NOVARTIS

Clinical Development

AMN107 (NILOTINIB)
TASIGNA

Oncology Clinical Protocol CAMN107A2409 / NCT01735955

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

Authors	[redacted]
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List of abbreviations

AE	Adverse event
AMN107	Nilotinib /Tasigna
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
BC	Blast crisis (of CML)
BCRP	Breast cancer resistance protein
BID	bis in diem, twice daily
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
CMR	Complete molecular response
CP	Chronic phase (of CML)
CRF	Case report/record form
CRO	Contract research organization
CSR	Clinical Study Report
CYP3A4	Cytochrome 3A4
DDI	Drug –drug interactions
EC	European Commission
ECG	Electrocardiogram
eCRF	Electronic Case report/record form
EDC	Electronic data capture
EMA	European Medicines Agency
EoT	End of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumors
h	Hour
H2	Histamine receptor
HBc Ab	Hepatitis B Core Antibody
HBs Ag	Hepatitis B Surface Antigen
HGC	hard gelatin capsules
HMG-CoA	Hydroxy-Methyl-Glutaryl-Coenzyme A
IB	Investigator brochure
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

[redacted]

MCyR	Major cytogenetic response
MRP2	Multi-resistance protein 2
o.d.	*Omnia die*/once a day
OC	Oral contraceptive
OCRDC	Oracle Clinical Remote Data Capture
OGD&GMA	Oncology Global Development & Global Medical Affairs
OS	Overall survival
p.o.	*Per os*/by mouth/orally
PAOD	Peripheral Artery Occlusive Disease
PDGRD- α	Platelet-derived growth factor receptors α
PFS	Progression-free survival
P-gp	P-glycoprotein
Ph	Philadelphia (chromosome)
PHI	Protected Health Information
PK	Pharmacokinetics
q.d.	*quaque die*/ once daily
QT	Q to T interval (ECG)
SAE	Serious adverse event
SCT	Stem cell transplantation
SmPC	Summary of Product Characteristics
SOC	system organ class
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)
US PI	United States Prescribing Information

[redacted]

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.
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study.
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.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
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.
Withdrawal of consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data.

[redacted]

Amendment 05 (30-Aug-2018)

Amendment rationale

The primary purpose of the amendment is to provide further clarity to the end of study definition and trial timelines:

- End of study is defined as the date when all patients have completed their last assessment per protocol thirty days after end of treatment visit
- Patients may continue on study treatment until need for a premature discontinuation criteria happened, 10 years after First Patient First Visit into this clinical trial or when study treatment becomes commercially available and reimbursed in the respective indication whichever comes first.

The First Patient First Visit occurred on 29-Mar-2013. 45 total patients' have been enrolled and 17 patients are ongoing.

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:

- Updated author list of protocol to reflect the team currently working on/managing the protocol.
- Glossary of terms updated with personal data term and revised definition of withdrawal of consent.

Protocol Summary Section updated to match the body of the protocol.

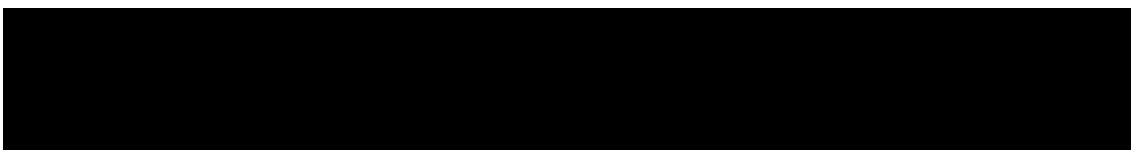
Section 2.6, Risks and benefits: number of countries in which nilotinib is approved was updated. Clarification that latest Investigator Brochure should be consulted was updated. Has been updated to clarify that the 10 years study duration is meant based on First Patient First Visit in the study and clarify study duration.

Section 4.1, Description of Study Design.was updated to clarify that trial is planned to be open for treatment for 10 years from First Patient First Visit on 29Mar2013 and clarify study duration.

Section 4.3, Definition of End of Study was updated to clarify the end of study definition. The end of study is defined as the date when all patients have completed their last assessment per protocol thirty days after end of treatment visit. Patients will continue study treatment until a discontinuation criteria is met, study treatment becomes commercially available for that indication, or 10 years after First Patient First Visit in this trial which occurred on 29-Mar-2013, whichever comes first.

Section 4.4, Early study termination: section has been updated per latest Novartis standard. Definition of end of study is defined in Section 4.3.

Section 6.1.5 has been updated to clarify that the 10 years study duration is meant based on First Patient First Visit in the study.



Section 6.3.1.1, Dose reduction guidelines for study drug-related non hematological toxicity: editorial update with reference to Table –2.

Table 6-2: updated to clarify that dose modification applies to 600 or 800mg total daily dose. Guidance for combined elevation of AST or ALT and total bilirubin was added per latest Novartis guidance.

Section 6-3-1-2: dose reduction guidelines for study drug-related hematological toxicity have been added to harmonize guidance across Novartis-sponsored Tasigna trials.

Table 6-3 summary of dose reduction guidelines for study drug-related hematological toxicity was added to harmonize guidance across Novartis-sponsored Tasigna trials.

Section 6.3.2 Dose reduction guidelines for study drug-related toxicity for pediatric patients: editorial update with reference to table 6-4.

Table 6-3: Hepato-biliary/Pancreas recommendation updated as guidance as to pancreas abnormality are handled in a separate section of Table 6-4.

Section 6.4.1, Prohibited concomitant therapy: additionnal guidance have been added as to CYP3A4 substrates and Drug with risk of Torsades de Pointe to hamonize with Novartis sponsored Tasigna trials. Cardiac monitoring updated: Documentation will be kept in source document.

Section 6.6, Study drug preparation and dispensation: editorial update, Table 6-5 reference was updated.

Section 6.6.1, Study treatment packaging and labelling: editorial update, Table 6-6 and table 6-7 reference were updated.

Section 7.1.3 has been updated to clarify that the 10 year study duration is based on First Patient First Visit in the study and to clarify study duration.

Section 7.1.5 has been updated to clarify that the 10 years study duration is meant based on First Patient First Visit in the study and to clarify study duration.

Section 7.1.5.1, Criteria for premature patient withdrawal has been updated to clarify that adverse event and disease progression based on physician assessment are captured as reason for premature patient withdrawal.

Section 7.1.6, Withdrawal of consent has been updated to align with revised standard Novartis template language.

Table 14-1, 14-2 and 14-3: the lists of CY3A4 inducers, inhibitors and substrates have been updated according to the Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated 2018). Reference to website where list of drug prolonging QT interval was updated.

Editorial modifications to correct typographical errors have been implemented as needed.

Amendment 04 (27-Jul-2016)

Amendment rationale

The main purpose of 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.

This roll-over study has been opened since 29-Mar-2013 with 45 total patients enrolled and 27 patients ongoing.

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:

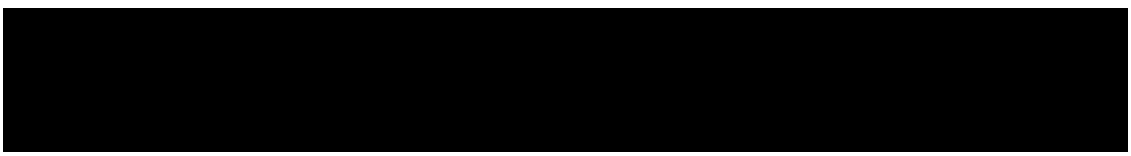
Section 6.3: Updated to clarify that investigators should refer to the approved local label for additional details regarding dose modifications and recommendations. If no approved local label is available, the SmPC or USPI for Tasigna should be used.

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

IRBs/IECs

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.



Summary of previous amendments

Amendment 03 (07-Apr-2016)

Amendment rationale

The main purpose of the amendment is:

- To change the primary endpoint to safety in order to better characterize the long-term safety of nilotinib
- 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. Some cases involving BCR-ABL TKI resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.
- To include the collection of all AEs (including non-serious AEs) and an investigator attestation of continued clinical benefit.

This roll-over study has been opened since 29-Mar-2013 with 45 total patients enrolled and 28 patients ongoing.

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:

Section 2.1: The purpose of the study has been updated to better characterize the long-term safety of nilotinib in patients who are on nilotinib treatment in a Novartis-sponsored study and are benefitting from the treatment as judged by the investigator.

Section 2.2: The rationale for the study design has been updated to better characterize the long-term safety of nilotinib in patients being treated in a current Novartis-sponsored study and who are benefitting from treatment with nilotinib.

Section 2.6: Risks and Benefits section added per the new protocol template.

Table 3-1: Updated with revised study objectives. The primary objective is to evaluate long term safety data. The secondary objective is to evaluate clinical benefit as assessed by the investigator.

Section 4.1: Updated to clarify that study is to better characterize the long-term safety and that all adverse events and serious adverse events will be collected continuously throughout the study. Additionally at every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

Section 5.3 Exclusion criteria #5 updated to clarify highly effective contraception methods and to exclude sexually active males unless they use a condom during intercourse while taking study drug and for 30 days after stopping treatment.

[redacted]

Section 6.1.5: Updated to specify that at every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment

Section 6.2 and 6.2.1 added per the new protocol template.

Section 6.3 added to include dose modifications for both adult and pediatric patients. Subsequent section numbers have been updated as a result.

Section 6.3.6 Hepatitis B reactivation was added to provide information on next steps for patients testing positive for hepatitis B virus.

Section 6.3.7 was added to provide follow-up information for drug-induced liver injury.

Section 6.4 added per the new protocol template. Subsequent section numbers were updated as a result.

Section 6.4.2 (Use of bisphosphonates) added per new protocol template; however, the section has been marked as "Not applicable" for this study.

Section 7.1: Updated to include Hepatitis B testing at the next possible visit.

Table 7-1: Updated to include investigator attestation of clinical benefit at every quarterly visit (12 weeks +/- 1 week), collection of relevant medical history, hepatitis B testing, all adverse events, and study evaluation completion page.

Section 7.1.2.3: Updated to include collection of relevant medical history.

Section 7.1.3: Updated to specify that the investigator is required to confirm that the patient continues to have clinical benefit at every quarterly visit and may continue receiving study treatment.

Section 7.1.4: Highly effective contraception definitions have been updated.

Previous section 7.1.4 updated to Section 7.1.5 (Discontinuation of study treatment).

Section 7.1.5 Updated to include the Study Evaluation Completion eCRF page to be completed for all patients at the end of the 30 day safety follow up.

Section 7.1.6 (Withdrawal of consent) and 7.1.8 (Lost to follow up) added per the new protocol template.

Section 7.1.7: Updated to include adverse events in safety follow up period.

Section 7.2.1: Updated to include investigator attestation of clinical benefit at every quarterly visit.

Section 7.2.2: Updated to clarify that safety will be monitored by collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

Section 7.2.2.1 was added to provide information on hepatitis B testing.

Section 7.2.3 (Pharmacokinetics) and 7.2.3.1 (Analytical methods) added per the new template but both sections are "not applicable" for this study.

Section 8: Updated with new AE/SAE reporting process.

[redacted]

Section 10: Updated statistical analysis section based on revised study objectives.

The protocol summary and list of abbreviations has also been updated based on the changes specified above.

IRBs/IECs

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.

[redacted]

Amendment 02

Amendment rationale

As of the release date of this amendment 41 patients have enrolled into the study.

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:

Section 1.2.1.2.1: 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 (Sections 6.2.1- 6.2.5).

Sections 6.2.1 to 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.

[redacted]

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

Section 8.1.1: Updated to clarify that medical monitoring as clinically indicated at the physician's discretion should include cardiovascular risk factors such as serum cholesterol and glucose levels amongst others. Update also includes the education of patient's on the reporting of clinical conditions of special interest.

Section 8.1.3: Updated to include 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.

IRBs/IECs

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.

[redacted]

Amendment 01

Amendment rationale

As of the release date of this amendment, 6 patients have been enrolled into the study and started on treatment.

This amendment is a global amendment and 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 be required, it is recommended that therapy with nilotinib be interrupted if possible.
- To add language clarifying the strengths of nilotinib allowed in the study to ensure patients can have access to the same strengths as specified in the parent protocol.
- To clarify that patients who are pregnant, withdrawn consent or have died must be withdrawn from the study.
- 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 summary as well as within the protocol sections below:

Section 2.3: Updated to clarify additional strengths of nilotinib can be provided if specified in the parent protocol.

Section 6.1.1: Updated to clarify additional strengths of nilotinib can be provided if specified in the parent protocol.

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 be required, it is recommended that therapy with nilotinib be interrupted if possible.

Table 6-2: Additional strengths of nilotinib can be provided if specified in the parent protocol.

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

[redacted]

IRBs/IECs

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.
Data analysis	The assessment of safety will be based mainly on the frequency of AEs and SAEs. Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits. As needed, safety information on patients from this protocol will link to the patient identifiers from the parent protocol.
Efficacy assessments	At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment
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, Oncology Global Development & Global Medical Affairs (OGD&GMA) 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	Tasigna roll-over study for continued use of nilotinib to patients receiving nilotinib in a Novartis-sponsored Oncology OGD&GMA study which has reached its objectives and who are benefiting from treatment with nilotinib.
Other assessments	Not applicable.
Population	Male and female patients, who are currently enrolled in a Novartis-sponsored, Oncology OGD&GMA nilotinib study, are benefiting from treatment with nilotinib and have fulfilled all their 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. Approximately 100 patients may enroll into this study.
Primary Objective(s) and Key Secondary Objective Key Secondary Objective	To evaluate long term safety data (SAEs and AEs).

[redacted]

Protocol number	CAMN107A2409
Purpose and rationale	The purpose of this study is to better characterize long-term safety data nilotinib in patients who are on nilotinib treatment in a Novartis-sponsored, Oncology Global Development & Global Medical Affairs (OGD&GMA) study and are benefiting from the treatment as judged by the investigator.
Safety assessments	All adverse events and serious adverse events will be collected continuously throughout the study. 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). For the safe and effective use of Tasigna, medical monitoring should be performed as clinically indicated at the physician's discretion; this should also include monitoring of cardiovascular risk factors such as serum cholesterol and glucose levels amongst others.
Secondary Objectives	To evaluate clinical benefit as assessed by the investigator
Sponsor and Clinical Phase	Novartis, IV.
Study design	This is a multi-center, open label, phase IV study to better characterize the long-term safety of nilotinib to patients being treated in current Novartis-sponsored, Oncology OGD&GMA 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. At this time, a 3 month supply of nilotinib will be dispensed to the patient/or as per local practice. Patients must return to the study center on a quarterly basis (every 12 weeks +/- 1 week) for resupply of study medication at which time drug dispensing and adverse event information will be collected. The patient may return to the clinic at any given time as per standard of care, however, only data from the quarterly visits will be recorded. All adverse events and serious adverse events will be collected continuously throughout the study. 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). For the safe and effective use of Tasigna, medical monitoring should be performed as clinically indicated at the physician's discretion, 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 treatment for 10 years from First Patient First Visit, which occurred on 29-Mar-2013, until study treatment becomes commercially available and is reimbursed in the respective indication or until such time that enrolled patients no longer need treatment with nilotinib, whichever comes earlier. Should nilotinib not be commercially available to patients at end of study due to local regulations, Novartis will make every effort to ensure that patients benefiting from treatment continue to have access to nilotinib without interruption of treatment in accordance with local regulation.
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.

[redacted]

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 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 1983, Heisterkamp 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 2006, Frazer 2007). Tyrosine kinase inhibitors that inhibit BCR-ABL (TKIs) 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 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 2010, Saglio 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

[redacted]

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 overall survival of 57 months (Verweij 2004, Blanke 2008a, Blanke 2008b, Bertucci 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 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 Philadelphia chromosome positive (Ph+) chronic myeloid leukemia in chronic phase and accelerated phase 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.

[redacted]

1.2.1.1 Non-clinical experience

For information on pre-clinical toxicity please refer to the current nilotinib [Investigator 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 responses. A 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 ≤ 0.01% and ≤ 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].

[redacted]

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. Overall survival 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 chronic phase CML 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 median average daily dose of nilotinib for CML-CP patients was 788.5 mg. The most frequently reported (>10%) drug-related adverse events (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 severe adverse events (SAEs) were thrombocytopenia (3.4%), neutropenia (2.2%), angina pectoris (2.8%) and pyrexia (2.5%).

Adverse events 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 thrombocytemia (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 Newly diagnosed 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.

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

1.2.1.2.3 Clinical pharmacokinetics and pharmacodynamics

The relationship of systemic exposure (C_{max}, 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 C_{max} 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 C_{max} of nilotinib (t_{max}) 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 C_{max} 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 C_{max} by 60% and $AUC_{0-\infty}$ by 29%, but the t_{max} and $t_{1/2}$ 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.

[redacted]

2 Rationale

2.1 Study rationale and purpose

The purpose of this study is to better characterize the long-term safety of nilotinib in patients who are on nilotinib treatment in a Novartis-sponsored, Oncology Global Development & Global Medical Affairs (OGD&GMA) 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 of the parent study 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 a multi-center, open label, phase IV study to better characterize the long-term safety of nilotinib in patients being treated in a current Novartis-sponsored, Oncology OGD&GMA 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). Additional strengths of nilotinib can be provided if specified in the parent protocol. 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.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

2.6 Risks and benefits

Tasigna is a marketed drug since 2007. Tasigna has shown considerable efficacy for the indications of newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) in chronic phase (CP) and chronic phase and accelerated phase (AP), Ph+ CML in adult patients resistant to or intolerant to previous therapy including imatinib. Tasigna

[redacted]

has also shown considerable efficacy for resistant patients who have failed treatment with Glivec and in patients with newly diagnosed Ph+ CML (CP). Based on the results of clinical trials such as [CAMN107A2101] and [CAMN107A2303], nilotinib is approved worldwide in 130 countries.

Please refer to the latest nilotinib [Investigators' Brochure] for the known anticipated safety concerns of the study drug; dosage and administration; precautions and potential risks; and use in specific populations (including pregnancy, lactation and fertility, elderly, renal and hepatic impairment and overdosage). The subjects to be enrolled will be patients currently experiencing clinical benefit as attested by investigators to better characterize the long-term safety of the compound. These subjects will get the opportunity to continue to derive medical benefit from the treatment with nilotinib by participating in this study.

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, regular clinical monitoring and proactive dose modification and toxicity management.

In case patients do not tolerate the dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. Dosing should always be adjusted/discontinued if the physician determines it is in the best interest of the patient.

Patients will continue to be treated in the roll-over protocol until they are no longer benefiting from the nilotinib, 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 therapy, pregnancy occurs or the patient dies, whichever comes first. The study is expected to remain open for treatment for 10 years from First Patient First Visit, which occurred on 29-Mar-2013, until study treatment becomes commercially available and is reimbursed in the respective indication, or until such time that enrolled patients no longer need treatment with nilotinib, whichever comes earlier. Should nilotinib not be commercially available to patients at end of study due to local regulations, Novartis will make every effort to ensure that patients benefiting from treatment continue to have access to nilotinib without interruption of treatment in accordance with local regulation.

It is understood that doses and schedule of nilotinib treatment will be different for each patient (depending on the parent study).

There may be unforeseen risks with nilotinib which could be serious. Refer to the latest nilotinib [Investigator's Brochure].

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		Refer to Section 10.4
To evaluate long-term safety data (SAEs and AEs)	Frequency and severity of AEs/SAEs	
Secondary		Refer to Section 10.5.2
To evaluate clinical benefit as assessed by the investigator	Proportion of patients with clinical benefit as assessed by the investigator at scheduled visits	

[redacted]

4 Study design

4.1 Description of study design

This is a multi-center, open label, phase IV study to better characterize the long-term safety of nilotinib in patients being treated in current Novartis-sponsored, Oncology OGD&GMA studies and who are benefiting from treatment with nilotinib.

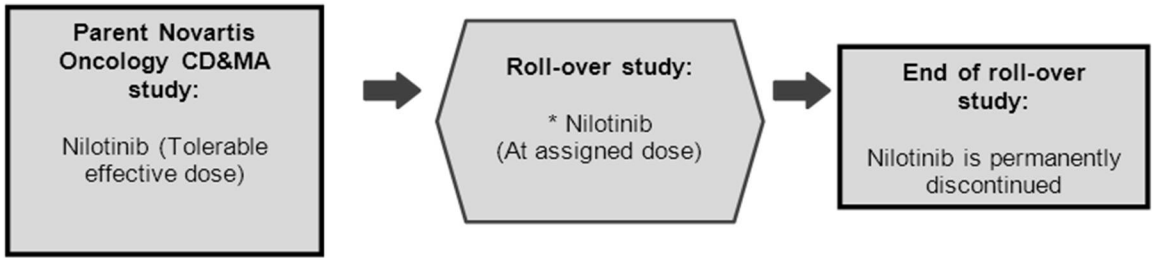
There will be no screening period for this study. At the enrollment visit the patient will be consented to the study and eligible patients will start their treatment with nilotinib. At this time, a 3 month supply of nilotinib will be dispensed to the patient/or as per local practice.

Patients must return to the study center on a quarterly basis (12 weeks +/- 1 week), for resupply of study medication at which time limited drug dispensing information will be collected. The patient may return to the clinic at any given time as per standard of care, however, only the quarterly visits will be recorded. All adverse events and serious adverse events will be collected throughout the study. For the safe and effective use of Tasigna, medical monitoring should be performed as clinically indicated at the physician's discretion; 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. At every quarterly visit (12 weeks +/- 1 week), the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

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 from First Patient First Visit, which occurred on 29-Mar-2013, until study treatment becomes commercially available and is reimbursed in the respective indication or until such time that enrolled patients no longer need treatment with nilotinib, whichever comes earlier. Should nilotinib not be commercially available to patients at end of study due to local regulations, Novartis will make every effort to ensure that patients benefiting from treatment continue to have access to nilotinib without interruption of treatment in accordance with local regulation.

Figure 4-1 Study design



[redacted]

4.2 Timing of interim analyses and design adaptations

No interim analyses are planned.

4.3 Definition of end of study

The end of study is defined as the date when all patients have completed their last assessment per protocol thirty days after end of treatment visit. The last assessment for each patient is the follow-up assessment that occurs 30 days after the patient's last dose of study treatment. Patients may continue on study treatment until one of the following criteria is met, whichever comes first:

- Discontinuation of study treatment per at least one of the premature patient withdrawal criteria are met (see Section 7.1.5 and Section 7.1.5.1)
- 10 years after the First Patient's First Visit into this clinical trial
- Study treatment becomes commercially available and is reimbursed in the respective indication.

Should nilotinib not be commercially available to patients at end of study due to local regulations, Novartis will make every effort to ensure that patients benefiting from treatment continue to have access to nilotinib without interruption of treatment in accordance with local regulation.

4.4 Early study termination

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, Oncology Clinical Development & Global Medical Affairs 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.

[redacted]

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 oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
    - In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

[redacted]

- 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 (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
- 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	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. Additional strengths of nilotinib can be provided if specified in the parent protocol. 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.

[redacted]

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 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, the patient dies, 10 years after First Patient First Visit into this clinical trial, or until study treatment becomes commercially available and reimbursed in the respective indication, whichever comes first. At every quarterly visit (12 weeks +/- 1 week), the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. A patient will reach the end of the roll-over study when nilotinib treatment is permanently discontinued.

6.2 Dose escalation guidelines

Not applicable.

6.2.1 Starting dose rationale

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.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For the purpose of these dose reduction guidelines, toxicity is defined as any adverse event (AE) which is, with reasonable likelihood according to investigator's judgment, caused by study drug.

[redacted]

According to International Conference on Harmonization (ICH) E6 the investigator is responsible for all trial-related medical decisions.

During and following a patient's participation in a trial, the investigator should ensure that adequate medical care is provided to a patient for any adverse events, including clinically significant laboratory values, related to the study drug.

If multiple dose-reducing toxicities are present, the greatest dose reduction schedule must be used.

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.

These changes must be recorded on the Dosage Administration Record CRF.

6.3.1.1 Dose reduction guidelines for study drug-related non-hematological toxicity and for ischemic vascular and cardiovascular events regardless of study drug relationship

A summary of dose reduction guidelines for study drug-related non-hematological toxicity and for ischemic vascular and cardiovascular events regardless of study drug relationship is presented in Table 6-2.

These guidelines provide general principles and recommendations intended to support the investigator's judgment and decisions about appropriate management of toxicity in the individual patient.

However, for those toxicities detailed in Table 6-2, the following rules (as detailed in the bullet points below) must be strictly followed:

- Any non-hematological toxicity Grade 3 or 4 must be resolved within 28 days to ≤ Grade 2 in order to resume study drug at the reduced dose. If a non-hematological toxicity Grade 3 or 4 does not resolve after 28 days, the patient must be discontinued from the study.
- If Grade 4 toxicity of the same type recurs despite nilotinib dose reduction to 400 mg QD the patient must be discontinued from the study.
- In case of Grade 3 pancreatitis, study drug treatment must be held and Novartis must be consulted immediately.
- In case of Grade 4 pancreatitis, study drug treatment must be permanently stopped and the patient must be discontinued from study.
- In case of Grade 4 liver toxicity, study drug treatment must be held and Novartis must be consulted immediately.
- In case of Grade 4 cardiac toxicity, study drug treatment must be permanently stopped and the patient must be discontinued from study.
- In case of recurrent QTcF prolongation to > 480 msec despite dose reduction the patient must be discontinued unless the reason for QTcF prolongation can be corrected (such as discontinuing or replacing of QT-prolonging concomitant drugs)

[redacted]

Table 6-2 Summary of nilotinib dose reduction guidelines for study drug-related non-hematologic toxicity and for ischemic vascular and cardiovascular events regardless of study drug relationship (adult patients)

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID) or Nilotinib 800 mg daily (as 400 mg BID)**
General non-hematological toxicity	
Grade 2 (persisting > 7 days with optimal supportive care)	The dose of nilotinib may be reduced to 400 mg QD at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient
≥ Grade 3	● Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen I→ 400 mg QD. ● If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. ● If Grade 4 toxicity recurs despite dose reduction to 400 mg QD I→ discontinue from the study.
Serum hypophosphatemia	
Grade 2-3	Continue nilotinib at 300 mg BID and start phosphate supplementation.
Grade 4	Hold study drug and consult Novartis.
Serum creatinine	
Grade 2 > 1.5 -3.0 x ULN	The dose of nilotinib may be reduced to 400 mg QD at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.
≥ Grade 3 ≥ 3.0 x ULN	● Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen I→ 400 mg QD. ● If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. ● If Grade 4 toxicity recurs despite dose reduction to 400 mg QD I→ discontinue from the study.
Hepato-biliary [bilirubin, SGPT (AST), SGOT (ALT)] **Note**: If hyperbilirubinemia is primarily due to the indirect bilirubin [with indirect bilirubin > direct bilirubin and direct bilirubin ≤ 1.5 x ULN and ALT ≤ Grade 1, AST ≤ Grade 1, ALP ≤ Grade 1, and hemolysis has been ruled out as per institutional guidelines (e.g. by determination of hepatoglobin)], nilotinib may be continued at the same dose, at the discretion of the investigator.	
Grade 2	The dose of nilotinib may be reduced to 400 mg QD at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.
≥ Grade 3	● Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen I→ 400 mg QD. ● If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. ● If Grade 4 toxicity recurs despite dose reduction to 400 mg QD I→ discontinue from the study.

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID) or Nilotinib 800 mg daily (as 400 mg BID)**
Combined elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT and AST and total) bilirubin value: • AST or ALT >3.0xULN combined with direct or total bilirubin >2.0 x ULN without evidence of cholestasis OR (Note to study team: If supported by available data) For patients with elevated baseline AST or ALT or total bilirubin value: • AST or ALT>2x baseline AND > 3.0 x ULN OR AST or ALT > 8.0 x ULN, combined with total bilirubin >2x baseline AND >2.0 x ULN	**Mandatory**: - Monitor for hemolysis. - If elevations of ALT and/or AST (>3.0 x ULN) and total bilirubin (>2.0 x ULN) without evidence of cholestasis[d] (ALKP < 2 x ULN) are observed simultaneously at the same visit: interrupt dose and monitor for hemolysis. If abnormality persists without evidence of hemolysis, permanently discontinue patient from study drug treatment. Recommendation: If elevations of direct or total bilirubin precede the elevations of ALT and or AST, monitor for hemolysis. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of liver function tests, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks.
Pancreatitis (with abdominal symptoms plus lipase elevation)	
Grade 2	● Hold study drug and perform abdominal CT with contrast to exclude pancreatic pathology. ● If CT is positive, continue to hold therapy and repeat CT, at investigator's discretion. ● If CT is negative, re-start nilotinib at 400 mg QD after recovery to ≤ Grade 1 is seen. ● If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. ● If toxicity recurs l→ discontinue from the study.
Grade 3	Hold study drug and consult Novartis.
Grade 4	Stop study drug. The patient must be discontinued from study.
Elevated lipase without symptoms	
≥ Grade 3	● Hold study drug. ● Re-start nilotinib at 400 mg QD after recovery to ≤ Grade 2 is seen. ● If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. ● If toxicity recurs without symptoms consider appropriate diagnostic procedures such as abdominal CT or ultrasound to exclude pancreatitis. After recovery to ≤ Grade 2, l→ continue dosing at 400 mg QD based on investigator's discretion.

[redacted]

Study drug and dose	Nilotinib 600 mg daily (as 300 mg BID) or Nilotinib 800 mg daily (as 400 mg BID)
Diarrhea **Note**: Anti-diarrheal medication is recommended at the first sign of loose stools or overt diarrhea. If diarrhea cannot be controlled with optimal anti-diarrheal treatments, take the following actions:	
≥ Grade 3	● Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen l→ 400 mg QD. ● If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study.
Vomiting **Note**: Antiemetic medication should be withheld until the patient experiences ≥ grade 1 vomiting then institute symptomatic therapy as appropriate. Antiemetics with the potential to prolong QT such as domperidone must be avoided. If nausea and vomiting cannot be controlled with optimal antiemetic treatment take the following actions:	
≥ Grade 3	● Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen l→ 400 mg QD. ● If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study.
Skin rash **Note**: Institute symptomatic therapy as appropriate. If skin rash does not resolve with optimal treatments, take the following actions:	
Grade 2	● The dose of nilotinib may be reduced to 400 mg QD at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.
≥ Grade 3	● Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen l→ 400 mg QD. ● If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. ● If Grade 4 toxicity recurs despite dose reduction to 400 mg QD l→ discontinue from the study.

[redacted]

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID) or Nilotinib 800 mg daily (as 400 mg BID)**
Cardiac QTc prolongation	
QTcF > 480 msec	● Hold study drug when an ECG with a QTcF > 480 msec. ● In addition to the procedures below, the investigator should follow their local standards of practice and treatment guidelines for treating prolonged QT intervals. ● Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. ● Concomitant medication usage must be reviewed for their potential to inhibit CYP3A4 and/or to prolong the QT-interval. ● Perform a repeat ECG within one hour of the first QTcF of > 480 msec. ● If QTcF remains > 480 msec, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 msec. ● Study drug may be restarted, at same dose, if reason for elevation of QTcF is identified and corrected so that QTcF returns to < 450 msec and to within 20 msec of baseline within 2 weeks. ● ECGs must be repeated 7 days after dose re-start for all patients who had therapy held due to QTcF > 480 msec. ● If the QTcF is repeated and is more than 20 msec greater than baseline or between 450 msec and 480 msec, the dose of study drug should be reduced to 400 mg QD. ● If QTcF of > 480 msec recurs, the patient is to be discontinued from the study. ● The investigator should contact Novartis regarding any questions that arise if a patient with QTcF prolongation should be maintained on study. ● **Note**: QTcB can be used in centers that do not have the ability to automatically measure QTcF for QTc prolongation. In patients with a heart rate lower than 60 per minute decisions are always based on QTcF because QTcB underestimates QT prolongation at heart rates below 60 per minute.
Study drug and dose	Nilotinib 600 mg daily (as 300 mg BID)
Ischemic vascular or cardiovascular events	
Grade 2*	● Hold study drug and refer patient for assessment by a vascular or cardiovascular specialist. ● Resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen l→ 400 mg QD. ● If another recurrence l→ discontinue from the study. ● If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Grade 3* or 4*	● Hold study drug and refer patient for assessment by a vascular or cardiovascular specialist. Consideration should be given for discontinuation from the study. The patient must be discontinued from the study if recovery to ≤ Grade 2 is greater than 28 days.
* Patient should be assessed for potential risk factors for the event including causality secondary to CML therapy.	
Cardiac "other"	
Grade 2 or Grade 3	● Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen l→ 400 mg QD. ● If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. ● If Grade 3 toxicity recurs despite dose reduction to 400 mg QD l→ discontinue from the study.
Grade 4	Stop study drug. The patient must be discontinued from the study.

[redacted]

6.3.1.2 Dose reduction guidelines for study drug-related hematological toxicity

A summary of dose reduction guidelines for ≥ Grade 3 study drug-related hematological toxicity for 300 mg BID or 400 mg BID dose is presented in Table 6-3. No dose adjustments should be made for Grade 1 or 2 hematologic toxicities. These guidelines provide some general principles as well as recommendations which are intended to support the investigator's judgment and decision about the appropriate management of toxicity in the individual patient. However, if a hematological toxicity does not resolve to ≤ Grade 2 within 28 days, the Novartis Clinical Trial Head must be consulted.

Table 6-3 Summary of dose reduction guidelines for study drug-related hematological toxicity

Study drug and dose	Nilotinib 600 mg daily (as 300 mg BID) or Nilotinib 800 mg daily (as 400 mg BID)
≥ Grade 3	Hold therapy and resume nilotinib at the full dose after recovery to ≤ Grade 2, if recovery occurs within 14 days If ≥ Grade 3 toxicity persists for 15-28 days or recurs, hold therapy and resume at next lower dose level after recovery to ≤ Grade 2: I→ 400 mg QD If recovery to ≤ Grade 2 is greater than 28 days, consult Novartis. If another recurrence is seen I→ discontinue.
Note: Dose of study drug need not be reduced or interrupted for hematological toxicity of Grade 2 or lower.	

When a patient on a dosage other than 300 mg BID or 400 mg BID experiences study drug-related Grade 3 or 4 hematologic toxicity, study dose will be held until the toxicity is resolved. If the toxicity does not resolve after 28 days of dose interruption, the patient must be discontinued from the study.

6.3.2 Dose reduction guidelines for study drug-related toxicity for pediatric patients

A summary of dose reduction guidelines for study drug-related toxicity for 230 mg/m^2 BID dosage is presented in Table 6-4.

[redacted]

Table 6-4 Recommended criteria for interruption and re-initiation of nilotinib for drug-related toxicities and for ischemic vascular and cardiovascular events regardless of study drug relationship

Worst toxicity NCI CTCAE grade	**During therapy**
No toxicity	**Maintain dose level**
Hematological - includes thrombocytopenia, neutropenia, leukopenia, and/or anemia	
Grade 1-2 Hematological	No dose interruptions or reductions
Grade 3-4 Hematological ● Note(1): No dose reductions will be performed for grade 3/4 anemia. If the patient develops anemia, s/he may be transfused at the discretion of the Investigator. ● Note(2) : Use of G-CSF and GM-CSF may be initiated with recurrent Grade 3 neutropenia after consulting with the sponsor. Refer to Section 6.3.2.5 for more details.	**First Occurrence:** 1. Hold nilotinib until recovery to grade ≤ 1. ● If recovery occurs within 2 weeks of the last day of dosing, resume nilotinib at the same daily dose. ● If recovery occurs more than 2 weeks but ≤ 4 weeks after the last day of dosing, resume nilotinib at: 2. 230 mg/m^2 once daily in AM or PM if prior dose was 230 mg/m^2 twice daily or contact Novartis if prior dose was 230 mg/m^2 once daily. **Second Occurrence:** 1. Hold nilotinib until recovery to grade ≤1. 2. Resume nilotinib at: 230 mg/m^2 once daily in AM or PM if prior dose was 230 mg/m^2 twice daily or contact Novartis if prior dose was 230 mg/m^2 once daily. If recovery to ≤ Grade 1 greater than 28 days, investigator will consult sponsor to define appropriate length of dosing reduction/interruption prior to discontinuation. The length of dose discontinuation should not exceed more than 2 months
Hepato- biliary	
Total bilirubin ≥ Grade 2 Note: If hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), , nilotinib may be continued at the same dose at the discretion of the Investigator.	**First Occurrence:** 1. Hold nilotinib until return to ≤ grade 1. 2. Resume nilotinib at: 230 mg/m^2 once daily in AM or PM if prior dose was 230 mg/m^2 twice daily or discontinue patient from the study if prior dose was 230 mg/m^2 once daily. **Second Occurrence:** Stop nilotinib and contact Novartis. If recovery to ≤ Grade 1 greater than 28 days, investigator will consult sponsor to define appropriate length of dosing reduction/interruption prior to discontinuation. The length of dose discontinuation should not exceed more than 2 months

[redacted]

Worst toxicity NCI CTCAE grade	**During therapy**
No toxicity	**Maintain dose level**
≥Grade 3 AST (SGOT) or ALT (SGPT)	**First Occurrence:** 1. Hold nilotinib until return to ≤ grade 1 (or baseline if disease related). 2. Resume nilotinib at: 230 mg/m^2 once daily in AM or PM if prior dose was 230 mg/m^2 twice daily or discontinue patient from the study if prior dose was 230 mg/m^2 once daily. **Second Occurrence:** Stop nilotinib and contact Novartis. If recovery to ≤ Grade 1 greater than 28 days, investigator will consult sponsor to define appropriate length of dosing reduction/interruption prior to discontinuation. The length of dose discontinuation should not exceed more than 2 months
Amylase and/or Lipase without symptoms ≥ Grade 3	**First Occurrence:** 1. Hold nilotinib until return to ≤ grade 1. 2. Abdominal CT with contrast to exclude pancreatic pathology. 3. Resume nilotinib at: 230 mg/m^2 once daily in AM or PM if prior dose was 230 mg/m^2 twice daily or contact Novartis if prior dose was 230 mg/m^2 once daily. **Second Occurrence:** Continue dosing, if asymptomatic and CT negative, at Investigator's discretion. If recovery to ≤ Grade 1 greater than 28 days, investigator will consult sponsor to define appropriate length of dosing reduction/interruption prior to discontinuation. The length of dose discontinuation should not exceed more than 2 months
Pancreatitis ≥ Grade 2 (abdominal symptoms with amylase and/or lipase elevation)	**First Occurrence:** 1. Hold nilotinib until return to ≤ grade 1 and perform abdominal CT. 2. If abdominal CT is negative, resume nilotinib when symptoms have resolved, with continued monitoring for recurrent symptoms at: 230 mg/m^2 once daily in AM or PM if prior dose was 230 mg/m^2 twice daily or discontinue patient from the study if prior dose was 230 mg/m^2 once daily. **Second Occurrence:** Stop nilotinib and discontinue patient from the study treatment. If recovery to ≤ Grade 1 greater than 28 days, investigator will consult sponsor to define appropriate length of dosing reduction/interruption prior to discontinuation. The length of dose discontinuation should not exceed more than 2 months

[redacted]

Worst toxicity **NCI CTCAE grade**	**During therapy**
No toxicity	**Maintain dose level**
Cardiac – QTc	
ECGs with a QTcF > 480 ms	1. In addition to the procedures below, the investigator should follow their local standards of practice and treatment guidelines for treating prolonged QT intervals. 2. Hold nilotinib when an ECG with a QTcF > 480 ms by automated reading is identified at the site. 3. Call the study's central ECG review laboratory immediately, request a manual read of ECG result and notify Novartis. 4. Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. 5. Perform a repeat ECG within one hour of the first QTcF of > 480 ms, and forward to the study's central ECG review laboratory for a manual reading. 6. If QTcF remains > 480 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms. 7. Nilotinib may be restarted at the same dose, if reason for elevation of QTcF is identified, corrected and QTcF returns to < 450 ms and to within 20 ms of baseline within 2 weeks. If QTcF is repeated and is more than 20 ms greater than baseline or between 450 ms and 480 ms the dose of nilotinib is to be reduced by half: ● 230 mg/m^2 once daily if prior dose was 230 mg/m^2 twice daily OR ● discontinue patient from treatment if prior dose was 230 mg/m^2 once daily. With resumption of nilotinib at the same or at a reduced dose after interruption of therapy due to QTcF > 480 ms, ECGs must be obtained on days 2, 3, and 8. 8. If QTcF > 480 ms recurs, stop nilotinib and contact Novartis. Forward all ECGs to the study's central ECG review laboratory. Any ECG with a QTcF >480 ms, not obtained by study provided ECG machine, must be forwarded by overnight delivery to the study's central ECG review laboratory. No dose re-escalation is allowed after dose reduction due to QTcF prolongation suspected to be related to nilotinib

[redacted]

Worst toxicity **NCI CTCAE grade**	**During therapy**
No toxicity	**Maintain dose level**
Ischemic cardiovascular events	
Grade 2*	**First Occurrence:** 1. Hold nilotinib and refer patient for assessment by a vascular or cardiovascular specialist. 2. Resume nilotinib at: 230 mg/m^2 once daily in AM or PM if prior dose was 230 mg/m^2 twice daily after recovery to ≤ Grade 1 is seen **Second Occurrence:** Stop nilotinib and contact Novartis If recovery to ≤ Grade 1 takes more than 28 days, the patient must be discontinued from the study.
Grade 3* or 4*	1. Hold therapy and refer patient for assessment by a vascular or cardiovascular specialist. 2. Consideration should be given for discontinuation from the study. 3. The patient must be discontinued from the study if recovery to ≤ Grade 2 takes more than 28 days
* Patient should be assessed for potential risk factors for the event including causality secondary to CML therapy	
Gastrointestinal	
Diarrhea Grade 3 or 4	**First Occurrence:** 1. Institute symptomatic therapy as appropriate. 2. If diarrhea cannot be controlled with optimal anti-diarrheal treatments, hold nilotinib until resolved to ≤ grade 1, then resume nilotinib at: 230 mg/m^2 once daily in AM or PM if prior dose was 230 mg/m^2 twice daily or discontinue patient from the treatment if prior dose was 230 mg/m^2 once daily. Anti-diarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea. **Second Occurrence:** If diarrhea cannot be controlled with optimal anti-diarrheal treatments, stop nilotinib and contact Novartis. If recovery to ≤ Grade 1 greater than 28 days, investigator will consult sponsor to define appropriate length of dosing reduction/interruption prior to discontinuation. The length of dose discontinuation should not exceed more than 2 months

[redacted]

Worst toxicity **NCI CTCAE grade**	**During therapy**
No toxicity	**Maintain dose level**
Vomiting Grade 3 or 4	**First Occurrence:** 1. Institute symptomatic therapy as appropriate. 2. If vomiting or nausea cannot be controlled with optimal antiemetic treatments, hold nilotinib until resolved to ≤ grade 1 then resume nilotinib at: 230 mg/m^2 once daily in AM or PM if prior dose was 230 mg/m^2 twice daily or discontinue patient from the treatment if prior dose was 230 mg/m^2 once daily. **Second Occurrence:** If vomiting or nausea cannot be controlled with optimal antiemetic treatments, stop nilotinib and contact Novartis. If recovery to ≤ Grade 1 greater than 28 days, investigator will consult sponsor to define appropriate length of dosing reduction/interruption prior to discontinuation. The length of dose discontinuation should not exceed more than 2 months
Dermatologic	
Skin rash Grade 2	**First Occurrence:** 1. Institute symptomatic therapy as appropriate. 2. If skin rash does not resolve with optimal treatments, hold nilotinib until resolved to ≤ grade 1, then resume nilotinib at the same daily dose. **Second Occurrence:** 1. Hold nilotinib instituting symptomatic therapy until recovery to grade ≤1. 2. Resume nilotinib at: 230 mg/m^2 once daily in AM or PM if prior dose was 230 mg/m^2 twice daily. If further recurrence, stop nilotinib and contact Novartis. If recovery to ≤ Grade 1 greater than 28 days, investigator will consult sponsor to define appropriate length of dosing reduction/interruption prior to discontinuation. The length of dose discontinuation should not exceed more than 2 months
Skin rash Grade 3 or 4	**First Occurrence:** 1. Hold nilotinib instituting symptomatic therapy as appropriate, until recovery to grade ≤ 1. 2. Resume nilotinib at: 230 mg/m^2 once daily in AM or PM if prior dose was 230 mg/m^2 twice daily. **Second Occurrence:** Stop nilotinib and contact Novartis. If recovery to ≤ Grade 1 greater than 28 days, investigator will consult sponsor to define appropriate length of dosing reduction/interruption prior to discontinuation. The length of dose discontinuation should not exceed more than 2 months

[redacted]

Worst toxicity **NCI CTCAE grade**	**During therapy**
No toxicity	**Maintain dose level**
Other clinically significant potentially treatment related adverse events	
Grade 3 or 4	**First Occurrence:** 1. Hold nilotinib instituting symptomatic therapy as appropriate, until recovery to grade ≤ 1. 2. Resume nilotinib at: 230 mg/m^2 once daily in AM or PM if prior dose was 230 mg/m^2 twice daily. **Second Occurrence:** Stop nilotinib and contact Novartis. If recovery to ≤ Grade 1 greater than 28 days, investigator will consult sponsor to define appropriate length of dosing reduction/interruption prior to discontinuation. The length of dose discontinuation should not exceed more than 2 months

[redacted]

Every attempt to re-escalate the dose of study treatment to the initial dose level should be made. This applies to dose reductions due to both hematological and non-hematological toxicities with the exception of dose reductions due to prolongation of QT interval. The dose should be re-escalated if the following criteria are met at least one month after dose reduction:

- All ≥ Grade 2 non-hematological toxicities have resolved to ≤ Grade 1
- All ≥ Grade 3 hematological toxicities have resolved to ≤ Grade 1
- Or alternatively, all ≥ Grade 3 hematological and non-hematological toxicities have resolved to ≤ Grade 2 and are manageable with supportive therapy

No dose re-escalations are allowed after dose reductions due to QTcF prolongation suspected to be related to nilotinib.

Investigators should refer to the approved local label for Tasigna as an additional resource. If no approved local label is available, the SmPC or USPI for Tasigna should be used.

All dosage changes must be recorded on the "Dosage Administration Record" CRF.

6.3.3 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.

6.3.4 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.

6.3.5 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.

6.3.6 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 Table 6-2 and Table 6-4 and the current nilotinib [Investigator's Brochure].

[redacted]

6.3.7 Hepatitis B reactivation

Hepatitis B virus testing should be performed during the study as indicated in Section 7.1 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 treatment. Carriers of hepatitis B virus who require treatment with nilotinib should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.

6.3.8 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 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 ($R \leq 2$), hepatocellular ($R \geq 5$), 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 testing 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 alkaline phosphatase.
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.

[redacted]

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.

6.4 Concomitant medications

6.4.1 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 I in Section 14.1). Should treatment with strong CYP3A4 inhibitors be required, it is recommended that therapy with nilotinib be interrupted if possible. Close monitoring of prolongation of the QT interval is indicated for patients who cannot avoid strong CYP3A4 inhibitors. 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 I in Section 14.1.

Every effort should be made NOT to administer strong CYP3A4 inhibitors CYP3A4 inhibitors may decrease the metabolism of nilotinib and thereby increase serum concentrations and increase exposure. If administration of a strong CYP3A4 inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy, study treatment must be STOPPED. Furthermore, increased awareness should be exercised when administering moderate inhibitors and/or multiple weak inhibitors. A list of these medications and inhibitor classifications can be found in Appendix 1; however, this list may not be comprehensive.

Every effort should be made NOT to administer strong CYP3A4 inducers **however, if** administration of a CYP3A4 inducer cannot be avoided during the study, temporary discontinuation of study treatment is NOT required. A list of these medications and inducer classifications can be found in Appendix 1, however, this list may not be comprehensive.

Antacid drugs:

Nilotinib has a pH-dependent solubility; therefore, in order not to impact nilotinib pharmacokinetics, administration of the following antacid 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

[redacted]

Drug with "Known risk of Torsades do Pointes," "Possible risk of Torsades de Pointes," or "Conditional risk of Torsades de Pointes":

Every effort should be made to avoid co-administering the study drug and drugs with a "Known risk of Torsades do Pointes," "Possible risk of Torsades de Pointes," or "Conditional risk of Torsades de Pointes" (as per https://crediblemeds.org/) during the course of the study:

- If concomitant administration of drugs with a "Known risk of Torsades de Pointes" is required and cannot be avoided, study drug must be interrupted. If, based on the investigator assessment and clinical need, study treatment is resumed, close ECG monitoring is advised.
- If during the course of the study, concomitant administration of a drug with "Possible risk" or "Conditional risk of Torsades de Pointes" is required, based on the investigator assessment and clinical need, study drug may be continued under close ECG monitoring to ensure patient safety.

A list of drugs associated with QT prolongation and/or Torsades de Pointes is available online

at https://crediblemeds.org/

All patients must avoid grapefruit, star fruit, pomegranate and Seville oranges during the study. The juices and products containing these fruits must also be avoided.

Cardiac Monitoring.

Cardiac monitoring is required upon re-initiation of nilotinib therapy at any point. An ECG must be obtained before the treatment re-initiation, 4 weeks after reinitiation and annually thereafter during nilotinib therapy. **A minimum washout period of 72 hours or longer is required (depending on the half-life of the CYP3A4 inhibitor or QT interval prolonging agent) prior to study drug re-initiation. Documentation will be kept in source document.**

6.4.2 Use of Bisphosphonates (or other concomitant agents)

Not applicable

6.5 Patient numbering, treatment assignment or randomization

6.5.1 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 through the Oracle Clinical RDC interface (OCRDC). Additionally an eCRF will be completed that identifies the patient by gender and date of birth and previous study, site/center and subject number.

[redacted]

6.5.2 Treatment assignment or randomization

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

6.5.3 Treatment blinding

Not applicable

6.6 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 eCRF.

Table 6-5 Preparation and dispensing

Study treatments	Dispensing	Preparation
Nilotinib	*Hard Gelatin Capsules (150mg and 200mg, additional strengths can be provided if specified in the parent protocol) 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.	Not applicable

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

6.6.1 Study treatment packaging and labeling

Nilotinib can be provided as local commercial material or global supply where appropriate and as per local regulations. Global supply will be as open label supply, packed and labeled under the responsibility of Novartis, Drug supply management. Study treatment labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient.

If nilotinib is sourced and labeled in-country, the locally-approved form and packaging of nilotinib will be used.

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 Brochure] for nilotinib dosing instructions and storage conditions.

[redacted]

Table 6-6 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
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.

6.6.2 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 6-7 Supply and storage of study treatments

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

6.6.3 Study drug compliance and accountability

6.6.3.1 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.

6.6.3.2 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.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 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 +/- 1 week is allowed. All data obtained from these assessments must be supported in the patient's source documentation.

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

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

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Reference Section	Enrollment	Quarterly (12 weeks +/- 1 week) visits during treatment phase	End of study treatment (EoT)	Safety Follow-up/End of study
Visit Number			**1**	**Visit 2,3,4 etc.**	**777**	778
Informed consent	D	7.1.2	x			
Patients' previous study, site and subject number	D	7.1.2.3	x			
Demography	D	7.1.2.3	x			
Relevant medical history/current medical conditions	D	7.1.2.3				
Inclusion/exclusion criteria	D	5.2 / 5.3.	x			
Nilotinib dosing	D	6.1.	x	X		
Pregnancy testing	D,S	7.1.4	x	Monthly (home)		x
Hepatitis screen	D	7.2.2.1		to be performed once and only once, at the next possible visit		
Confirmation of Clinical Benefit from Study Treatment	D	6.1.5	x	X	x	
Adverse events and serious adverse events	D	8.1 / 8.2.	Continuous			x
End of study treatment	D	7.1.5			x	
Study Evaluation Completion	D	7.1.5				x

[redacted]

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 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.

7.1.2.1 Eligibility screening

Not applicable.

7.1.2.2 Information to be collected on screening failures

Not applicable.

7.1.2.3 Patient demographics and other baseline characteristics

For patients that are eligible to participate in this roll-over study, the patients' gender, date of birth and previous study, site/center and subject number and relevant medical history will be collected.

7.1.3 Treatment period

The starting dose of nilotinib should be the same as the last dose that was given in the parent nilotinib study. A 3 month supply of nilotinib will be dispensed to the patient/or as per local practice.

Patients must return to the study center on a quarterly basis (12 weeks +/- 1 week), for resupply of study medication at which time limited drug dispensing and adverse event information will be collected. At every quarterly visit (12 weeks +/- 1 week), the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. At this time the dose of nilotinib is based on the investigator's judgment. The study is expected to remain open for 10 years from the First Patient First Visit in this clinical study, until study treatment becomes commercially available and is reimbursed in the respective indication or until such time that enrolled patients no longer need treatment with nilotinib, whichever comes earlier. Should nilotinib not be commercially available to patients at end of study due to local regulations, Novartis will make every effort to ensure that patients benefiting from treatment continue to have access to nilotinib without interruption of treatment in accordance with local regulation.

7.1.4 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/locally available or urine pregnancy test) before enrolling into the study.

[redacted]

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 oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

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/locally 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.)

7.1.5 Discontinuation of study treatment

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,the patient dies, 10 years after First Patient First Visit into this clinical trial or when study treatment becomes commercially available and reimbursed in the respective indication, whichever comes first. Should nilotinib not be commercially available to patients at end of study due to local regulations, Novartis will make every effort to ensure that patients benefiting from treatment continue to have access to nilotinib without interruption of treatment in accordance with local regulation. At the time the patient 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

[redacted]

reason for stopping the study treatment (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. The completion of the Study Evaluation Completion eCRF page will be required any time a patient discontinues from the study and must be completed 30 days after the end of 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 eCRF 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. Adverse event,
5. Disease progression,
6. Patient/guardian decision*,
7. Physician decision,
8. Patient is non-compliant to protocol requirements,
9. Protocol deviation,
10. Patient becomes pregnant*,
11. 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 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient

[redacted]

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

7.1.7 Follow up for safety evaluations

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 adverse events or serious adverse events (SAEs) 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.

Data collected should be added to the Adverse Events eCRF.

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

7.2.2 Safety and tolerability assessments

Safety will be monitored by collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 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 should have testing performed at the next possible visit in order to identify chronic carriers.

7.2.3 Pharmacokinetics

Not applicable.

7.2.3.1 Analytical method

Not applicable.

7.2.3.2 Additional biomarker assessments

Not applicable.

7.2.4 Resource utilization

Not applicable.

7.2.5 Patient reported outcomes

Not applicable.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event 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 informed consent constitute adverse events 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).

Any ongoing adverse events from the parent study will be captured as medical history in the roll-over database. Any AE that begins (or worsens) after signing of the informed consent for the roll-over and during the 30-day (or 28-day) safety follow up period defined in the parent protocol should be reported in both clinical databases.

[redacted]

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (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 Adverse Event.

Adverse events will be assessed according to the current version of Common Terminology Criteria for Adverse Events (CTCAE).

If CTCAE grading does not exist for an adverse event, 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 through the EOT eCRF page.

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

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (start and end dates)
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, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events 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 adverse event 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, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will

be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events 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 adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 events (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the [Investigator Brochure].

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].

[redacted]

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

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 serious adverse events:
    - 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 serious adverse event

8.2.2 Reporting

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

Any SAE that begins or worsens after signing of the informed consent for the roll-over and during the 30-day (or 28-day) safety follow up period defined in the parent protocol should be reported as an adverse event in both clinical databases; however, only one SAE report will be sent to Novartis.

- Any SAE that begins or worsens during the 30-day (or 28-day) safety follow up period specified in the parent study should have an SAE report submitted to Novartis with the parent protocol study number.
- Any SAE that begins or worsens after the 30-day (or 28-day) safety follow up period specified in the parent study should have an SAE report submitted to Novartis with the roll-over protocol study number.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes 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

[redacted]

interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

It is important to use the right SAE form with the correct protocol number for these two scenarios, to avoid confusion in SAE processing. For a patient already on the roll-over protocol but follow up information is reported for the previous SAEs in the parent protocol, it must be clearly labeled that this is for the parent protocol number.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

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 submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE 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 Drug Safety and Epidemiology (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 Drug Safety and Epidemiology (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 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 Brochure]. Additional safety information collected between [Investigator 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 AEs) 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

[redacted]

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 staff is 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.

[redacted]

10 Statistical methods and data analysis

10.1 Analysis sets

The following analysis sets will be used for statistical analysis and data reporting.

10.1.1 Full Analysis Set

Not applicable.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication after enrolling into the roll-over protocol.

10.1.3 Dose-determining analysis set

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data characteristics will be summarized descriptively for the Safety Set.

10.3 Treatments (study treatment, compliance)

Dose administration data will be summarized using the Safety Set.

10.4 Primary objective

The primary objective is to evaluate long term safety as assessed by the occurrence of AEs/SAEs.

10.4.1 Variable

See Section 10.5.3.

10.4.2 Statistical hypothesis, model, and method of analysis

No hypothesis will be tested.

10.4.3 Handling of missing values/censoring/discontinuations

Not applicable.

10.4.4 Supportive analyses

No supportive analysis will be performed.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

The secondary objective of the study was to evaluate clinical benefit as assessed by the investigator. Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits.

[redacted]

10.5.3 Safety objectives

The assessment of safety will be based mainly on the frequency of AEs and SAEs.

10.5.3.1 Analysis set and grouping for the analyses

The overall observation period will be divided into two mutually exclusive segments:

1. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
2. post-treatment period: starting at day 30+1 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

Summary tables of adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the post-treatment periods) will be listed and those collected during the post treatment period are to be flagged.

The incidence of treatment emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

10.5.3.3 Other safety data

Not applicable.

10.5.3.4 Tolerability

Not applicable.

10.6 Interim analysis

Not applicable.

10.7 Sample size calculation

Not applicable.

10.8 Power for analysis of key secondary variables

Not applicable.

[redacted]

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 CRFs.

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.

Additional consent form

Not applicable.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

[redacted]

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

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, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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.

[redacted]

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.

[redacted]

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14 Appendices

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

A list of drugs that are inducers and inhibitors and substrates of CYP3A4 is provided below. Patients should be instructed not to take grapefruit, star fruit, pomegranate, 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, inducers and substrates may be found at http://medicine.iupui.edu/flockhart.

Table 14-1 Medications that can induce CYP3A4

Category	Drug Names
Strong inducers of CYP3A4[1]	avasimibe, carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John's wort (*Hypericum perforatum*)[4]
Moderate inducers of CYP3A4[2]	bosentan, dabrafenib, efavirenz, etravirine, genistein[5], lersivirine , lopinavir, modafinil, nafcillin, semagacestat[6], talviraline[6], telotristat, thioridazine, tipranavir/ritonavir
Weak inducers of CYP3A4[3]	amprenavir, aprepitant, armodafinil, artesunate/mefloquine, bexarotene, boceprevir, brivacetam, clobazam, danshen (*Salvia miltiorrhiza*)[4], dexamethasone, echinacea (*Echinacea purpurea*)[1], elvitegravir-cobicistat-emtricitabine-tenofovir (Stribild), eslicarbazepine, ginkgo (*Ginkgo biloba*)[4], ginseng[4], glycyrrhizin[5], isavuconazole, lesinurad, methylprednisolone, nevirapine, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), oritavancin, oxcarbazepine, pioglitazone, pleconaril, prednisone, pretomanib, primidone, quercetin[5], raltegravir, ritonavir, rufinamide, sarilumab, sirukumab, sorafenib, sulfinpyrazone, telaprevir, terbinafine, ticagrelor, ticlopidine, topiramate, troglitazone[6], vemurafenib, vicriviroc/ritonavir, vinblastine, yin zhi huang[4]

[1] A strong inducer for a specific CYP is defined as an inducer that decreases the AUC of a sensitive substrate for that CYP by equal or more than 80%.

[2] A moderate inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 50-80%.

[3] A weak inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 20-50%.

[4] Herbal product

[5] Food product

[6] Drugs not available on US market

This list was based on information from the FDA's "Guidance for Industry, Drug Interaction Studies", from the Indiana University School of Medicine's "Clinically Relevant" Table, from 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 January 2018) for update or more details.

[redacted]

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.

Category	Drug Names
Strong inhibitors of CYP3A4[1]	atazanavir/ritonavir[7], boceprevir, cobicistat, conivaptan, clarithromycin, danoprevir/ritonavir[7], darunavir/ritonavir[7], elvitegravir/ritonavir[7], grapefruit juice[6], idelalisib, indinavir, indinavir/ritonavir[7], itraconazole, ketoconazole, lopinavir/ritonavir[7], mibefradil, nefazodone, nelfinavir, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[7], posaconazole, ritonavir, saquinavir/ritonavir[7],, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir[7], troleandomycin, , voriconazol
Moderate inhibitors of CYP3A4[2]	aprepitant, amprenavir, asafoetida resin (*Ferula asafoetida*)[4], atazanavir, cimetidine, casopitant, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, grapefruit juice[6], imatinib, isavuconazole, netupitant, nilotinib, *Schisandra sphenanthera* (nan wu wei zi)[4], tofisopam, verapamil
Weak inhibitors of CYP3A4[3]	almorexant, alprazolam, amiodarone, amlodipine, atorvastatin, azithromycin, berberine[4], bicalutamide, blueberry juice[8], brodalumab, chlorzoxazone, cilostazol, clotrimazole, cranberry juice[8], daclatasvir, delavirdine, evacetrapib, everolimus, flibanserin, fluvoxamine, fosaprepitant (IV), fostamatinib, garden cress seeds (*Lepidium sativum*)[5], ginkgo (*Ginkgo biloba*)[4], goldenseal (*Hydrastis canadensis*)[4], grazoprevir, guan mai ning[4], isoniazid, ivacaftor, lacidipine, linagliptin, lomitapide, obeticholic acid, oral contraceptives, palbociclib, pazopanib, peppermint oil[5], piperine[5], pomelo (*Citrus grandis*)[5], propiverine, ranitidine, ranolazine, resveratrol[4], roxithromycin, Seville orange juice[5], simeprevir, sitaxentan, suvorexant, tabimorelin, tacrolimus, teriflunomide, ticagrelor, tolvaptan, tong xin luo[4]

[1] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by equal or more than 5-fold.

[2] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

[3] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-foldbut equal to or more than 1.25-fold.

[4] Herbal product

[5] Food product

[6] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

[7] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database.

[8] The effect of certain fruit juices varies widely among brands and is concentration-, dose-, and preparation-dependent.

This list is based on information from the FDA's "Guidance for Industry, Drug Interaction Studies", from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database. Please note that this is not an exhaustive list. Please refer to footnotes. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated January 2018) for update or more details.

[redacted]

Table 14-3 CYP3A4 substrates: Narrow therapeutic index, sensitive, and others.

Category	Drug Names
Narrow Therapeutic index substrates of CYP3A4[1]	alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfanadine, thioridazine
Sensitive substrates of CYP3A4[2]	alfentanil, alpha-dihydroergocryptine, almorexant , alisoporivir, aplaviroc, aprepitant, atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, cobimetinib, conivaptan, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutinib, indinavir, isavuconazole, ivabradine, ivacaftor, levomethadyl (LAAM), lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, paritaprevir, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, tacrolimus, terfenadine, ticagrelor, tilidine, tipranavir, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin
Other Substrates of CYP3A4[3]	alprazolam, ambrisentan, amlodipine, antipyrine, aripiprazole, artemether, avosentan, boceprevir, bosentan, buprenorphine, *Cannabis sativa*[4], carbamazepine, dexloxiglumide, dextromethorphan, diazepam, docetaxel, enzalutamide, gemigliptin, halofantrine, imipramine, lansoprazole, lidocaine, linagliptin, loperamide, loratadine, losartan, lurasidone, macitentan, methadone, mirodenafil, montelukast, morphine, nelfinavir, netupitant, nevirapine, nifedipine, nilotinib, nitrendipine, omeprazole, ospemifene, oxycodone, paclitaxel, pazopanib, pioglitazone, quinine, ranolazine, repaglinide, rifabutin, ritonavir, roflumilast, saxagliptin, selegiline, sertraline, sibutramine, sotrastaurin, telaprevir, theophylline, tirilazad, tolterodine, udenafil, vincristine, voriconazole

[1] Narrow therapeutic index substrates are drugs whose exposure-response relationship indicates that increases in their exposure levels by the concomitant use of an inhibitor may lead to serious safety concerns or drugs which have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood (thus safe and effective use requires careful dosage titration and patient monitoring).

[2] Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.

[3]Other substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.

[4]Tetrahydrocannabinol (∆9THC) and cannabidiol (CBD) are major constituents. ∆9THC is primarily metabolized by CYP2C9 to an active metabolite 11-hydroxy-∆9-THC (11-OH-THC). CBD is extensively metabolized by CYP2C19 and CYP3A4 to eight monohydroxylated metabolites. The effects of multiple daily doses of rifampicin 600 mg for 10 days, ketoconazole 400 mg for 6 days and omeprazole 40 mg for 6 days on the PK of ∆9THC, 11-OH-THC and CBD after a single dose (4 sprays) of an oromucosal spray were determined in a randomized, crossover, parallel study in three groups of 12 male subjects. Ketoconazole increased the Cmax and AUC0-24 of ∆9THC by 1.2- and 1.8-fold, respectively, increased the Cmax and AUC0-24 of 11-OH-THC by 3.0- and 2.6-fold, respectively, and increased the Cmax and AUC0-24 of CBD by 2- and 2-fold, respectively. Rifampicin decreased the Cmax and AUC24 of ∆9THC by 40 and 20%, respectively, decreased the Cmax and AUC0-24 of 11-OH-THC by 85 and 87%, respectively, and decreased the Cmax and AUC24 of CBD by 50 and 60%, respectively. There were no effects of omeprazole on the plasma concentrations of all three cannabis constituents.

This list of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from 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 January 2018) for update or more details.

[redacted]

Guidance on QT prolongation agents

A list of drugs associated with QT prolongation and/or Torsades de Pointes is available online at https://crediblemeds.org/

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