelosuppression and associated complications are expected events during leukemia therapy. Myelosuppression and associated simple complications such as fever, infections, bleeding and related hospitalizations, will, except as noted above, not be reported as individual AEs, but will be summarized in annual report to the IRB. Expected Grade 4 events, as specified in the protocol, will not be reported in an expedited fashion, but will be reported in the annual report. **Leukemia-Specific Adverse Event Recording Guidelines**

- 11.4 Each serious adverse event (but not pregnancies) must be reported by the investigator to Novartis within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported serious adverse event must also be reported to Novartis within 24 hours of receiving it. If the serious adverse event has not been previously documented (new occurrence) and it is thought to be related to the study (or therapy), the Medical Safety Expert of the Clinical Safety & Epidemiology (CS&E) Department may contact the investigator to obtain further information. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same drug (or therapy) that this serious adverse event has been reported.

#### Reporting Procedures

The investigator must complete the Serious Adverse Event Report Form in English, assess the relationship to study treatment and send the completed form by fax 1.888.299.4565 within 24 hours to the local Novartis Clinical Safety & Epidemiology (CS&E) Department ensuring that the form is accurately and fully completed,. The original and the duplicate copies of the Serious Adverse Event Form, and the fax confirmation sheet must be kept at the site.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The form and fax confirmation sheet must be retained. Pregnancy follow-up should describe the outcome of pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

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