NOVARTIS

Clinical Development

AMN107 (NILOTINIB)
TASIGNA

Protocol CAMN107A1201 / NCT01863745

An open label, multi-center nilotinib roll-over protocol for patients who have completed a previous Novartis-sponsored nilotinib study and are judged by the investigator to benefit from continued nilotinib treatment

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Table of contents

List of appendices

List of tables

List of figures

List of abbreviations

AE	Adverse event
AMN107	Nilotinib /Tasigna
Anti HBc	Hepatitis B Core Antibody
AP	Accelerated phase (of CML)
AUC	Area under the plasma concentration-time curve
AUC (0-∞)	Area under the plasma concentration-time curve extrapolated to infinity
b.i.d.	bis in diem, twice daily
BC	Blast crisis (of CML)
BCRP	Breast cancer resistance protein
CCyR	complete cytogenetic response
CHR	Complete hematological response
Cmax	The maximum (peak) observed plasma drug concentration after oral dose administration (mass X volume-1)
CML	Chronic myeloid /myelogenous leukemia
CP	Chronic phase (of CML)
CRF	Case report/record form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Event
CYP3A4	Cytochrome P450 3A4
DDI	Drug –drug interactions
DS&E	Drug Safety and Epidemiology
EC	Ethical Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EoT	End of treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumors
H2	Histamine receptor
HBc Ab	Hepatitis B Core Antibody
HBs Ag	Heptitis B Surface Antigen
HGC	hard gelatin capsules
HMG-CoA	Hydroxy-Methyl-Glutaryl-Coenzyme A
ICH	International Conference on Harmonization
ICVE	Ischemic Cerebrovascular Events
IEC	Independent Ethics Committee
IHD	Ischemic Heart Disease
IIT	Investigator initiated trial
IN	Investigator Notification
IRB	Institutional Review Board

IUD	Intrauterine device
IUS	Intrauterine system
MCyR	Major cytogenetic response
MRP2	Multi-resistance protein 2
OS	Overall survival
PAOD	Peripheral Artery Occlusive Disease
PDGFR	Platelet-derived growth factor receptors
PFS	Progression-free survival
P-gp	P-glycoprotein
Ph	Philadelphia (chromosome)
PHI	Protected Health Information
PPS	Per Protocol Set
q.d.	quaque die/ once daily
QT	Q to T interval (ECG)
REB	Research Ethics Board
SAE	Serious adverse event
SCT	Stem cell transplantation
SmPC	Summary of Product Characteristics
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1/2	The elimination half-life associated with the terminal slope of a semi logarithmic concentration-tine curve (time)
TKI	Tyrosine kinase inhibitors
Tmax	The time to reach maximum (Cmax) plasma drug concentration after oral dose administration (time)

Glossary of terms

Dose level	The dose of drug given to the patient (total daily dose).
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in approved indication/dosage.
Other study treatment	Any drug administered to the patient as part of the required study procedures that were not included in the investigational treatment.
Parent study	The original Novartis-sponsored, Oncology Clinical Development & Medical Affairs study where the patient was first enrolled and received nilotinib treatment.
Patient number	A unique identifying number assigned to each patient who enrolls in the study.
Roll-over study	A roll-over study allows patients from multiple parent studies spanning multiple indications to continue to be treated within one study after the completion of the parent study/ies.
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.

Amendment 04 (05-Apr-2018)

Amendment rationale

This roll-over study has been opened since 25-Jun-2013 with 15 total patients enrolled and 4 patients ongoing as of 1st-Apr-2018.

The main purpose for the amendment is:

- To correct an error in the language regarding pregnancy outcome collection. Pregnancy outcomes from female partners of any males who took study treatment will not be collected in this study as nilotinib is not genotoxic and no effects on sperm count, motility, or on fertility were noted in animal studies.
- To extend the study duration from 5 years to 10 years to collect and assess long-term safety of nilotinib in patients who are on nilotinib treatment .
- To add the section on follow up on potential drug-induced liver injury (DILI) cases. This section was added to be aligned with current protocol template. No new safety signal, related to liver function AEs were observed as of 1st-Apr-2018.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following changes have been implemented:

List of abbreviations updated.

Section 2.1, 2.2, Table 3-1, 4.1, 5.2, 10.4 and 10.6: Delete the department name.

Section 4.1, 4.3, 4.4, 7.1.2 and 10: Updated the study opening duration to 10 years.

Section 6.2: Title is corrected to appropriate one.

Section 6.2.6: Section is added to provide follow-up information for drug-induced liver injury.

Section 8.4: Section is updated. Pregnancy outcomes from female partners of any males who took study treatment will not be collected in this study.

Section 10.1.1: The definition of full analysis set was updated.

Section 10.3: The analysis for duration of exposure and dose intensity was updated.

Section 10.4.2: The analysis for adverse events was updated.

Section 11.5: Section is updated to be aligned with current protocol template.

Section 14.1: Appendix 1 is corrected the clerical error.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 03

Amendment rationale

The main purpose for the amendment is:

- To include hepatitis B virus testing as one of the study procedures, to identify study patients who may be at risk of hepatitis B reactivation. Reactivation of hepatitis B virus can occur in patients who are chronic carriers of this virus and are receiving a drug of the BCR-ABL TKI class such as nilotinib/imatinib. Some cases involving BCR-ABL TKI resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Changes to the protocol

- List of abbreviations updated
- Section 6.2.5 Hepatitis B reactivation was added to provide information on next steps for patients tested positive for hepatitis B virus.
- Section 7 Visit schedule and assessments were updated to include the hepatitis B testing once and only once at the next possible visit.
- Section 7.1.4 Serology-Hepatitis B testing was added to provide information on hepatitis B testing.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 02

Amendment rationale

The main purpose for the amendment is:

- To incorporate guidance for the management of:
  - Serum cholesterol increases
  - Blood glucose increases
  - Other cardiac risk factors
  - Ischemic vascular or ischemic cardiovascular events occurring in patients treated with nilotinib.
- To update the exclusion criteria relating to male patient's use highly effective contraception to be aligned with the current Investigator Brochure.
- To incorporate precaution of use for antacid drugs aligned with Tasigna® Prescribing Information and SmPC.
- To define ischemic vascular and ischemic cardiovascular events as Clinical conditions of special interest, and their reporting to the Investigator.
- To update the list of medications that can inhibit CYP3A4.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following changes were implemented in the protocol summary as well as within the protocol sections below:

Updated to include information on efficacy response rate, ischemic vascular and ischemic cardiovascular event reported from the 60-month analysis on the CAMN107A2303 study.

Section 4.1: Updated to clarify that medical monitoring as clinically indicated at the physician's discretion should also include cardiovascular risk factors such as serum cholesterol and glucose levels amongst others.

Section 5.3: An exclusion criterion is updated to reflect that male patients are no longer required to use highly effective contraception during the study and for 30 days after the final dose of nilotinib.

Section 6.2: Updated to include guidelines for the management of patients in sub-section listed below (Section 6.2.1 to Section 6.2.5).

Section 6.2.1 to Section 6.2.4: Sub-sections added to share guidance for the management of cholesterol increases, glucose increases, other cardiac risk factors and ischemic vascular or cardiovascular events.

Section 6.2.1: Updated to Section 6.2.5 to include precaution for the use of antacid drugs and CYP3A4 inhibitors.

Section 7.1.3: Updated to include guidelines for highly effective contraception (as defined in exclusion criterion 5).

Section 8.1.2: Added the guidance on clinical conditions of special interest.

Section 14.1: Appendix 1 is updated to add information on CYP3A4 inducer classification and the list of CYP3A4 inhibitors.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 01

Amendment rationale

This amendment has been implemented to address the following changes for the study:

- To add monthly pregnancy tests for female patients of child bearing potential to reflect the requirement of highly effective contraception for patients on nilotinib treatment.
- To add language clarifying that dose modifications will be based on guidelines provided in the parent protocol, as well as investigator's judgment.
- To add language clarifying that should treatment with strong CYP3A4 inhibitors or inducers be required, it is recommended that therapy with nilotinib be interrupted.
- To clarify that patients who are pregnant, withdrawn consent or have died must be withdrawn from the study.
- To add the patients' ethnicity in patient demographics to collect in eCRFs.
- To address other administrative and typographical corrections noted in the original protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following changes were implemented in the protocol sections below:

Section 6.2: Updated to clarify that dose modifications will be based on guidelines provided in the parent protocol as well as investigator's judgment.

Section 6.2.1: Updated to clarify that should treatment with strong CYP3A4 inhibitors or inducers be required, it is recommended that therapy with nilotinib be interrupted.

Table 7-1: Monthly pregnancy testing added in the Visit evaluation table.

Section 7.1.3: Updated to add a section regarding pregnancy testing for female patients of child bearing potential.

Section 7.1.1.3: Updated to add patients' ethnicity as patient demographics.

Section 7.1.4.1: Updated to clarify that patients who are pregnant, withdraw consent or have died must be withdrawn from the study.

IRB /IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Protocol summary

Brief title	An open label, multi-center nilotinib roll-over protocol for patients who have completed a previous Novartis-sponsored nilotinib study and are judged by the investigator to benefit from continued nilotinib treatment.
Efficacy assessments	Not applicable.
Exclusion criteria	Patient has been permanently discontinued from nilotinib study treatment in the parent study due to unacceptable toxicity, non-compliance to study procedures, withdrawal of consent or any other reason. Patient has participated in a Novartis sponsored combination trial where nilotinib was dispensed in combination with another study medication and is still receiving combination therapy.
Inclusion criteria	Patient is currently enrolled in a Novartis- sponsored clinical study receiving nilotinib and has fulfilled all their requirements in the parent study. Patient is currently benefiting from the treatment with nilotinib, as determined by the investigator. Patient has demonstrated compliance, as assessed by the investigator, with the parent study protocol requirements.
Investigation type	Drug
Investigational and reference therapy	Nilotinib≤ 800 mg/day
Key words	Nilotinib, long-term safety, roll-over study
Other assessments	Not applicable
Population	Male and female patients who are currently enrolled in a Novartis-sponsored clinical study, are benefiting from treatment with nilotinib, and have fulfilled all requirements in the parent study. All objectives of the parent study must have been reached, and the study must be in the process of being completed & reported.
Primary Objective(s) and Key Secondary Objective	To collect and assess long-term safety of nilotinib to patients receiving nilotinib in a Novartis-sponsored clinical study which has reached its objectives and who are benefiting from treatment with nilotinib.
Protocol number	CAMN107A1201
Purpose and rationale	The purpose of this study is to collect and assess long-term safety of nilotinib in patients who are on nilotinib treatment in a Novartis-sponsored clinical study and are benefiting from the treatment as judged by the investigator.
Safety assessments	Reported adverse events (AEs) will be collected continuously throughout the study .For the safe and effective use of nilotinib, medical monitoring should be performed as clinically indicated at the physician's discretion. Medical monitoring should also include monitoring of cardiovascular risk factors such as serum cholesterol and glucose levels amongst others.
Sponsor and Clinical Phase	Novartis, II.

Study design	This is an open label, multi-center, phase II study to collect and assess long-term safety of nilotinib to patients being treated in current Novartis-sponsored clinical studies and who are benefiting from treatment with nilotinib. There will be no screening period for this study. At the enrollment visit the patient will be consented to the study and eligible patients will start their treatment with nilotinib. Patients must return to the study center on a yearly basis (+/- 3 months) for resupply of study medication at which time limited drug dispensing information will be collected. The patient may return to the study center at any given time as per standard of care, however, only one study visit per year will be scheduled and AEs reported at general medical care will be collected continuously throughout the study. For the safe and effective use of nilotinib, medical monitoring should be performed as clinically indicated at the physician's discretion. Medical monitoring this should also include monitoring of cardiovascular risk factors such as serum cholesterol and glucose levels amongst others. Patients will continue to be treated until they are no longer benefiting from nilotinib treatment, develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue nilotinib therapy or the patient dies, whichever comes first. A patient will reach the end of study when nilotinib treatment is permanently discontinued and the end of treatment visit has been performed. The study is expected to remain open for 10 years or until such time that enrolled patients no longer need treatment with nilotinib, whichever comes earlier.
Study type	Interventional.
Title	An open label, multi-center nilotinib roll-over protocol for patients who have completed a previous Novartis-sponsored nilotinib study and are judged by the investigator to benefit from continued nilotinib treatment.

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Overview of chronic myeloid leukemia (CML)

Chronic myeloid leukemia (CML) is a hematologic disorder associated with a specific chromosomal translocation known as the Philadelphia (Ph) chromosome detected in 95% of patients (Nowell and Hungerford 1960, Rowley 1973). The molecular consequence of the translocation is the fusion of the ABL proto-oncogene to the BCR gene resulting in the production of an activated form of the Abl protein-tyrosine kinase (Bartram et al. 1983, Heisterkamp et al. 1983). Clinically, CML progresses through three distinct phases of increasing refractoriness to therapy: chronic phase (CP), accelerated phase (AP) and blast crisis (BC). Most patients however present in the chronic phase at the time of diagnosis, characterized by splenomegaly and leukocytosis with generally few symptoms. CML comprises 15% of adult leukemias, with an approximate incidence of 1-2 per 100,000 per year and median age of presentation of 45 to 55 years of age (Weisberg et al. 2006, Frazer et al. 2007). Tyrosine kinase inhibitors (TKIs) that inhibit BCR-ABL are the gold standard treatment for BCR-ABL positive CML. Imatinib (Glivec®, Gleevec®; Novartis Pharma AG, Basel, Switzerland) was the first TKI approved for this indication and revolutionized the treatment of CML. Imatinib is the TKI with the longest follow-up with estimated progression-free survival of 81%, freedom from progression to AP/BC of 92% and estimated overall survival (OS) of 85% at 8 yrs for newly diagnosed CP-CML patients (93% when only CML-related deaths and those prior to stem cell transplantation (SCT) were considered) (Deininger et al. 2009).

Nilotinib (Tasigna®; Novartis Pharma AG, Basel, Switzerland) and dasatinib (Sprycel®; Bristol-Myers Squibb, Wallingford, CT, USA) are approved for treatment of patients with Ph+ CML who have failed prior therapies including imatinib and for newly diagnosed patients. Both nilotinib and dasatinib have recently demonstrated superiority over imatinib in head-to-head clinical studies in patients newly diagnosed with Ph+ CML (Kantarjian et al. 2010, Saglio et al. 2010).

1.1.2 Overview of gastrointestinal stromal tumors (GIST)

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract and are thought to originate from the interstitial cells of Cajal. GISTs are malignant tumors most commonly resulting from activating mutations in the receptor tyrosine kinase KIT (CD117) or the platelet-derived growth factor receptors α (PDGFRα) (Demetri et al. 2010). Approximately 85% of KIT (CD117)-positive GISTs harbors an activating mutation in the KIT oncogene and 5-8% of GISTs have mutated PDGFRα gene. Mutations in KIT exon 11 are the most common (67%) while KIT exon 9 mutations are found in 10-12% of GISTs. Mutations in KIT exons 13 and 17 are rare. The remaining cases harbor no mutation and are referred to as “Wildtype” GIST (Corless and Heinrich 2008).

GISTs can arise anywhere along the GI tract but are most common in the stomach and small intestine (Demetri et al. 2010). The majority of KIT exon 9 mutations arise in small intestinal GISTs, while most PDGFRα mutations are found in gastric GISTs. KIT exon 11 mutations are

distributed throughout the GI tract. Response to systemic therapies in the metastatic /inoperable disease setting is related to the identified activating mutations in GIST and the development of subsequent resistance mutations (Corless and Heinrich 2008).

The mainstay of therapy for patients with primary GIST is surgical resection. However, surgery alone is generally not curative; the 5-year disease specific survival is reported to be 54%. Recurrence rates exceeding 50% within 2 years of resection of primary GIST and approximating 90% after re-excision (DeMatteo et al. 2000), underscored the need for effective postoperative treatment.

Imatinib is the first-line therapy for metastatic GIST with a median progression free survival (PFS) reported between 18 months (Phase III) and 29 months (Phase II) and a median OS of 57 months (Verweij et al. 2004, Blanke et al. 2008a, Blanke et al. 2008b, Bertucci et al. 2012). For patients whose disease has progressed during, or who are intolerant to imatinib therapy, sunitinib (Sutent®; Pfizer) is the available second line treatment (Demetri et al. 2006).

Nilotinib also inhibits the tyrosine kinase activity of KIT and PDGFRα which are associated with GISTs. However, although nilotinib and imatinib exhibit similar potencies against the KIT and PDGFR target enzymes, they exhibit major differences in cell transport. Thus Prenen (Prenen et al. 2006) has demonstrated that in two GIST cell lines, intracellular levels of nilotinib are much higher (7-10 fold) than those of imatinib, at physiologically relevant concentrations of the two agents. The ability of nilotinib to achieve higher intracellular concentrations in GIST cells might be the reason that nilotinib has shown anti-proliferative activity at physiologically relevant concentrations in imatinib-resistant GIST48 and GIST430 cells (Dileo et al. 2006).

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of Nilotinib

Nilotinib (Tasigna®, AMN107) is a highly potent and selective inhibitor of both wild-type and imatinib-resistant forms of the tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive (Ph+) leukemia cells. BCR-ABL is a constitutively active tyrosine kinase and drives the pathology of chronic myelogenous leukemia, a myeloproliferative disorder characterized by a clonal expansion of hematopoietic stem cells expressing the BCR-ABL gene. The therapeutic concept of BCR-ABL tyrosine kinase inhibition is an effective treatment modality for Ph+ CML as inhibition of BCR-ABL kinase activity with nilotinib results in apoptosis of Ph+ CML cells.

Nilotinib is currently approved for the treatment of adult patients with Ph+ chronic myeloid leukemia in CP and AP resistant to or intolerant to at least one prior therapy including imatinib and for the treatment of adult patients with newly diagnosed Ph+ CML in CP.

Nilotinib also inhibits a small number of receptor tyrosine kinases, including the stem cell factor kinase (KIT), platelet-derived growth factor kinases (PDGFRα and PDGFRβ), colony stimulating factor receptor kinase (CSF-1R), discoidin domain receptor kinases (DDR1 and DDR-2) and ephrin receptor kinase (EphB4). Consequently, the activity of nilotinib has also is also being explored in other potential indications.

1.2.1.1 Non-clinical experience

For information on pre-clinical toxicity please refer to the current nilotinib [Investigator's Brochure] (IB).

1.2.1.2 Clinical experience

1.2.1.2.1 Human safety and tolerability data

Imatinib-naïve CML patients:

The efficacy of nilotinib in patients with newly diagnosed Ph+ CML-CP has been evaluated in a phase III multi-center open label, randomized study [CAMN107A2303/ENESTnd] comparing nilotinib to imatinib in adult patients with newly diagnosed CML-CP. This study is ongoing and showed continuing superiority of nilotinib vs. imatinib at 12, 24, 36, 48 and 60 months follow-up in terms of cytogenetic and molecular responsesA total of 846 newly diagnosed CML-CP patients were randomized into the study of which 484 patients were still receiving core treatment as of the 60-month cut-off date (141 patients (49.8%) in the imatinib arm, 169 patients (59.9%) in the nilotinib 300 mg BID arm and 174 patients (61.9%) in the nilotinib 400 mg BID arm). A total of 362 patients discontinued core study treatment. The study met its primary efficacy endpoint at the 12-month analysis time point: the MMR rate was significantly higher in the nilotinib arms compared to the imatinib arm. By 60 months, the MMR rate remained higher in the nilotinib arms than in the imatinib arm, indicating that the superiority of both nilotinib arms over the imatinib arm persists with longer follow-up. Furthermore, the proportions of patients achieving molecular response of $\leq 0.01\%$ and $\leq 0.0032\%$ by 60 months were higher in the nilotinib arms than in the imatinib arm.

Ischemic Vascular and Ischemic Cardiovascular Events Reported for CAMN107A2303 (ENESTnd Study):

Newly-diagnosed or worsened Ischemic Vascular and Ischemic Cardiovascular Events such as Ischemic Heart Disease (IHD), Ischemic Cerebrovascular Events (ICVE) or Peripheral Artery Occlusive Disease (PAOD) have occurred in a relatively small number of CML-CP patients while on study medication. However, such events have been reported with higher frequency on the nilotinib treatment arms compared with the imatinib treatment arm. Up to the data cut-off for the 60 month analysis (30-Sep-2013), the number of patients reported with these events is as follows:

- Nilotinib 300 mg BID: IHD, 11 (3.9%); ICVE, 4 (1.4%); PAOD, 7 (2.5%)
- Nilotinib 400 mg BID: IHD, 24 (8.7%); ICVE, 9 (3.2%); PAOD, 7 (2.5%)
- Imatinib 400 mg QD: IHD, 5 (1.8%); ICVE, 1 (0.4%); PAOD, 0 (0.0%)

The majority of reported ischemic vascular and ischemic cardiovascular events were in patients with associated risks (e.g., advanced age, hypertension, hyperlipidemia, hypercholesterolemia, smoking, diabetes mellitus, pre-existing peripheral vascular disease). The background incidence of these events has not been established for the CML patient population.

A detailed description of efficacy and safety data can be found in the current nilotinib [Investigator's Brochure].

Imatinib-resistant or -intolerant hematologic diseases:

Data from a Phase I/II [CAMN107A2101]open-label study indicated that nilotinib treatment resulted in hematologic and cytogenetic responses in patients who had received prior TKIs (including imatinib). In this study a total of 321 CML-CP patients were evaluated for efficacy. Of these, 70.4% were imatinib-resistant and 29.6% were imatinib-intolerant. Patients were treated with nilotinib 400 mg b.i.d. OS at 24 months was 87%. In terms of efficacy, 165 patients (51.4%) achieved a major cytogenetic response (MCyR), which was the primary efficacy variable. This study also analyzed the effect of 400 mg b.i.d. nilotinib in a group of 49 CML-CP patients with prior TKI treatment other than imatinib. At 24 months follow-up, study discontinuation rate was 69.4% (38.8% due to disease progression and 12.2% due to AEs). Efficacy parameters included 77.1% complete hematological response (CHR) for those not in CHR at baseline, 42.9% MCyR, 22.4% complete cytogenetic response (CCyR) and 89% overall survival.

The Phase I/II study in imatinib-resistant or -intolerant chronic phase Japanese CML patients [CAMN107A1101] showed that the efficacy profiles in Japanese patients were similar to those in non-Japanese patients (Usuki et al. 2012).

The median average daily dose of nilotinib for CML-CP patients in [CAMN107A2101] was 788.5 mg. The most frequently reported (>10%) drug-related AEs in CML-CP patients, based on 24-month data and 321 patients, included rash (30.8%), thrombocytopenia (28.0%), pruritus (26.2%), nausea (24.6%), fatigue (20.2%), headache (17.8%), neutropenia (15.0%), constipation (13.4%), anemia (13.1%), lipase increased (12.8%), vomiting (12.8%), diarrhea (12.1%), alanine aminotransferase increase (10.6%), myalgia (10.3%). In CML-CP patients, the most frequent serious adverse events (SAEs) were thrombocytopenia (3.4%), neutropenia (2.2%), angina pectoris (2.8%) and pyrexia (2.5%).

AEs that were associated with discontinuation of treatment with nilotinib were reported in 21.2% of all patients and 16.8% of these events were of Grade 3 or 4 severity. The most frequent AEs associated with discontinuation were neutropenia and thrombocytopenia, which occurred in 10 (3.1%) patients each.

The most frequent Grade 3 or 4 AEs were neutropenia (3.1%), thrombocytopenia (2.8%) and thrombocythemia (1.2%); all other events occurred at a frequency lower than 1%.

A detailed description of efficacy and safety data can be found in the current nilotinib [Investigator's Brochure].

1.2.1.2.2 GISTs:

The *in vitro* activity of nilotinib in imatinib resistant GIST cell lines has been confirmed in [CAMN107A2103] a Phase I study in patients with imatinib-resistant or intolerant GISTs. As nilotinib is not subject to the same cellular transport mechanisms as imatinib, it is effective in both imatinib-sensitive and imatinib-resistant GIST cells. The median progression free survival of nilotinib in imatinib-resistant GIST patients was 168 (5.6 months) days in the CAMN107A2103 study.

With the success of the CAMN107A2103 it was reasonable to assume that nilotinib may have similar or improved efficacy over imatinib in GIST patients.

In the phase III study [CAMN107G2301] patients with unresectable and/or metastatic GIST who have either not received prior therapy with a TKI or who have recurrent GIST after stopping adjuvant therapy, were randomized to either nilotinib or imatinib therapy. The primary objective of this study is to compare PFS of nilotinib and imatinib when used as initial therapy in this patient population.

However the study had to be closed to further recruitment at the request of the Data Monitoring Committee since the futility boundary was exceeded in an interim futility analysis (e.g. this means that there was an extremely low likelihood that continuing with the study would have resulted in a significantly positive outcome in favor of nilotinib). There are no plans to initiate new studies of nilotinib in the GIST patient population.

In general, the safety profile in GIST patients was similar to that in CML patients, with the exception of a lower incidence of hematologic toxicity.

The global phase III study[CAMN107A2201] and Japan phase II study [CAMN107D1201] in patients with GIST who have progressed on or are intolerant to both imatinib and sunitinib showed that nilotinib has generally been well tolerated in this disease setting and the safety profiles are similar between Japanese and non-Japanese in this disease setting.

A detailed description of efficacy and safety data can be found in the current nilotinib [Investigator's Brochure].

1.2.1.2.3 Clinical pharmacokinetics and pharmacodynamics

The relationship of systemic exposure (Cmax, AUC) over the range of 50 to 1200 mg nilotinib given once a day was assessed in patients with imatinib resistant or intolerant CML. With once daily dosing steady-state nilotinib Cmax and AUC increased with increasing dose from 50 mg to 400 mg in a generally dose-proportional manner, but appeared to plateau at dose levels of 400 mg and higher. Using a twice daily dosing regimen partially overcame the dose-limiting exposure, with daily steady-state serum nilotinib exposure at 400 mg twice daily dose (b.i.d.) being approximately 35% greater than with 800 mg once daily dose (q.d.). However, there was no further relevant increase in nilotinib exposure observed with the administration of 600 mg b.i.d. With multiple oral doses of nilotinib, steady-state conditions were achieved by day 8 after initiating nilotinib treatment. There was a 2-fold or 3.8-fold accumulation with q.d. or b.i.d. dosing, respectively. The median time to reach Cmax of nilotinib (Tmax) was 3 hours. Terminal elimination half-life of nilotinib was estimated to be approximately 17 hours.

The bioavailability of nilotinib is increased when the drug is given with a meal. Compared to the fasted state, nilotinib AUC is increased by 15% (administered 2 hours after a light meal), 29% (30 minutes after a light meal), or 82% (30 minutes after high fat meal), and the Cmax increased by 33% (2 hours after a light meal), 55% (30 minutes after a light meal), or 112% (30 minutes after high fat meal). Concurrent intake of grapefruit juice increased the nilotinib Cmax by 60% and AUCinf by 29%, but the Tmax and T1/2 were not altered.

Nilotinib is metabolized by the liver, primarily via CYP3A4. Metabolism of nilotinib leads to the formation of several minor metabolites, none of which contributes significantly to the pharmacological activity of the drug. Unchanged nilotinib represents the predominant circulating component in serum (approximately 88% of the total drug-related serum exposure).

Strong inhibitors or inducers of CYP3A4 can significantly alter the pharmacokinetics and systemic exposure of nilotinib in humans.

Nilotinib is a substrate of P-gp, but is neither a Multi-resistance protein 2 (MRP2) nor a Breast Cancer Resistance Protein (BCRP) substrate.

2 Rationale

2.1 Study rationale and purpose

The purpose of this study is to collect and assess long-term safety of nilotinib in patients who are on nilotinib treatment in a Novartis-sponsored clinical study and are benefiting from the treatment as judged by the investigator. Which parent studies are eligible to participate in the roll-over study will be decided by Novartis, Investigator initiated trials (IITs) will not be included. All objectives prescribed in the parent study protocol must have been reached, and the parent study must be in the process of being completed and reported.

Patients will continue to receive nilotinib until one of the following occurs: the patient is no longer benefiting from the treatment, unacceptable toxicity develops, consent is withdrawn, there is non-compliance with the protocol, the investigator feels it is no longer in the patient's best interest to continue therapy, or the patient's death.

2.2 Rationale for the study design

This is an open label, multi-center, phase II study to collect and assess long-term safety of nilotinib to patients being treated in a current Novartis-sponsored clinical study and who are benefiting from treatment with nilotinib.

The study will not include a screening phase as patients will transfer directly from parent studies and will commence treatment with nilotinib as soon as they are consented and meet the inclusion criteria of the roll-over protocol.

2.3 Rationale for dose and regimen selection

Nilotinib can be provided as 200 mg and 150 mg hard gelatin capsules (HGC). The starting dose of nilotinib should be the same dose which was given in the parent nilotinib study. After the starting dose, the dose of nilotinib is based on the investigator's judgment.

Nilotinib in different formulations and strengths can be used in the roll-over study once they are approved and marketed.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary To collect and assess long-term safety of nilotinib to patients receiving nilotinib in a Novartis-sponsored clinical study which has reached its objectives and who are benefiting from treatment with nilotinib.	Frequency and nature of AEs.	Refer to Section 10

4 Study design

4.1 Description of study design

This is an open label, multi-center, phase II study to collect and assess long-term safety of nilotinib to patients being treated in current Novartis-sponsored clinical studies and who are benefiting from treatment with nilotinib.

There will be no screening period for this study. At the enrollment visit the patient will be consented to the study and eligible patients will start their treatment with nilotinib.

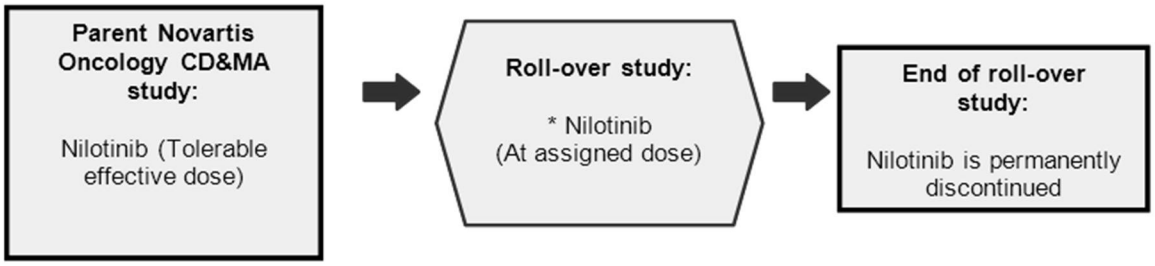
Patients must return to the study center on a yearly basis (+/- 3 months) for resupply of study medication at which time limited drug dispensing information will be collected. The patient may return to the study center at any given time as per standard of care, however, only one study visit per year will be scheduled and AEs reported at general medical care will be collected continuously throughout the study. For the safe and effective use of nilotinib, medical monitoring should be performed as clinically indicated at the physician's discretion. Medical monitoring should also include monitoring of cardiovascular risk factors such as serum cholesterol and glucose levels amongst others.

Patients will continue to be treated until they are no longer benefiting from nilotinib treatment, develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue nilotinib therapy or the patient dies, whichever comes first.

A patient will reach the end of study when nilotinib treatment is permanently discontinued and the end of treatment visit has been performed.

The study is expected to remain open for 10 years or until such time that enrolled patients no longer need treatment with nilotinib, whichever comes earlier.

Figure 4-1 Study schema



*Note: The starting nilotinib dose will be the same as the last dose in the parent study.

4.2 Timing of interim analyses and design adaptations

No interim analyses are planned.

4.3 Definition of end of the study

End of study is defined as either 10 years duration or when all patients on this study have permanently discontinued nilotinib treatment and the end of treatment visit has been performed for each patient, whichever comes earlier.

4.4 Early study termination

The study is expected to remain open for 10 years or until such time that enrolled patients no longer need treatment with nilotinib, whichever comes earlier.

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's health interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patient is currently enrolled in a Novartis-sponsored clinical study receiving nilotinib and has fulfilled all their requirements in the parent study.
2. Patient is currently benefiting from the treatment with nilotinib, as determined by the investigator.

3. Patient has demonstrated compliance, as assessed by the investigator, with the parent study protocol requirements.
4. Willingness and ability to comply with scheduled visits, treatment plans and any other study procedures.
5. Written informed consent obtained prior to enrolling in roll-over study.
    - If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Patient has been permanently discontinued from nilotinib treatment in the parent study due to unacceptable toxicity, non-compliance to study procedures, withdrawal of consent or any other reason.
2. Patient has participated in a Novartis sponsored combination trial where nilotinib was dispensed in combination with another study medication and patient is still receiving combination therapy.
3. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval or inducing Torsade de Pointes and the treatment cannot be either safely discontinued at least one week prior to nilotinib treatment or switched to a different medication prior to start of nilotinib treatment and for the duration of the study (Please see Appendix 1 for link to list of agents that prolong the QT interval).
4. 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.
5. 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 30 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 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) 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+b or a+c or b+c):
        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.

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 Investigator/Study Doctor needs to be informed immediately and ongoing study treatment with nilotinib has to be stopped immediately.

6 Treatment

6.1 Study treatment

Terms related to study treatment are defined below:

- Study treatment and investigational treatment refer to nilotinib.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Total daily dose	Frequency and/or Regimen
Nilotinib /AMN107	*Hard Gelatin Capsule for oral use	≤800 mg	**Daily

* Different formulations and strengths can be used once they are approved and marketed.
**If total daily dose is 600 mg it is taken as 300 mg b.i.d. If total daily dose is 800 mg it is taken as 400 mg b.i.d.

Nilotinib can be provided as 200 mg and 150 mg hard gelatin capsules. The investigational treatment is to be stored in a secure locked area while under the responsibility of the investigator. Receipt and dispensing of investigational treatment must be recorded by an authorized person at the investigator's site.

The starting dose of nilotinib should be the same as the last dose that was given in the parent nilotinib study. After this, the dose of nilotinib is based on the investigator's judgment.

Nilotinib must NOT be taken with food. No food should be consumed for at least 2 hours before the dose is taken and no additional oral intake other than water should be consumed for at least one hour after the dose is taken. This instruction should be followed if patient is to take nilotinib once or twice a day. If nilotinib is taken twice a day (when 300-400 mg b.i.d.) patients should be instructed to take nilotinib each morning and evening approximately 12 hours apart.

Each dose of nilotinib should be taken with a glass of water. If the morning or the evening dose is delayed for more than 4 hours, the patient should skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing.

Nilotinib can be provided as local commercial material or global supply where appropriate and as per local regulations. As per Novartis procedures, investigational treatment will only be shipped directly to the investigational sites.

Nilotinib in different formulations and strengths can be used once they are approved and marketed.

Refer to the latest [Investigator's Brochure] for nilotinib dosing instructions and storage conditions.

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

The starting dose of nilotinib should be the same as the last dose that was given in the parent nilotinib study. After this, the dose of nilotinib is based on the investigator's judgment.

6.1.5 Treatment duration

Patients will continue to be treated until they are no longer benefiting from nilotinib treatment, develop unacceptable toxicities, withdraw consent, are non-compliant with the protocol, the investigator feels it is no longer in the patient's best interest to continue nilotinib therapy or the patient dies, whichever comes first. A patient will reach the end of the roll-over study when nilotinib treatment is permanently discontinued.

6.2 Dose modifications

Dose modifications will be based on guidelines provided in the parent protocol as well as on investigator's judgment. Additional guidelines for the management of patients including recommendations for the clinical management of cardiovascular risk factors and related events are listed in the sub-sections below.

6.2.1 Management of cholesterol increases

Blood lipid panel tests should be performed as clinically indicated throughout the study. If test results warrant intervention, investigators should follow their local standards of practice or treatment guidelines, which may recommend treatment even for grade 1 cholesterol elevation. Before prescribing a lipid lowering medication, the possibility of drug-drug interactions should be considered due to the moderate inhibitory effect of nilotinib on CYP3A4 isoenzyme that is involved in the metabolic pathway of some statins (HMG-CoA reductase inhibitors). A list of these drugs is listed in Appendix 1 in Section 14.1.

6.2.2 Management of glucose increases

Blood glucose tests should be performed as clinically indicated throughout the study. If blood glucose results warrant intervention, investigators should follow their local standards of practice and treatment guidelines in order to normalize blood glucose levels.

6.2.3 Management of other cardiac risk factors

Patients should be assessed or monitored for any other cardiac risk factors such as family history, cardiovascular events in the past medical history, smoking, hypertension, and obesity. If the assessment for presence of any other cardiovascular risk factors warrants intervention, investigators should follow their local standards of practice or treatment guidelines.

6.2.4 Management of ischemic vascular or cardiovascular events

Newly-diagnosed or worsened ischemic vascular or cardiovascular events have occurred in a relatively small number of CML-CP patients while on study medication. If a patient experiences such an adverse event, the Investigator should ensure that the patient is assessed by a vascular or cardiovascular specialist. For further recommendations regarding the management of ischemic vascular or cardiovascular-related events refer to the current nilotinib [Investigator's Brochure].

6.2.5 Hepatitis B reactivation

Hepatitis B virus testing should be performed during the study as indicated in Section 7.1.4 to identify patients who may be at risk for Hepatitis B reactivation. Experts in liver disease and in the treatment of hepatitis B should be consulted for patients who test positive for hepatitis B virus during nilotinib/imatinib treatment. Carriers of hepatitis B virus who require treatment with nilotinib/imatinib should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.

6.2.6 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as alkaline phosphatase (ALP) elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and ALP.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented. In this study, result of laboratory test is not collected on the eCRF but these events should be reported as AEs/SAEs on the eCRF, and should be monitored and verified with source data on site by the field monitor.

6.2.7 Prohibited concomitant therapy

In general, concomitant medications/therapies deemed necessary for the supportive care of the patient is permitted.

Avoid the concomitant use of strong CYP3A4 inhibitors and inducers (refer to Appendix 1 in Section 14.1). Should treatment with strong CYP3A4 inhibitors or inducers be required, it is recommended that therapy with nilotinib be interrupted. Close monitoring of prolongation of the QT interval is indicated for patients who cannot avoid strong CYP3A4 inhibitors or inducers. For further details refer to the current nilotinib [Investigator's Brochure].

Cytochrome P450 3A4 substrates:

Nilotinib is a moderate CYP3A4 inhibitor *in vivo*. Because of the potential risk for drug-drug interactions, the systemic exposure of other drugs known to be sensitive substrates of CYP3A4 and also to have a narrow therapeutic index should be used with caution. A list of these drugs is listed in Appendix 1 in Section 14.1.

Antacid drugs:

Nilotinib has a pH-dependent solubility, therefore, in order not to impact nilotinib pharmacokinetics, administration of the following antiacid drugs (if necessary) should be as follows:

- H2 blocker (e.g. famotidine) may be administered approximately 10 hours before or approximately 2 hours after the dose of nilotinib,
- Antacids (e.g. magnesium hydroxide, simethicone) may be administered approximately 2 hours before or approximately 2 hours after the dose of nilotinib.

6.3 Patient numbering, treatment assignment or randomization

6.3.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled in the roll-over study and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator.

6.3.2 Treatment assignment or randomization

All consented patients who meet all the inclusion criteria and none of the exclusion criteria are eligible to receive nilotinib.

6.3.3 Treatment blinding

Not applicable.

6.4 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Table 6-2 Preparation and dispensing

Study treatments	Dispensing	Preparation
Nilotinib	*Hard Gelatin Capsules (150 mg and 200 mg) including instructions for administration will be dispensed by study personnel on an outpatient basis. Patients will be provided with an adequate supply of study treatment for self-administration at home until at least their next scheduled annual (+/- 3 months) study visit. Or, patients can be provided with supply of study treatment needed until the next visit if the visit is scheduled within a year.	Not applicable

* Different formulations and strengths can be used once they are approved and marketed.

6.4.1 Study drug packaging and labeling

Study treatment labels will be in Japanese and comply with the legal requirements of Japan. They will include storage conditions for the drug but no information about the patient.

Nilotinib in different formulations and strengths can be used once they are approved and marketed.

Refer to the latest [Investigator's Brochure] for nilotinib dosing instructions and storage conditions.

Table 6-3 Packaging and labeling

Study treatment	Packaging	Labeling
Nilotinib	Capsules in bottles*	As per local requirements

* For centrally supplied medication. If nilotinib is sourced and labeled in-country/locally, the locally-approved form, packaging and labeling of nilotinib will be used.

6.4.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the nilotinib should be stored according to the instructions specified on the drug labels and in the current [Investigator's Brochure].

Table 6-4 Supply and storage of study treatments

Study treatment	Supply	Storage
Nilotinib	Centrally or locally supplied by Novartis	Refer to study treatment label or local product information

6.4.3 Study drug compliance and accountability

6.4.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.4.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.4.3.3 Handling of other study treatment

Not applicable.

6.4.4 Disposal and destruction

The drug supply can only be destroyed once the study drug accountability check has been performed by the monitor. The study drug supply can be destroyed at the local Novartis facility, by Drug Supply group or by a third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. A visit window of +/-3 months is allowed. All data obtained from these assessments must be supported in the patient's source documentation.

Hepatitis B testing will be performed once and only once, at the next possible visit.

The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

Table 7-1 Visit evaluation schedule

	Category	Protocol Reference Section	Enrollment	Annual (+/- 3 months) visits during treatment phase	End of study treatment (EoT)	Safety Follow-up
Visit Number			**1**	**Visit 2,3,4 etc.**	**777**	
Informed consent	D	7.1.1	x			
Patients' previous study, site and subject number	D	6.3	x			
Demography	D	7.1.1.3	x			
Inclusion/exclusion criteria	D	5.2 / 5.3	x			
Nilotinib dosing	D	6.1	x	x		
Pregnancy testing	D,S	7.1.3	Monthly (at home)		x	x
Serology-Hepatitis B Testing	S	7.1.4	ONLY once after patient is consented to amendment 5			
AEs	D	8.1	← Continuous →			x
End of study treatment	D	7.1.5			x	

7.1.1 Screening

At the enrollment visit the patient will need to complete a written informed consent. There will be no screening period for this study. Once consented, patients will be evaluated for eligibility via the inclusion and exclusion criteria.

7.1.1.1 Eligibility screening

Not applicable.

7.1.1.2 Information to be collected on screening failures

Not applicable.

7.1.1.3 Patient demographics and other baseline characteristics

For patients that are eligible to participate in this roll-over study, an eCRF will be completed that identifies the patients'gender, date of birth, ethnicity and previous study, site/center and subject number.

7.1.2 Treatment period

The starting dose of nilotinib should be the same as the last dose that was given in the parent nilotinib study. A yearly supply of nilotinib will be dispensed to the patient/or as per local practice. Or, patients can be provided with supply of study treatment needed until the next visit if the visit is scheduled within a year.

Patients must return to the study center on a yearly basis (+/- 3 months) for resupply of study medication at which time limited drug dispensing information will be collected. At this time the dose of nilotinib is based on the investigator's judgment.

The study is expected to remain open for 10 years or until such time that enrolled patients no longer need treatment with nilotinib, whichever comes earlier.

7.1.3 Pregnancy and assessment of fertility

Since highly effective contraception is required during the study, female patients of child bearing potential are required to test negative for a pregnancy (either with serum testing if routinely available or urine pregnancy test) before enrolling into the study.

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 30 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 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) 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+b or a+c, or b+c):
  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

If patient has tested negative at the end of study on the parent study, no pregnancy testing is required if enrollment into this study is carried out on the same day or within few days (maximum 5 days) from each other.

Female patients of child bearing potential are required to perform monthly home urine pregnancy tests and complete a simple diary with the dates and the outcome of the home urinary test while on study treatment and during safety follow-up (30 days after the final dose of study medication).

A pregnancy test (either with serum testing if routinely available or urine pregnancy test) on female patients of child bearing potential is required at the final study visit.

Any positive results will be recorded in the database and followed up as per Section 8.4.

(Note: In terms of pregnancy prevention in a pediatric population, the detailed guidance in the parent protocol could be followed.)

7.1.4 Hepatitis B testing

Patients will be tested once for the following hepatitis B serologic markers: hepatitis B surface antigen (HBs Ag) and antibodies to hepatitis B core antigen (HBc Ab / anti HBc). Patients currently on nilotinib/imatinib should have testing performed at the next possible visit in order to identify chronic carriers.

7.1.5 End of treatment visit including study completion and premature withdrawal

Patients will continue to be treated until they are no longer benefiting from nilotinib treatment, develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue nilotinib therapy or the patient dies, whichever comes first.

At the time the patients discontinues study treatment, a visit should be scheduled as soon as possible, at which time the assessments listed for the End of Treatment (EOT) visit will be performed. End of Treatment information will be completed in the eCRF giving the date and reason for stopping the study treatment (see Section 7.1.5.1). e.g. physician decision, disease progression, cause of death, lost to follow up, withdrawal of consent, etc.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for a safety evaluation during the 30 days following the last dose of study treatment.

Patients who discontinue study treatment should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's withdrawal from the study and record this information on the appropriate CRF page.

A patient will reach the end of study when nilotinib treatment is permanently discontinued and there will be **no** further follow-up study visits.

7.1.5.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

Patients may be withdrawn from the study if any of the following occur:

1. Death*.
2. Lost to follow-up.
3. Staying in the study would be harmful.
4. Patient/guardian decision*.
5. Physician decision.
6. Patient is non-compliant to protocol requirements.
7. Protocol deviation.
8. Patient becomes pregnant*.
9. Study terminated by sponsor.

*Note: Patients who are pregnant, withdrawn consent or have died must be withdrawn from the study.

7.1.5.2 Replacement policy

Not applicable.

7.1.6 Safety follow-up period

All patients must be followed up for safety evaluations for 30 days after the last dose of study treatment. At the end of this period, the investigator should contact the patient to inquire about any AE observed during this period. This could be done via a phone contact. Following this there are **no** further follow-up study visits.

Patients lost to follow up should be recorded as such on the appropriate eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.2 Assessment types

7.2.1 Efficacy assessments

Not applicable.

7.2.1.1 Additional biomarker assessments

Not applicable.

7.2.2 Resource utilization

Not applicable.

7.2.3 Patient reported outcomes

Not applicable.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after dosing constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

AEs that begin or worsen after dosing should be recorded in the Adverse Events CRF. AE monitoring should be continued for at least 30 days following the last dose of study treatment. AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though End of Treatment.

The occurrence of AEs should be sought by non-directive questioning of the subject after signing informed consent and at each visit during the study. AEs also may be detected when they are volunteered by the subject between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each AE should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates or Ongoing at End of Study)

3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, concomitant medication taken, non-drug therapy taken, hospitalization/prolonged hospitalization)
5. Whether it is serious, where a SAE is defined as in Section 8.2.1

All AEs should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it. Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

8.1.2 Adverse events of special interest

Ischemic vascular and ischemic cardiovascular events include (but are not limited to) the events listed below. Patients should be educated on the clinical symptoms of such events to ensure accurate reporting to the Investigator.

- Ischemic Heart Disease (IHD): angina pectoris, coronary artery disease, acute myocardial infarction and coronary artery stenosis
- Ischemic Cerebrovascular Events (ICVE): ischemic cerebrovascular accident, and transient ischemic attack
- Peripheral Artery Occlusive Disease (PAOD): intermittent claudication, arterial stenosis of a limb

If patients experience ischemic vascular or ischemic cardiovascular events (i.e. ischemic, cardiac, cerebrovascular or peripheral artery-related), carefully consider guidance provided in the current nilotinib [Investigator's Brochure].

The Investigator should ensure that the patient is assessed by a vascular or cardiovascular specialist.

8.1.2.1 Definitions and reporting

Not applicable.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect

- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Note that hospitalizations for the following reasons should not be reported as SAEs:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a SAE

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and for 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

SAEs information will be collected in the Novartis safety database.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis DS&E department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable. This is an open-label study.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis DS&E. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided nilotinib [Investigator's Brochure]. Additional safety information collected between [Investigator's Brochure] updates will be communicated in the form of INs. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

Not applicable.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened SAEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRFs is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staffs are required to respond promptly to queries and to make any necessary changes to the data.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Statistical analysis will be performed when all patients discontinued the trial or 10-year follow up was completed, whichever comes earlier. Those analyses results will be used to document the summary of the safety.

10.1 Analysis sets

10.1.1 Full Analysis Set

No Full Analysis Set (FAS) is defined for this trial.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of Nilotinib.

10.1.3 Per-Protocol Set

No Per-Protocol Set (PPS) is defined for this trial.

10.2 Patient demographics/other baseline characteristics

Patient demographics and baseline characteristics such as age will be listed by patient.

10.3 Treatments (study treatment, concomitant therapies, compliance)

Study drug administration record will be listed by patient.

The duration of exposure in days to Nilotinib is defined as the time between the date of last dosing and the date of first dosing. It includes periods of temporary interruption of Nilotinib. The duration of exposure will be calculated for each patient, and will not be summarized. It will be used for dose intensity.

The dose intensity defined as the ratio of the cumulative dose to the duration of exposure may be calculated and summarized.

10.4 Primary objective

Primary objective of this trial is to collect and assess the long-term safety of Nilotinib to patients receiving nilotinib in a Novartis-sponsored clinical study (/ies) which has reached its objectives and who are benefiting from treatment with Nilotinib.

10.4.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used.

10.4.2 Adverse events (AEs)

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

All AE data (including those from pre-study and post-treatment period) will be listed by patient and those collected during the pre-study is to be flagged. The incidence of AE will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of AE, relation to study drug. Note that AEs from pre-study will not be analyzed.

Deaths reportable as SAEs and non-fatal serious AEs will be listed by patient.

10.4.3 Other safety data

Not applicable.

10.4.4 Pharmacokinetics and biomarkers

No pharmacokinetics and biomarkers will be assessed.

10.5 Interim analysis

No interim analysis is planned.

10.6 Sample size calculation

No formal sample size calculation is required for this trial since only Japanese patients who are still on treatment in Novartis-sponsored clinical study (/ies) will be enrolled in this trial.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with [Section 4.9 of the ICH E6 GCP], and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept

at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial [ICH E6 Section 8] and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site, prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

13 References (available upon request)

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14 Appendices

14.1 Appendix 1: Guidance on concomitant medications with CYP3A and QTc prolongation potential interactions.

A list of drugs that are inducers and inhibitors of CYP3A4 is provided below.

Patients should be instructed not to take grapefruit, St. John's Wort or Seville (sour) orange juice while receiving study treatment throughout the study due to potential CYP3A4 induction or inhibition.

As the information listed below may not be all inclusive, a list of CYP3A4 inhibitors and inducers may be found at http://medicine.iupui.edu/flockhart.

Table 14-1 Medications that can induce CYP3A4

Strong inducers	Moderate inducers	Weak inducers	Unclassified inducers
avasimibe	bosentan	amprenavir	topiramate
carbamazepine	efavirenz	aprepitant	
dexamethasone*	etravirine	armodafinil (R-modafinil)	
phenobarbital	modafinil	echinacea	
phenytoin	nafcillin	garlic	
rifabutin	ritonavir	gingko	
rifampin	talviraline	glycyrrhizin	
rifapentin*	tipranavir	methylprednisolone	
St. John's wort		nevirapine	
		oxcarbazepine	
		pioglitazone	
		prednisone	
		pleconaril	
		rufinamide	
		troglitazone	
* Discrepancies on the level of induction of these drugs exist in the literature, however, they are listed in the "strong inducers" group in order to be consistent with the Tasigna Labeling			

Note:

- Inducer classification:
  - Strong inducers may result in a substrate area under curve (AUC) decreased by ≥ 80%.
  - Moderate inducers may result in a substrate AUC decreased by 50-80%.
  - Weak inducers may result in a substrate AUC decreased by 20-50%.
- This list is compiled based on the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to Novartis Oncology Clinical

Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated 30 August 2010) for update or more details.

Table 14-2 Medications that can inhibit CYP3A4

List of medication metabolized by CYP3A4, strong, moderate and weak inhibitors of CYP3A4 to be used with caution.

CYP3A4 substrates permitted but patients should be carefully monitored for drugs indexed 1 and 2		**Strong inhibitors**	**Moderate inhibitors**	**Weak inhibitors**
alfentanil[1,2]	fentanyl[2]	clarithromycin	aprepitant	alprazolam
fluticasone[1]	diergotamine[2]	conivaptan	atazanavir	AMD070
cyclosporine[2]	adinazolam	indinavir	cimetidine	amlodipine
maraviroc[1]	alprazolam	itraconazole	ciprofloxacin	azithromycin
midazolam[1]	amlodipine	ketoconazole	darunavir	bicalutamide
alpha-dihydroergocryptine[1]	aripiprazole	lopinavir	diltiazem	chlorzoxazone
sildenafil[1]	chlorpheniramine	mibefradil	erythromycin	cilostazol
tipranavir[1]	diazepam	nefazodone	fluconazole	cyclosporine
triazolam[1]	estazolam	nelfinavir	grapefruit juice	fluvoxamine
perospirone[1]	nisoldipine	posaconazole	imatinib	ginkgo
darifenacin[1]	quinine	ritonavir	tofisopam	goldenseal
ebastine[1]	trazodone	saquinavir	verapamil	isoniazid
eletriptan[1]	nitrendipine	telithromycin		lacidipine
eplerenone[1]	mevastatin	troleandomycin		M100240
everolimus[1]	lovastatin[1]	voriconazole		oral contraceptives
felodipine[1]	atorvastatin[1]			peppermint oil
brotizolam[1]	simvastatin[1]			propiverine
budesonide[1]	fluvastatin			ranitidine
buspirone[1]				ranolazine
sirolimus[1,2]				roxithromycin
ergotamine[2]				Seville orange juice
				tabimorelin

[1] Sensitive substrates: drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

[2] Substrates with narrow therapeutic index (NTI): drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

Note:

- Inhibitor classification:
  - Strong inhibitors may result in a substrate AUC > 5-fold increase.
  - Moderate inhibitors may result in a substrate AUC ≥ 2-fold increase and < 5-fold increase.
  - Weak inhibitors may result in a substrate AUC ≥ 1.25-fold increase and < 2-fold increase.

This list is compiled based on the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated 30 August 2010) for update or more details.

Guidance on QT prolongation agents

Please see http //azcert org/medical-pros/drug-lists/bycategory.cfm (or similar) for a comprehensive list of agents that prolong the QT interval.