NOVARTIS

Clinical Development

AMN107 (Nilotinib, Tasigna)

Protocol Synopsis CAMN107ECN02E1 / NCT02272777

An open-label multi-center study of imatinib and nilotinib in CAMN107ECN02 on-treatment patients with Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase after the end of CAMN107ECN02 core study （ENESTChina extension study）

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List of abbreviations

AE	Adverse Event
AP	Accelerated Phase
BC	Blast Crisis
BID	Twice a day
CDS	Core Data Sheet
CP	Chronic Phase
CRF	Case Report/Record Form
CRO	Contract Research Organization
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
GPP	Good Pharmacoepidemiology Practices
IEC	Independent Ethics Committee
IN	Investigator Notification
IRB	Institutional Review Board
QD	Once a day
REB	Research Ethics Board
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
WHO	World Health Organization

Protocol number	CAMN107ECN02E1
Title	An open-label multi-center study of imatinib and nilotinib in CAMN107ECN02 on-treatment patients with Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase after the end of CAMN107ECN02 core study（ENESTChina extension study）
Brief title	Study of imatinib and nilotinib in CAMN107ECN02 on treatment patients with CML-CP (ENESTChina extension study）
Sponsor and Clinical Phase	Novartis, IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	In the core study CAMN107ECN02, 267 patients were 1:1 randomized to receive imatinib or nilotinib treatment. Per protocol of CAMN107ECN02, patients can have at least 3 calendar years treatment and will complete all the treatment in CAMN107ECN02 this year. By 24 months, 86.5% of patients in imatinib arm and 86.3% in nilotinib arm achieved complete cytogenetic response (CCyR). At 24 month, 48.9% patients in imatinib arm and 61.2% in nilotinib arm achieved major molecular response (MMR). Both treatments showed good safety profile in CAMN107ECN02. Patients in CAMN107ECN02 may need continuous treatment when they complete the core study. Protocol of CAMN107ECN02 mentioned offering possibility of extended treatment to patients who derive benefit from the study treatment, in the opinion of the investigator at the end of study CAMN107ECN02. Therefore, extension study of CAMN107ECN02 is necessary. Nilotinib has not yet been approved for treatment of newly diagnosed CML-CP in China. The purpose of this extension study is to provide extended nilotinib treatment to patients in nilotinib arm of CAMN107ECN02. To cover the promise and insure the same right to the patients in imatinib arm, extended imatinib treatment will also be provided.
Primary Objective(s) and Key Secondary Objective	To assess safety of nilotinib and imatinib in newly diagnosed Ph+ CML-CP.
Secondary Objectives	Not applicable
Study design	The extension study follows the core study CAMN107ECN02, which is an open-label, two armed study. All patients enrolled in this

	extension study should be able to benefit from the treatment given in CAMN107ECN02 per investigator's evaluation. Therefore, in this extension study patient will continue treatment of the drug (imatinib or nilotinib) which they are taking at the end of CAMN107ECN02. Treatment arms in CAMN107ECN02 will be retained. As long as we get EC approval and agreement from investigators, the selected sites for CAMN107ECN02 will be applied in this extension study. Patients will be enrolled after eligibility evaluation. During the study, follow-up visits at a frequency of 6 months are required referring to the core study and recommendation in Chinese CML guideline. No data collection plan is included in this extension study except safety data. Investigator will be asked to report AE, SAE and pregnancy in order to ensure compliance with pharmacovigilance requirement. AE&SAE information will be recorded in CRF and included in clinical database. In addition, SAE and pregnancy will be reported to Novartis safety database. The extension study will start from first patient last dose date in CAMN107ECN02 and end at the time of nilotinib first line treatment commercially available in China.
Population	The patients who can continue to derive benefit from the study treatment that he/she takes in CAMN107ECN02, in the opinion of the investigator, at the end of the core study can be enrolled in this extension study. 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. Up to 230 patients will be enrolled.
Inclusion criteria	Patients eligible for inclusion in this extension phase have to meet all of the following criteria: 1. Patient is currently on treatment in the core study CAMN107ECN02 2. Patient who continues to derive benefit more than risk from the study treatment he/she takes in CAMN107ECN02, in the opinion of the investigator at the end of the study 3. Written informed consent must be obtained prior to enrolling in the extension study
Exclusion criteria	Patients eligible for this extension phase must not meet any of the following criteria: 1. Progression to CML-AP or BC 2. Patient whose treatment assigned in CAMN107ECN02 is not appropriate any longer, per investigator's assessment.

	3. History of non-compliance to medical regimens, or patients who are considered potentially unreliable and/or not cooperative. 4. Women who are (a) pregnant and(b) women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and at least 14 days after last dose of study medication. Highly effective contraception methods include: • 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 screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject. • Combination of any two of the following (a+b or a+c, or b+c): a) Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. b) Placement of an intrauterine device (IUD) or intrauterine system (IUS) c) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository 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.
Investigational and reference therapy	Nilotinib (300mg BID，400mg QD) and imatinib（recommended on 600mg QD，400mg QD and 300mg QD）
Efficacy assessments	Not to be collected
Safety assessments	Safety will be monitored by collecting of the adverse events at every

	visit.
Other assessments	Not applicable
Data analysis	In this study, safety data will be descriptively summarized, and all data collected will be listed. Categorical data will be presented as frequencies and percentages.
Key words	ENESTChina extension study, nilotinib, imatinib, Philadelphia chromosome positive chronic myelogenous leukemia

Amendment 1

This amendment mainly aims to change CAMN107ECN02E1 from a drug supply program to a study. Primary objective and endpoint which is related to AE&SAE is added. Requirement of collecting AE/SAE data and summary statistics plan is added to serve the objective. Exclude criteria is revised to exclude woman who is pregnant or who is with child bearing potential without highly effective methods of contraception. Dosage adjustment, patient assessment and mandatory criteria of premature discontinuation due to safety are clarified. In addition, there are also a lot of changes or reorganization due to change of protocol template.

Change to the protocol

Except revision and reorganization due to template change, other changes related to content are listed below：

Section 1 Background

- Detailed background information of study drug is added including safety and efficacy summary

Section 2 Rationale

- Clarify that the study is extension study of the core study CAMN107ECN02

Section 2.2 Rationale for the study design

- Add the AE&SAE data collection plan

Section 3 Objectives and endpoint

- Add objective and endpoint of the study to assess safety.

Section 4.1 Description of study design

- Clarify required follow up visit frequency of 6 months
- Clarify safety data will be collected on CRF besides requirement of reporting SAE/pregnancy to Novartis safety database.

Section 4.4 Early study termination

- Add process for early study termination

Section 5 Population

- Move the criterion about compliance from inclusion criteria to exclusion criteria.
- Add an exclusion criterion to exclude pregnant women and women of child bearing potential.

Section 6.1 Study treatment

- Clarified starting dose.
- Add instruction of nilotinib and imatinib administration

Section 6.3.1 Dose modification and dose delay

- Add dose modification guideline
- Add suggested management of cholesterol increase, glucose increase, other cardiac risk factor, ischemic vascular or cardiovascular events.
- Add guideline for toxicity follow up

Section 6.4 Concomitant medication

- Add this section to avoid concomitant medication with risk of drug-drug interaction with study drug.

Section 6.5 Patient numbering, treatment assignment or randomization

- Add this section to specify how to number patient in this study.

Section 6.6 Study drug preparation and dispensation

- Remove the not applicable drug request process.
- Clarify the requirement of recording of study drug compliance and accountability

Section 7 visit schedule and assessments

- Add mandatory scheduled visit and content of every visit
- Add requirement of monthly urine pregnancy test at home.
- Clarify enrollment process

Section 7.1.5 End of the treatment visit including study completion and premature withdrawal

- Revise reason list of patient withdraw

Section 7.1.6 Follow up period

- Clarify that there is only one follow up visit and it can be done via phone.

Section 8 Safety monitoring and reporting

- Delete the requirement of non-serious to Novartis DS&E via AE report form, because CAMN107ECN02E1 follows safety reporting requirement of interventional study.

Section 9 Data collection and management

- Rewrite this section to meet requirement of data management and collection for study.

- Add the plan of site monitoring because CAMN107ECN02E1 is study.

Section 10 Statistical methods and data analysis

- Add a descriptive summary plan at the end of the study. Some details of analysis plan is provided.

Section 11 Ethical consideration and administrative procedures

- Add this section to clarify administrative procedures including responsibility of investigator and IRB/IEC/REB, informed consent, study documentation, record keeping, audit.

Section 14 Appendix

- Provide a list of CYP3A4 inducer and inhibitor.

1 Background

Imatinib, the first BCR-ABL kinase inhibitor has been approved as treatment of newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) in many countries including China.

Nilotinib is a second-generation inhibitor of BCR-ABL, with a similar mechanism of action to imatinib, but with greater binding affinity for wild-type BCR-ABL kinase and improved target selectivity. The efficacy of nilotinib compared to imatinib and its overall positive benefit/risk ratio for the treatment of patients with newly diagnosed CML-CP was established in the pivotal study CAMN107A2303. Tasigna (nilotinib) has been approved for the treatment of patients with newly diagnosed Ph+ CML-CP in 99 countries.

In 2010, Novartis initiated Chinese registration study CAMN107ECN02 (ENESTChina). In the core study, 267 Chinese adult patients with newly diagnosed Ph+ CML in chronic phase (CP) were enrolled. This study is extension study of CAMN107ECN02.

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Chronic myelogenous leukemia (CML) is a hematological stem cell disorder associated with a specific chromosomal translocation resulting in the Philadelphia (Ph) chromosome detected in 95% of patients (Nowell and Hungerford 1960, Rowley 1973). The molecular consequence of the translocation is the fusion of the Abl proto-oncogene to the Bcr gene resulting in the production of an activated form of the Abl protein-tyrosine kinase (Bartram, et al 1983, Heisterkamp, et al 1983). Expression of the BCR-ABL protein is capable of inducing leukemias in mice, implicating the protein as the cause of these diseases (Daley, et al 1990, Kelliher, et al 1990). Clinically, CML progresses through three distinct phases of increasing refractoriness to therapy: chronic phase (median duration 3-4 years; median survival up to 10 years with allogeneic bone marrow transplant and 5-6 years with interferon), accelerated phase (median duration 3-9 months; median survival 8-18 months), and blast crisis (median survival 3-6 months) (Enright and McGlave 2000). Most patients however present in the chronic phase, characterized by splenomegaly and leukocytosis with generally few symptoms. The following sections will review response criteria and summarize the clinical trial.

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

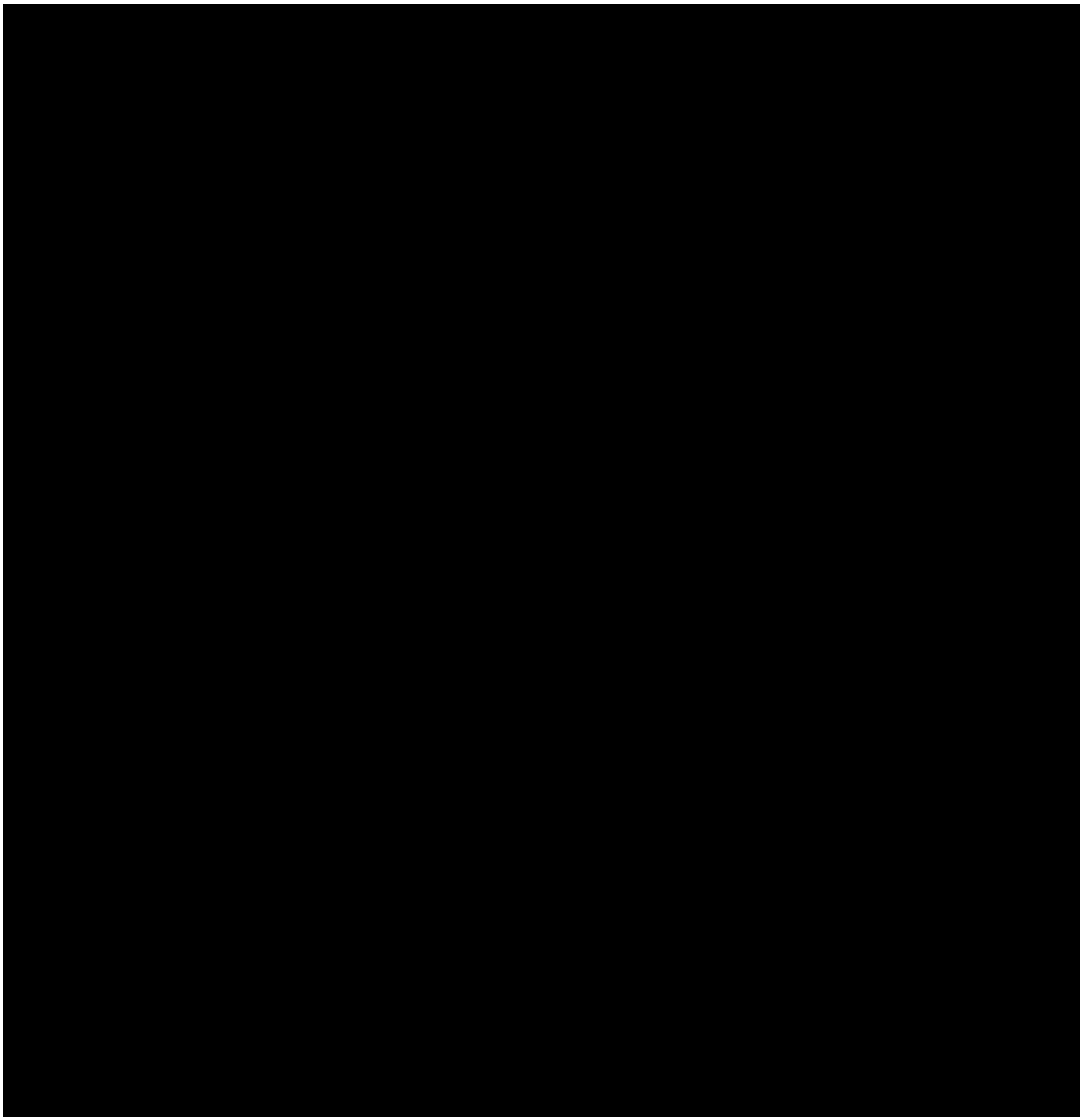
1.2.1 Overview of nilotinib

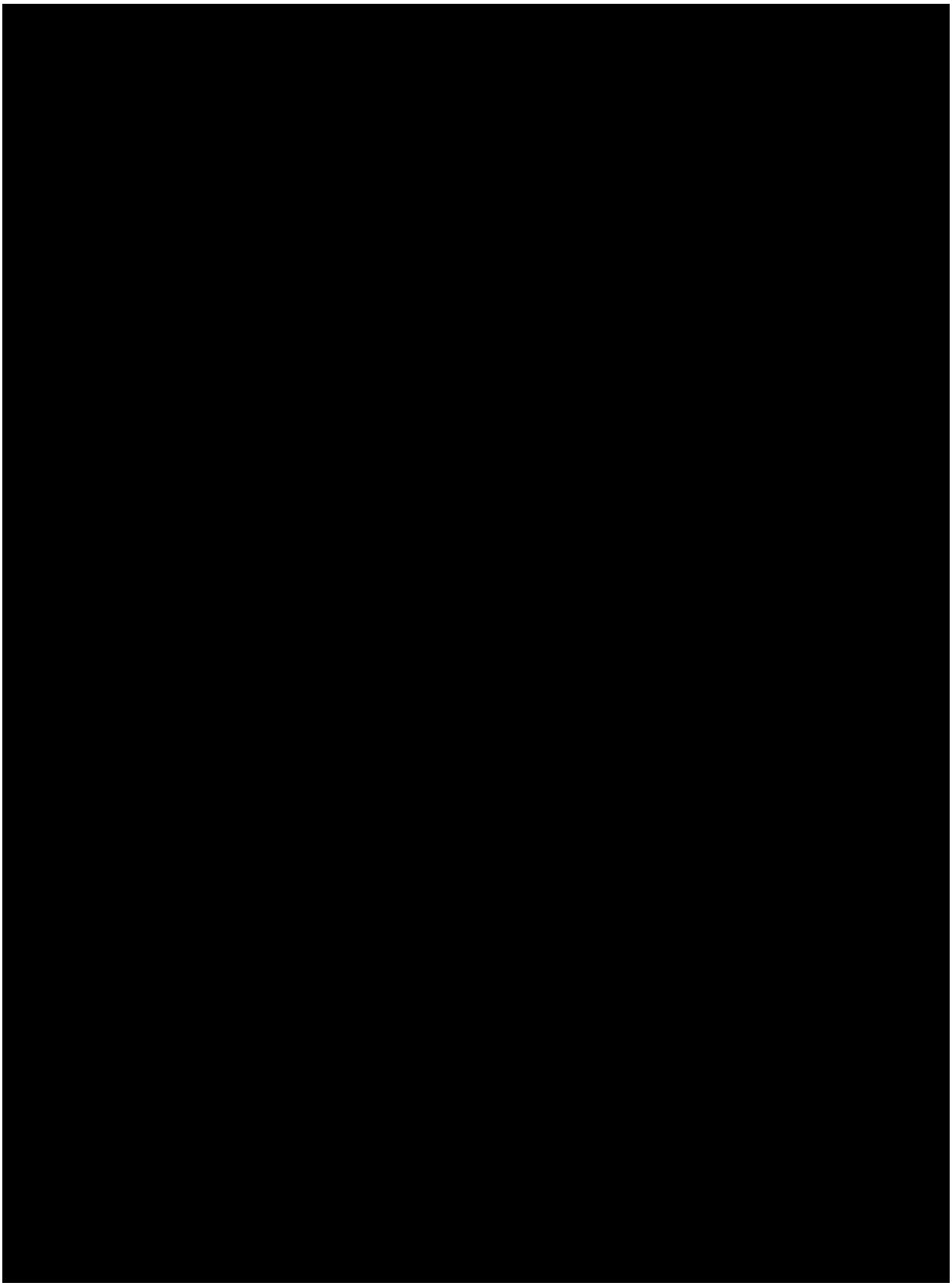
Nilotinib is a novel aminopyrimidine, available as an oral formulation that is an ATP competitive inhibitor of the protein tyrosine kinase activity of BCR-ABL, which prevents the activation of BCR-ABL dependent mitogenic and anti-apoptotic pathways (e.g. PI-3 kinase and STAT5), leading to the death of the BCR-ABL phenotype. Nilotinib also inhibits other oncogenic kinases including the FIP1L1-PDGFRA tyrosine kinase, which is often associated with hypereosinophilic syndrome and chronic eosinophilic leukemia, and the stem cell factor receptor c-Kit tyrosine kinase, which is associated with systemic mastocytosis and gastrointestinal stromal tumors. Following oral administration to animals, nilotinib is moderately absorbed with approximately 30% bioavailability, and is well tolerated.

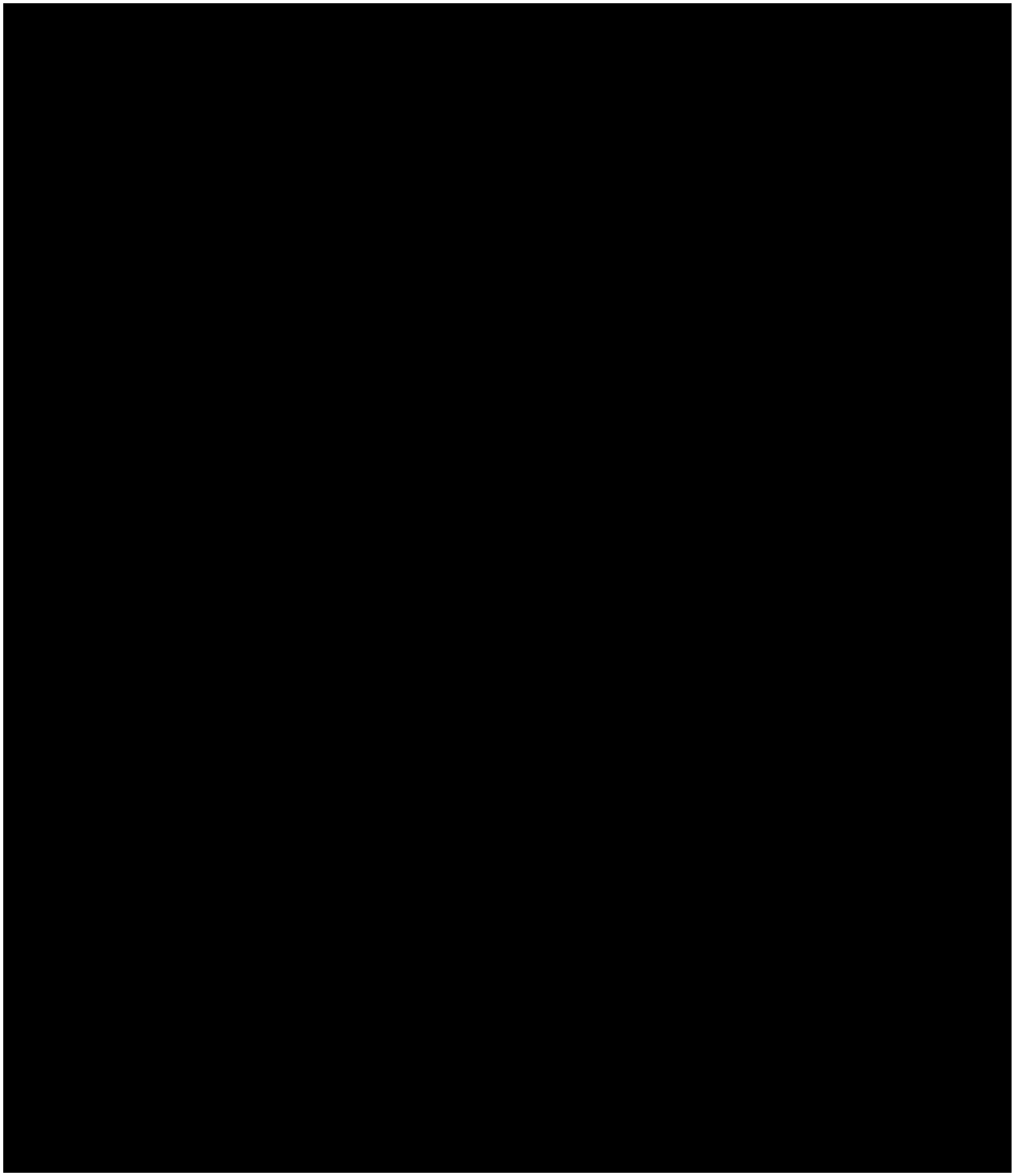
Data from preclinical studies demonstrate that nilotinib achieves higher intracellular concentrations than Gleevec/Glivec, and that nilotinib inhibits BCR-ABL tyrosine kinase activity and induces apoptosis at lower concentrations than Gleevec/Glivec (Le Coutre 2004, White 2005). In addition, two investigator-initiated trials with nilotinib 400 mg BID in newly diagnosed chronic phase Ph+ CML are ongoing. These pilot studies and the ongoing phase III study ENESTnd are described below.

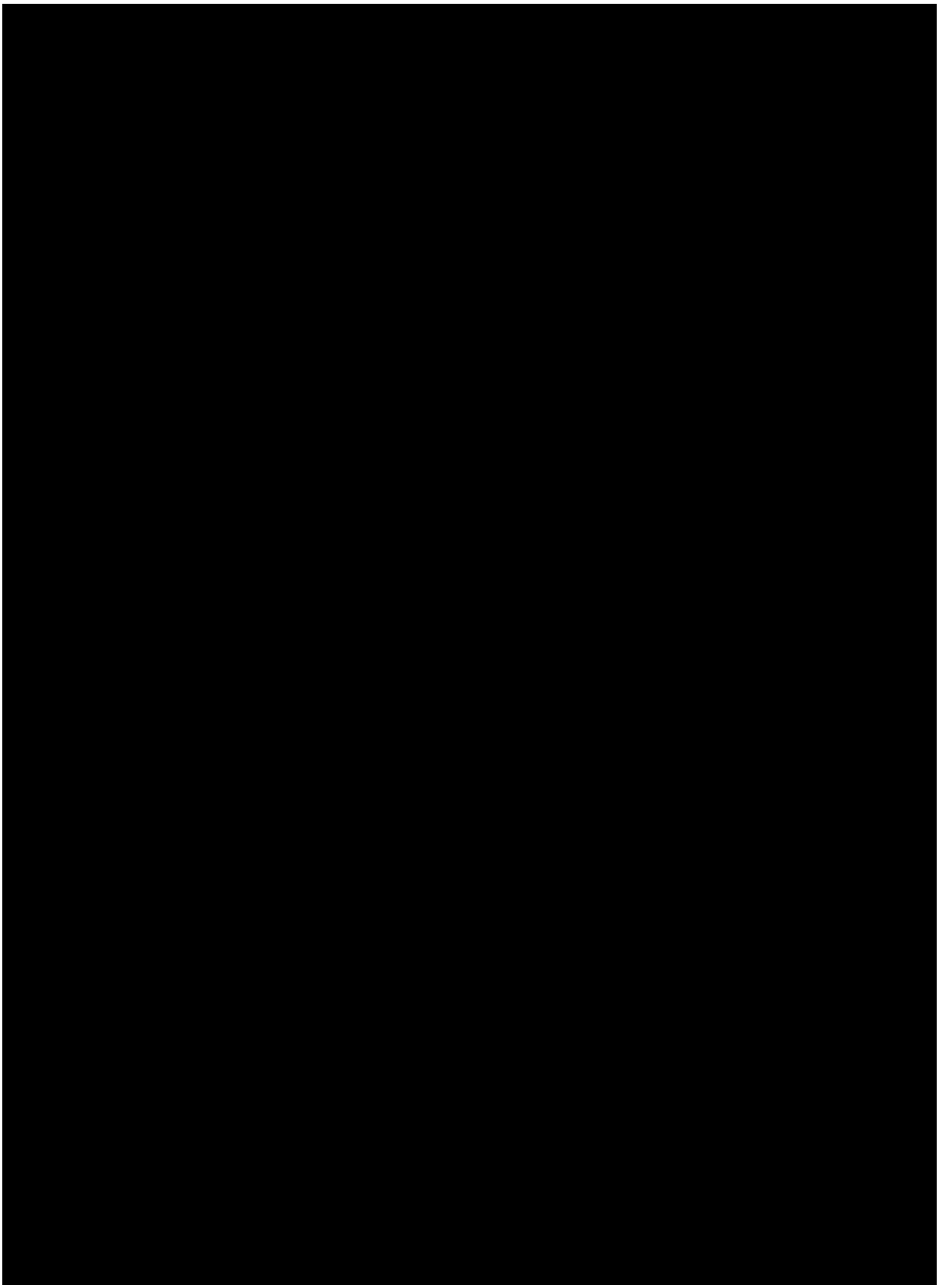
1.2.1.1 Non-clinical experience

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









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1.2.2 Over view of imatinib

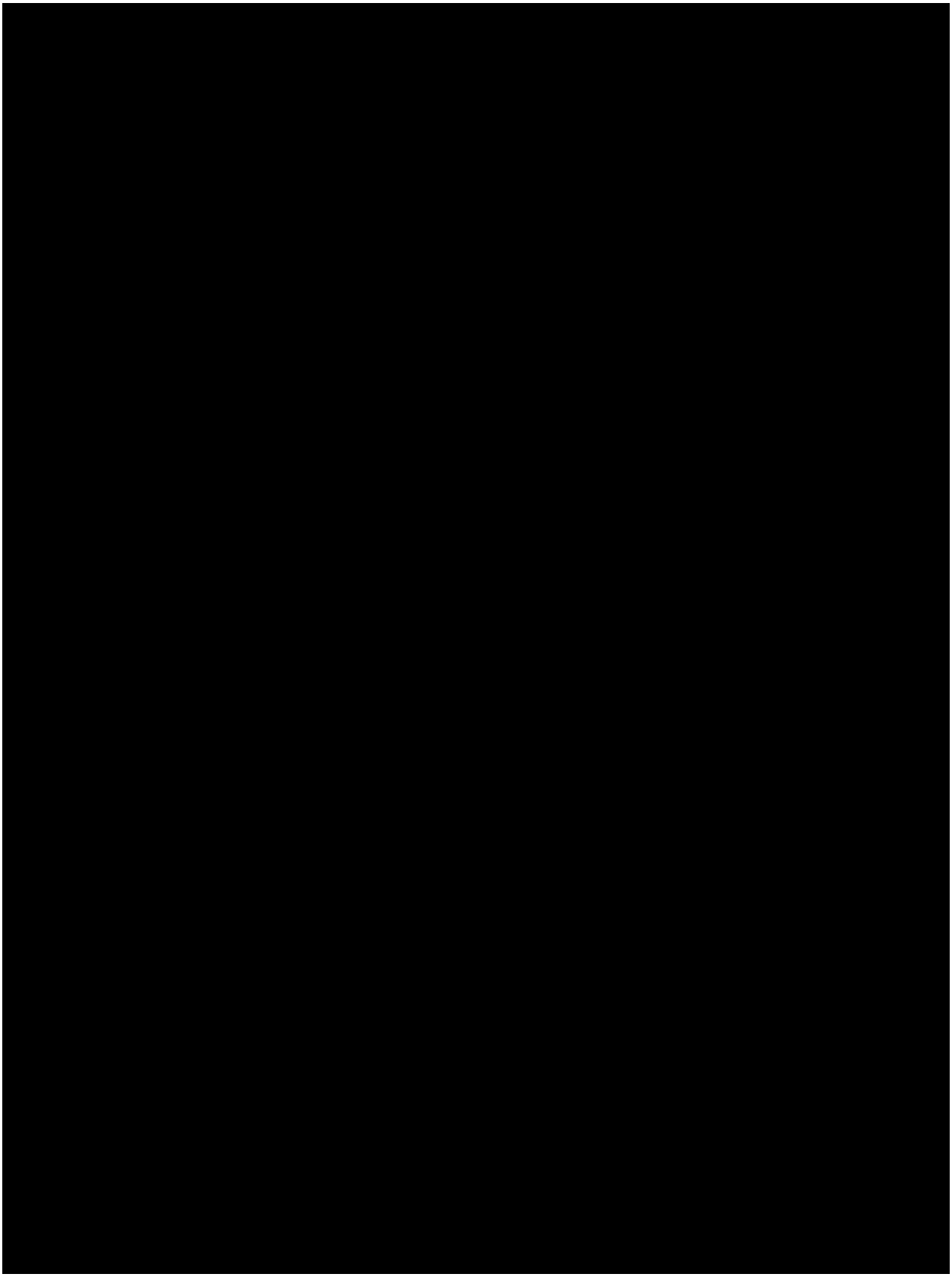
Imatinib mesylate (Gleevec/Glivec) is a protein-tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase, the constitutively active tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces apoptosis in BCR-ABL positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive (Ph+) chronic myeloid leukemia. Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events. Imatinib is currently approved in most countries throughout the world. Imatinib was originally approved by the FDA in May 2001 and by the European Commission (EC) in November 2001 for the treatment of adult patients with Philadelphia chromosome (BCR-ABL) positive CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis. Following the initial approval, the FDA and EC in December 2002 approved imatinib for patients with newly diagnosed Philadelphia chromosome (BCR-ABL) positive (Ph+) CML including pediatric patients, for whom bone marrow transplantation is not considered first line therapy.

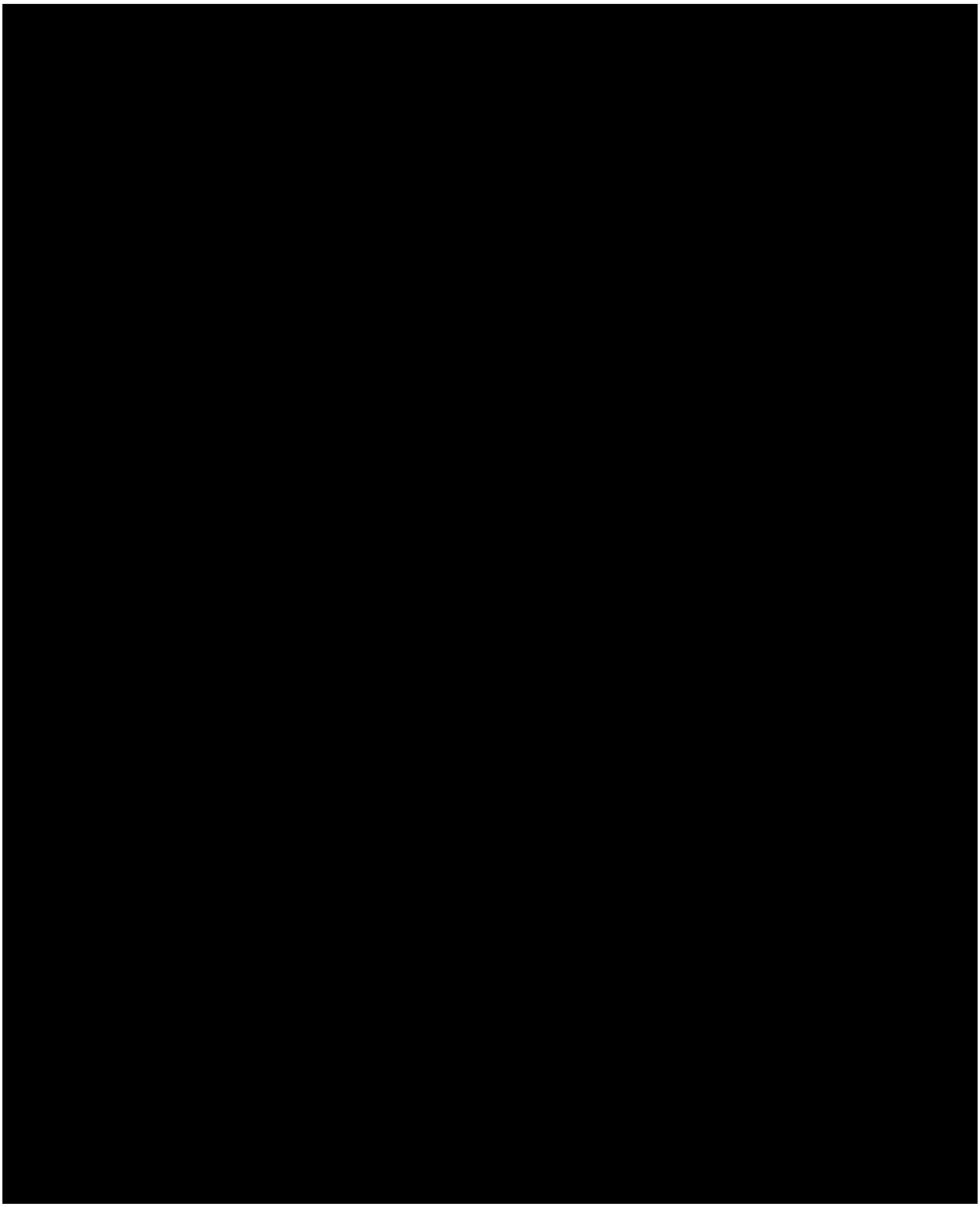
The approved recommended dosage of imatinib is 400 mg/day for adult patients in chronic phase and 600 mg/day for adult patients in accelerated phase or blast crisis. A phase III, randomized study for imatinib (TOPS) comparing a starting dose of 400 mg/day versus 800 mg/day was conducted in newly diagnosed Ph+ CML-CP patients but did not show evidence of superiority of the 800 mg/day dose compared to 400mg/day.

1.2.2.1 Non-clinical experience

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

[redacted]





[redacted]

2 Rationale

2.1 Study rationale and purpose

[redacted]

Patients in CAMN107ECN02 may need continuous treatment when they complete the core study. Protocol of CAMN107ECN02 mentioned offering possibility of extended treatment to patients who derive benefit from the study treatment, in the opinion of the investigator at the end of study CAMN107ECN02. Therefore, extension study of CAMN107ECN02 is necessary. Nilotinib has not yet been approved for treatment of newly diagnosed CML-CP in China. The purpose of this extension study is to provide extended nilotinib treatment to patients in nilotinib arm of CAMN107ECN02. To cover the promise and insure the same right to the patients in imatinib arm, extended imatinib treatment will also be provided.

2.2 Rationale for the study design

As the extension study is for on-treatment patient from core study who can derive benefit from continuous treatment at the end of core study, this study design mainly follows that of the core study on treatment to have two treatment arms.

Since core study will provide 3-year efficacy data and safety data of nilotinib in Chinese adult with newly diagnosed CML-CP, and imatinib have been approved as treatment in this indication for 6 years, this extension study only aim to get AE&SAE data.

2.3 Rationale for dose and regimen selection

All dosages in core study are permitted in this study. Flexibility of dose adjustment is left to investigator based on their medical assessment. Since cross over is only feasible in patient who is not tolerant or is suboptimal responder to the treatment in core study, which should be deemed as not benefit from previous treatment, extension study won't permit cross over between the two treatments.

2.4 Rationale for choice of combination drugs

Not applicable

2.5 Rationale for choice of comparators drugs

Patients who benefit from imatinib treatment should continue imatinib treatment to maintain response. Therefore, patients from this arm will be kept on imatinib treatment in extension study.

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 assess safety of nilotinib and imatinib in Chinese adult with	Frequency of AE/SAE	

Objective	Endpoint	Analysis
newly diagnosed Ph+ CML-CP		
Key secondary Not applicable		
Other secondary Not applicable		
Exploratory Not applicable		

4 Study design

4.1 Description of study design

The extension study follows the core study CAMN107ECN02, which is an open-label, two armed study. All patients enrolled in this extension study should be able to benefit from the treatment given in CAMN107ECN02 per investigator's evaluation. Therefore, in this extension study patient will continue treatment of the drug (imatinib or nilotinib) which they are taking at the end of CAMN107ECN02. Treatment arms in CAMN107ECN02 will be retained. As long as we get EC approval and agreement from investigators, the selected sites for CAMN107ECN02 will be applied in this extension study.

Patients will be enrolled after eligibility evaluation. During the extension study, follow-up visits at a frequency of 6 months are required referring to the core study and recommendation in Chinese CML guideline (Wang JX, 2013). No data collection plan is included in this extension study except safety data. Investigator will be asked to report AE, SAE and pregnancy in order to ensure compliance with pharmacovigilance requirement. AE&SAE information will be recorded in CRF and included in clinical database. In addition, SAE and pregnancy will be reported to Novartis safety database.

4.2 Timing of interim analyses and design adaptations

Not applicable

4.3 Definition of end of the study

The extension study will start from first patient last dose date in CAMN107ECN02 and end at the time of nilotinib first line treatment commercially available in China. The criteria of study end are applicable to both nilotinib arm and imatinib arm. After the extension study, patients will be able to get treatment by prescription if continuous treatment is necessary. As for patients who cannot afford imatinib or nilotinib, they can follow PAP process to apply GIPAP or TIPAP and get drug donation if they can pass economic and medical assessment.

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 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 patients who continuously derive benefit from the study treatment that he/she takes in CAMN107ECN02, in the opinion of the investigator, at the end of the core study can be enrolled in this extension study.

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 extension phase have to meet all of the following criteria:

1. Patient is currently on treatment in the core study CAMN107ECN02

2. Patient who continues to derive benefit more than risk from the study treatment he/she takes in CAMN107ECN02, in the opinion of the investigator at the end of the study

3. Written informed consent must be obtained prior to enrolling in the extension study.

5.3 Exclusion criteria

Patients eligible for this extension phase must not meet any of the following criteria:

1. Progression to CML-AP or BC

2. Patient whose treatment assigned in CAMN107ECN02 is not appropriate any longer, per investigator's assessment.

3. History of non-compliance to medical regimens, or patients who are considered potentially unreliable and/or not cooperative.

4. Women who are (a) pregnant and (b) women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and at least 14 days after last dose of study medication. Highly effective contraception methods include:

- 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 screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.

- Combination of any two of the following (a+b or a+c, or b+c):

a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks 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.

6 Treatment

6.1 Study treatment

Study treatment: nilotinib or imatinib, which follows the treatment assignment in the core study CAMN107ECN02

Study drugs: nilotinib (AMN107, Tasigna) or imatinib (STI571, Gleevec/Glivec)

6.1.1 Dosing regimen

Patients will continue treatment of the drug they are taking at the end of CMAN107ECN02. Treatment switch between imatinib and nilotinib when transferred from CAMN107ECN02 to this extension study is not permitted. During the extension study, patients who need treatment switch should be regarded as unable to derive benefit from continuous treatment and should be withdrawn from the extension study.

The starting dose should be the same as the last dose that was given in the core study. After this, dose is based on the investigator's judgment. All the doses permitted in CAMN107ECN02 will be acceptable in this extension study, (Table 6-1). The doses are also consistent with the recommendation for newly diagnosed CML-CP patients by Novartis CDS (core data sheet) of imatinib or nilotinib. Investigator can select appropriate dose among them for every patient. Necessary dose adjustment among the doses is recommended during the study in case of toxicity or unsatisfactory response (please refer to section 6.3).

Table 6-1 Recommended dosing

Drug	Dose
Imatinib	400mg QD, 300mg QD, 600mg QD
Nilotinib	400mg QD, 300mg BID

6.1.1.1 Nilotinib administration

Patients in nilotinib arm will take 300 mg twice daily by mouth each morning and evening approximately 12 hours apart, or 400mg once daily.

Nilotinib should NOT be taken with food. Patients should take nilotinib on an empty stomach. No food should be consumed for 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. Patients should be instructed to swallow capsules whole with a full 250-mL glass of water, and not to chew them. All patients must avoid grapefruit, star fruit, and Seville (bitter) oranges during the study. The juices of these fruits must also be avoided. Vomited doses should not be repeated.

All dosages prescribed and dispensed to the patient, as well as all dose changes and missed doses during the study must be recorded on the Nilotinib Dosage Administration Record CRF.

6.1.1.2 Imaitnib administration

Patients in imatinib 400 mg daily arm will receive imatinib daily dose of 300mg, 400mg or 600mg all at once every day.

Imatinib should be taken with food and a large glass of water. All patients must avoid grapefruit, star fruit, and Seville (bitter) oranges during the study. The juices of these fruits must also be avoided. Vomited doses should not be repeated.

All dosages prescribed and dispensed to the patient, as well as all dose changes and missed doses during the study must be recorded on the Nilotinib Dosage Administration Record CRF.

6.1.2 Ancillary treatments

Not applicable

6.1.3 Rescue medication

Not applicable

6.1.4 Guidelines for continuation of treatment

Not applicable

6.1.5 Treatment duration

Patient may continue treatment with the study drug all through the extension study, unless treatment is early discontinued at the discretion of the investigator or withdrawal of consent.

In every visit, investigator should assess safety and efficacy to decide whether the patient should continue treatment in the extension study.

6.2 Dose escalation guidelines

Not applicable

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The following guidelines are recommended.

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

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

According to ICH E6 the investigator is responsible for all trial-related medical decisions. During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial.

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 the list below, in Table 6-2 and Table 6-3.

These guidelines provide general principles (such as dose-interruption until recovery rather than continuing study drug treatment at a lower dose as the first step in case of significant toxicity) and recommendations intended to support the investigator's judgment and decisions about appropriate management of toxicity in the individual patient.

The following guidelines must be strictly followed:

- No dose reductions below 300 mg/day for imatinib or 400 mg/day of nilotinib will be allowed. If a patient cannot tolerate a minimum dose of 300 mg/day of imatinib or 400 mg/day of nilotinib he or she must be discontinued from the study.
- Any non-hematological toxicity must be resolved within 28 days in order to resume study drug at the reduced dose. If a non-hematological toxicity does not resolve after 28 days, the patient must be discontinued.
- In case of pancreatitis of Grade 3 study drug treatment must be interrupted and the Sponsor must be consulted immediately.
- In case of pancreatitis of Grade 4 study drug treatment must be permanently stopped and the patient must be discontinued from study.
- In case of liver toxicity of Grade 4 study drug treatment must be interrupted and the Sponsor must be consulted immediately.
- In case of related cardiac toxicity of Grade 4 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

Table 6-2 Summary of dose reduction guidelines for study drug-related non-hematological toxicity and for ischemic vascular and cardiovascular events regardless of study drug relationship – IMATINIB

Study drug and dose	Imatinib 400 mg	Imatinib 600 mg daily (as 600 mg QD)
General non-hematological toxicity		
Grade 2 (persisting > 7 days with optimal supportive care)	Hold therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume imatinib at 300 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen l→ discontinue.	Hold therapy and resume imatinib at 600 mg after recovery to ≤Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume at next lower dose level l→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen l→ discontinue.
≥ Grade 3	Hold therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume imatinib at 300 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen l→ discontinue.	Hold therapy and resume imatinib 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 another recurrence is seen l→ discontinue.
Serum hypophosphatemia		
Grade 2	Continue imatinib at 400 mg QD and start phosphate supplementation	Continue imatinib at 600 mg QD and start phosphate supplementation
Grade 3-4	Hold therapy, start phosphate supplementation and resume imatinib at 400 mg QD after recovery to ≤ Grade 2 is seen. If grade 3-4 hypophosphatemia recurs despite supplementation, hold therapy again until recovery to ≤ Grade 2 is seen and then resume imatinib at 300 mg QD. If another recurrence of grade 3-4 hypophosphatemia is seen consult sponsor.	Hold therapy, start phosphate supplementation and resume imatinib at 600 mg QD after recovery to ≤ Grade 2 is seen. If grade 3-4 hypophosphatemia recurs despite supplementation, hold therapy again until recovery to ≤ Grade 2 is seen and then resume imatinib at 400 mg QD. If another recurrence of grade 3-4 hypophosphatemia is seen consult sponsor

Study drug and dose	Imatinib 400 mg	Imatinib 600 mg daily (as 600 mg QD)
Serum Creatinine		
Grade 2 > 1.5 -3.0 x ULN	Hold therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume imatinib at 300 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue.	Hold therapy and resume imatinib at 600 mg after recovery to ≤Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume at next lower dose level I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue.
≥ Grade 3 ≥ 3.0 x ULN	Hold therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume imatinib at 300 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue.	Hold therapy and resume imatinib next lower dose level after recovery to ≤ Grade 1 is seen I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue.
Hepato-biliary [bilirubin, SGPT(AST), SGOT (ALT)] Note: If hyperbilirubinemia is primarily due to the indirect bilirubin component (with indirect bilirubin > direct bilirubin and direct bilirubin ≤ 15 µmol/L) 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), imatinib may be continued at the same dose, at the discretion of the investigator.		
Grade 2	Hold therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume imatinib at 300 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue.	Hold therapy and resume imatinib at 600 mg after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume at next lower dose level I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue.

Study drug and dose	**Imatinib 400 mg**	**Imatinib 600 mg daily (as 600 mg QD)**
≥ Grade 3	Hold therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume imatinib at 300 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue.	Hold therapy and resume imatinib next lower dose level after recovery to ≤ Grade 1 is seen I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue.
Pancreatitis (with abdominal symptoms plus amylase and/or lipase elevation)		
Grade 2	Hold therapy 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 imatinib at 400 mg 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 I→ discontinue.	Hold therapy 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 at the next lower dose level after recovery to ≤ Grade 1 I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs I→ discontinue.
Grade 3	Hold therapy and consult Sponsor	Hold therapy and consult Sponsor
Grade 4	Hold therapy. The patient must be discontinued from study	Hold therapy. The patient must be discontinued from study

Study drug and dose	Imatinib 400 mg	Imatinib 600 mg daily (as 600 mg QD)
Elevated amylase and/or lipase without symptoms		
≥ Grade 3	Hold therapy Re-start imatinib at 300 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 without symptoms consider appropriate diagnosis procedures such as abdominal CT or ultrasound to exclude pancreatitis. After recovery to ≤ Grade 1, I→ continue dosing at 300 mg QD based on investigator's discretion	Hold therapy and re-start imatinib at the next lower dose level after recovery to ≤ Grade 1 I→ 400 mg QD; If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs without symptoms consider appropriate diagnosis procedures such as abdominal CT or ultrasound to exclude pancreatitis. After recovery to ≤ Grade 1, I→ continue dosing based on investigator's discretion
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 therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume imatinib at 300 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs I→ discontinue.	Hold therapy and resume imatinib next lower dose level after recovery to ≤ Grade 1 is seen I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs I→ discontinue.
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 therapy and resume imatinib at 400 mg QD; after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume imatinib at 300 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs I→ discontinue.	Hold therapy and resume imatinib next lower dose level after recovery to ≤ Grade 1 is seen I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs I→ discontinue.

Study drug and dose	**Imatinib 400 mg**	**Imatinib 600 mg daily (as 600 mg QD)**
Skin rash **Note: Institute symptomatic therapy as appropriate. If skin rash does not resolve with optimal treatments, take the following actions:**		
Grade 2	Hold therapy and resume imatinib at 400 mg QD; after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume imatinib at 300 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue.	Hold therapy and resume imatinib at 600 mg after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume at next lower dose level I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue.
≥ Grade 3	Hold therapy and resume imatinib at 400 mg QD; after recovery to ≤ Grade 1 is seen If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume imatinib at 300 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue	Hold therapy and resume imatinib next lower dose level after recovery to ≤ Grade 1 is seen I→ 400 mg QD If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue.

Study drug and dose	Imatinib 400 mg	Imatinib 600 mg daily (as 600 mg QD)
Cardiac QTc prolongation		
QTcF > 480 msec	Hold therapy when an ECG with a QTcF > 480 msec by automated reading is identified at the site. • 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 the QTcF returns to < 450 msec and is within 20 msec of baseline within 2 weeks. 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 is to be reduced as follows: • Imatinib 400 mg not to be dose reduced. • Imatinib 600 mg daily will be reduced to 400 mg daily. ECGs must be repeated 7 days after dose re-start for all patients who had therapy held due to QTcF > 480 msec. If QTcF of > 480 msec recurs, the patient must be discontinued. The investigator should contact the sponsor 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	Imatinib 400 mg	Imatinib 600 mg daily (as 600 mg QD)
Ischemic vascular and Ischemic Cardiovascular events		
Grade 2	Hold therapy and refer patients for assessment by a vascular or cardiovascular specialist. Resume imatinib at 400 mg QD after recovery to ≤ Grade 1 is seen. If another recurrence is seen l→ discontinue . If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. The event should be evaluated to determine the relationship to study treatment (i.e. suspected or not suspected). Additionally, the patient should be assessed for other potential risk factors for the event.	Hold therapy and refer patient for assessment by a vascular or cardiovascular specialist. Resume imatinib next lower dose level after recovery to ≤ Grade 1 is seen l→ 400 mg QD. Further dose de-escalation to highest tolerable dose allowed if appropriate. Patients who do not tolerate 300 mg QD must discontinue treatment. If another recurrence is seen l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. The event should be evaluated to determine the relationship to study treatment (i.e. suspected or not suspected). Additionally, the patient should be assessed for other potential risk factors for the event.
Grade 3 or Grade 4	Hold therapy, and refer patient for assessment by a vascular or cardiovascular specialist. Consideration should be given for discontinuation from the study for event. The patient must be discontinued from the study if recovery to Grade 2 is greater than 28 days. The event should be evaluated to determine the relationship to study treatment (i.e. suspected or not suspected). Additionally, the patient should be assessed for other potential risk factors for the event.	Hold therapy, and refer patient for assessment by a vascular or cardiovascular specialist. Consideration should be given for discontinuation from the study for event. The patient must be discontinued from the study if recovery to Grade 2 is greater than 28 days. The event should be evaluated to determine the relationship to study treatment (i.e. suspected or not suspected). Additionally, the patient should be assessed for other potential risk factors for the event.

Table 6-3 Summary of dose reduction guidelines for study drug-related non-hematological toxicity and for ischemic vascular and cardiovascular events regardless of study drug relationship- NILOTINIB

Study drug and dose	Nilotinib 600 mg daily (as 300 mg BID)
General non-hematological toxicity	
Grade 2 (persisting > 7 days with optimal supportive care)	Hold therapy and resume nilotinib at 300 mg BID after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume nilotinib at 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study If another
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs I→ discontinue.
Serum hypophosphatemia	
Grade 2	Continue nilotinib at 300 mg BID and start phosphate supplementation.
Grade 3-4	Hold therapy, start phosphate supplementation and resume nilotinib at 300 mg BID after recovery to ≤ Grade 2 is seen. If grade 3-4 hypophosphatemia recurs despite supplementation, hold therapy again until recovery to ≤ Grade 2 is seen and then resume nilotinib at 400 mg QD. If another recurrence of grade 3-4 hypophosphatemia is seen consult sponsor.
Serum creatinine	
Grade 2 > 1.5 -3.0 x ULN	Hold therapy and resume nilotinib at 300 mg BID after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume nilotinib at 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another
≥ Grade 3 ≥ 3.0 x ULN	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs I→ discontinue.

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID)**
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 ≤ 15 µmol/L) 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 hapatoglobin), nilotinib may be continued at the same dose, at the discretion of the investigator.**	
Grade 2	Hold therapy and resume nilotinib at 300 mg BID after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume nilotinib at 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If another recurrence is seen I→ discontinue.
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study If toxicity recurs I→ discontinue.
Pancreatitis (with abdominal symptoms plus amylase and/or lipase elevation)	
Grade 2	Hold therapy 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 I→ discontinue.
Grade 3	Hold therapy and consult sponsor
Grade 4	Hold therapy. The patient must be discontinued from study
Elevated amylase and/or lipase without symptoms	
≥ Grade 3	Hold therapy 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 without symptoms consider appropriate diagnostic procedures such as abdominal CT or ultrasound to exclude pancreatitis. After recovery to ≤ Grade 1, I→ continue dosing at 400 mg QD based on investigator's discretion.
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:**	

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID)**
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs I→ discontinue.
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 therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs I→ discontinue.
Skin rash **Note: Institute symptomatic therapy as appropriate. If skin rash does not resolve with optimal treatments, take the following actions:**	
Grade 2	Hold therapy and resume at nilotinib 300 mg BID after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume nilotinib at 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study If another recurrence is seen I→ discontinue
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen I→ 400 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs I→ discontinue.

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID)**
Cardiac QTc prolongation	
QTcF > 480 msec	Hold dosing when an ECG with a QTcF > 480 msec by automated reading is identified at the site. 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. 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 ECGs must be repeated 7 days after dose re-start for all patients who had therapy held due to QTcF > 480 msec. If QTcF of > 480 msec recurs, the patient is to be discontinued. The investigator should contact the sponsor regarding any questions that arise if a patient with QTcF prolongation should be maintained on study.
Ischemic vascular and Ischemic Cardiovascular event	
Grade 2	Hold therapy 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 is seen l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. The event should be evaluated to determine the relationship to study treatment (i.e. suspected or not suspected). Additionally, the patient should be assessed for other potential factors for the event.
Grade 3* or Grade 4*	Hold therapy, and refer patient for assessment by a vascular or cardiovascular specialist. Consideration should be given for discontinuation from the study for event. The patient must be discontinued from the study if recovery to ≤ Grade 2 is greater than 28 days. The event should be evaluated to determine the relationship to study treatment (i.e. suspected or not suspected). Additionally, the patient should be assessed for other potential factors for the event.
* Patient should be assessed for potential risk factors for the event including causality secondary to CML therapy.	

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID)**
Cardiac "other"	
Grade 2 or Grade 3	Hold therapy 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.

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 is presented in Table 6-4 and Table 6-5. No dose adjustments should be made for Grade 1 or 2 hematologic toxicity for either imatinib or nilotinib. These guidelines provide some general principles (such as dose-interruption until recovery rather than continuing study drug treatment at a lower dose as the first step in case of significant toxicity) 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.

Table 6-4 Summary of dose reduction guidelines for study drug-related hematological toxicity – IMATINIB

Study drug and dose	Imatinib 400 mg daily	Imatinib 600 mg daily (as 600 mg QD)
≥ Grade 3	Hold therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 1, if recovery occurs within 14 days If toxicity persists for 15-28 days or recurs, hold therapy and resume at next lower dose level after recovery to ≤ Grade 1: I→ 300 mg QD. If recovery to ≤ Grade 1 is greater than 28 days, consult sponsor. If another recurrence is seen I→ discontinue.	Hold therapy and resume at 600 mg QD after recovery to ≤ Grade 1, if recovery occurs within 14 days If toxicity persists for 15-28 days or recurs, hold therapy and resume at next lower dose level after recovery to ≤ Grade 1: I→ 400 mg QD If recovery to ≤ Grade 1 is greater than 28 days, consult sponsor. 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.		

Table 6-5 Summary of dose reduction guidelines for study drug-related hematological toxicity – NILOTINIB

Study drug and dose	Nilotinib 600 mg daily (as 300 mg BID)
≥ Grade 3	Hold therapy and resume at nilotinib 300 mg BID after recovery to ≤ Grade 1, if recovery occurs within 14 days If toxicity persists for 15-28 days or recurs, hold therapy and resume at next lower dose level after recovery to ≤ Grade 1: I→ 400 mg QD If recovery to ≤ Grade 1 is greater than 28 days, consult sponsor. 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.	

6.3.1.3 Summary of guidelines for dose re-escalation of imatinib

Re-escalation of the dose of imatinib to the previously administered dose level (i.e., dose level from which dose was reduced) is permitted. This applies to either dose reductions due to hematological or non-hematological toxicities if the following criteria are met for 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

For patients whose imatinib dose was 400 mg prior to dose reduction to 300 mg, the dose would be increased to 400 mg if the above described criteria are met at least one month after dose reduction.

For patients whose imatinib dose was 600 mg (as 600 mg QD) prior to dose reduction to 400 mg, the dose would be increased to 600 mg (as 600 mg QD) if the above criteria are met at least one month after dose reduction.

For patients whose imatinib dose was 600 mg (as 600 mg QD) prior to dose reduction to 300 mg, the dose would be increased to 400 mg if the above criteria are met at least one month before increasing the dose to 600 mg (as 600 mg QD).

For patients whose imatinib dose was reduced, dose re-escalation should be done in a step- wise manner by increasing the dose by one dose-level at a time (i.e., 300 to 400 to 600 mg). Subsequent dose escalation to the next dose-level should be done at least one month later.

6.3.1.4 Summary of guidelines for dose re-escalation of nilotinib

Re-escalation of the dose of nilotinib to the previously administered dose level (i.e., dose level from which dose was reduced) is permitted. This applies to either dose reductions due to hematological or non-hematological toxicities 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.

For patients whose nilotinib dose was 600 mg (as 300 mg BID) prior to dose reduction to 400 mg QD, the dose would be increased to 600 mg (as 300 mg BID) if the above described criteria are met at least one month after dose reduction.

6.3.1.5 Suggested management of selected adverse events for imatinib and nilotinib

Dose reduction guidelines listed in Table 6-2, Table 6-3, Table 6-4, and Table 6-5 must be followed. Additional guidelines for management of patients are listed below.

6.3.1.5.1 Management of cholesterol increases

Blood lipid panel tests should be performed at baseline and throughout the study as indicated in the visit schedule. 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 or imatinib on CYP3A4 isoenzyme that is involved in the metabolic pathway of as some statins (HMG-CoA reductase inhibitors) are also metabolized via the CYP3A4 pathway.

6.3.1.5.2 Management of glucose increases

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

6.3.1.5.3 Management of other cardiac risk factors

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

6.3.1.5.4 Management of ischemic vascular or cardiovascular events

Newly-diagnosed or worsened ischemic vascular or cardiovascular events have occurred in a relatively small number of CML-CP patients while on study medication. If a patient experiences such an adverse event the Investigator should ensure that the patient is assessed by a vascular or cardiovascular specialist. Further recommendations for the management of ischemic vascular or cardiovascular-related events are outlined in Table 6-2 or Table 6.3.

6.3.1.5.5 Management of myelosuppression

Myelosuppression can occur at any time during imatinib or nilotinib therapy. Use of colony stimulating growth factors (G-CSF and GM-CSF) such as sargramostim, filgrastim, and pegfilgrastim may be initiated with recurrent grade 3 neutropenia. The use of recombinant erythropoietin is also permitted as per local clinical practice.

6.3.1.5.6 Management of skin rash/pruritus

In most cases, rash is mild, self-limiting, and manageable with antihistamines or topical steroids. A short course of oral steroids may be initiated for the management of more severe cases. Prednisone 25 mg is recommended for one week or until rash has resolved.

6.3.1.5.7 Management of edema

Patients should be monitored closely for peripheral edema and rapid weight gain. The use of diuretics may be initiated for the management of edema. Patients who develop ≥ Grade 3 edema associated with cardio-respiratory symptoms should receive immediate medical evaluations for the development of concomitant cardiac or respiratory diagnoses as indicated, such as an echocardiogram and a chest X-ray. Other medical tests may also be necessary to best manage the medical condition.

6.3.1.5.8 Management of liver toxicity

Routine LFTs should be performed throughout the study as indicated in the visit schedule. Dose reduction may be warranted and the decision to continue imatinib or nilotinib needs to be made in light of the clinical situation (see dose reduction table). Alternative etiologies for LFT abnormalities such as viral hepatitis should be considered as clinically indicated.

6.3.1.5.9 Dose modification for patients on nilotinib and oral anticoagulants other than coumarin derivatives

For patients on treatment with oral anticoagulants other than coumarin derivatives (see Section 7.6.4) , the following guidelines will apply for thrombocytopenia: If platelets ≤ 100 x 10^9/L, withhold treatment with study drug until recovery to at least > 100 x 10^9/L and resume treatment at same dose. If recurrence of platelets ≤ 100 x 10^9/L, then withhold treatment until recovery to at least > 100 x 10^9/L and resume treatment at the minimum dose of 300 mg/day for imatinib. The nilotinib dose may be reduced to a minimum of 400 mg/day. If the platelet count remains below 100 x 10^9/L, then imatinib or nilotinib should be ceased or management with anticoagulation therapy re-evaluated at the discretion of the Investigator.

6.3.1.5.10 Platelet aggregation inhibitors

For patients on treatment with platelet aggregation inhibitors and platelets ≤ 100 x 10^9/L, modification of platelet aggregation inhibitor therapy and/or study drug interruption/dose reduction should be considered by the investigator as clinically appropriate. Advice from SMC may be requested via the Sponsor.

6.3.2 Follow-up for toxicities

Patients whose treatment is permanently discontinued due to a study drug related adverse event or abnormal laboratory value is recommended to must be followed at least once a week for 4 weeks, until resolution or stabilization of the event, whichever comes first. All patients will be followed for serious adverse events for 30 days following the last dose of study drug.

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., hyperglycemia, skin toxicity and diarrhea are provided in Section 6.3.1. Refer to preclinical toxicity and or clinical data found in the [Investigator's Brochure].

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Cytochrome P450 3A4 substrates

Both nilotinib and imatinib are 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.

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 (famotidine) may be administered approximately 10 hours before or approximately 2 hours after the dose of nilotinib,

- Antacid (hydroxide/magnesium hydroxide/simethicone) may be administered approximately 2 hours before or approximately 2 hours after the dose of nilotinib.

Cytochrome P450 2D6 and 2C9 substrates

Caution should be exercised when co-administering imatinib with substrates of CYP2D6 and CYP2C9.

Others

Patients should be informed of a possible drug interaction with acetaminophen (paracetamol) and asked to restrict the use of over-the-counter and prescription medicines containing acetaminophen (paracetamol). As such, special care has to be given to the concomitant use of acetaminophen/paracetamol (e.g., Tylenol® or Percocet®) with imatinib and nilotinib.

Patients on anticonvulsants should have regular monitoring of plasma concentration of these agents.

6.4.3 Prohibited concomitant therapy

The concomitant administration of investigational drugs other than imatinib or nilotinib is not allowed. The administration of any other anticancer agents including chemotherapy and biologic agents is **not** permitted.

All patients must avoid grapefruit, star fruit, and Seville (bitter) oranges during the study. The juices of these fruits must also be avoided.

During the course of the study, concomitant administration of agents known to prolong the QT interval is contraindicated. Please see azcert.org/medical-pros/drug-lists/printable-drug-list.cfm for a comprehensive list of agents that prolong the QT interval.

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

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

6.5.2 Treatment assignment or randomization

In this extension study, enrolled patients take the treatment they are having at the end of the core study. There will not be treatment assignment or randomization again in the beginning of the extension study.

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 CRF.

Novartis will be responsible for supply of labelled drug. Drug strength (Table 6-6 Drug supply) will be the same as in the core study. Drug will be dispensed to patients by whole bottles/boxes. Patient should bring the drug bottles or boxes with remaining drug back to investigator in every scheduled or unscheduled visit.

Table 6-6 Drug supply

Drug	Strength
Imatinib	100mg tablet
Nilotinib	150mg capsule; 200mg capsule

Investigator need to finish medical assessment to judge whether patient can still derive benefit from continuous treatment in very visit.

6.6.1 Study drug packaging and labeling

Medication labels will be in the local language and comply with the legal requirements of China. They will include storage conditions for the drug and the medication number but no information about the patient.

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, nilotinib and imatinib the study treatment should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

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 study drug supply can be destroyed at the local Novartis facility, Drug Supply group or 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. All data obtained from these assessments must be supported in the patient's source documentation.

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Enrollment	Follow up during treatment Every 6 (+/-1) months	End of study treatment (EOT)	End of study (EOC)
Visit Name (NCDS studies) or Visit Number (NOVDD studies)			1	Visit 2,3,4 etc.	777	
Patients' previous study, site and subject number	D	7.1.2	x			
Obtain Informed Consent	D	7.1.2	x			
Demography	D	7.1.2	x			
Inclusion/exclusion criteria	D	7.1.2.1	x			
Urine pregnancy test *	D	7.2.2.5	x	x	x	
Adverse event	D	8	x	x	x	x
Study Drug administration	D	6.1 ,6.2 and 6.3	x	x	x	

*Urine pregnancy test should be done monthly at home

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.

For those patients who don't meet inclusion/exclusion criteria, the Demography CRF page must also be completed. No other data of these patients will be entered into the clinical database.

7.1.2.1 Eligibility screening

Not applicable

7.1.2.2 Information to be collected on screening failures

Not applicable

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment period

Study treatment can be given as soon as eligibility is confirmed. Treatment will last till the end of the extension study or premature discontinuation of patients.

During treatment period, safety information including AE/SAE is required to be collected in CRF. Urine pregnancy test must be done every month as home and the result should be input in CRF when patient come back for visit.

Dosage and drug administration and any change should be recorded all through the study.

7.1.5 End of treatment visit including study completion and premature withdrawal

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed. An End of Treatment Phase Disposition CRF page should be completed, giving the date and reason for stopping the study treatment.

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

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

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

7.1.5.1 Criteria for premature patient withdrawal

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

- discovery of patient ineligibility;
- pregnancy;
- intolerance which requires treatment permanently discontinuation
- death
- lost to follow-up
- staying in the study would be inappropriate（investigators can withdraw patients if treatment provided by the extension study cannot benefit them or is not the best available treatment for them any longer）
- patient is non-compliant to protocol requirement

- Other reasons: patient can be withdrawn from the extension study before closing of it for any other reason

7.1.5.2 Replacement policy

Not applicable

7.1.6 Follow up period

All patients must have safety evaluations for 30 days after the last dose of study treatment.

At the end of this period, the investigator should contact the patient to inquire about any AE observed during this period. This could be done via a phone contact. Following this there are no further follow-up study visits.

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

7.2 Assessment types

7.2.1 Efficacy assessments

This extension study will not include efficacy data collection. Therefore, efficacy assessment is not mandatory. But it is still recommended that every patient can be assessed for hematology response, cytogenetic response and molecular response every 6 months.

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.

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).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) 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 Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, which is the same as in the core study.

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 though a Death form.

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) or

Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable).

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. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)

7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

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.

Signs and symptoms clearly associated with the disease under study should NOT be reported as AEs unless they are newly emergent (i.e. not previously observed in the patient), judged by the Investigator to be unusually severe or accelerated, or if the Investigator considers deterioration of disease-related signs and symptoms to be caused directly by the study drug. If there is any uncertainty about an AE being due solely to the disease under study, it should be reported as an AE or SAE as appropriate.

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 event (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.

8.2 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

The core study CAMN107ECN02 requires 30 days safety follow up after last dose. SAE reported from both the core study and this extension study will be captured in Novartis safety database. To avoid data duplication in Novartis safety database, SAE reporting is exempted in this study if the very event has been reported as SAE in the core study CAMN107ECN02.

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

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

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

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, 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

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 Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatments and 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 Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. 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.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before extension study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, 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, and laboratory data, electrocardiograms, the results of any other tests or assessments if related to AE/SAE and dose adjustment. All information recorded on CRFs 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 CRF 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 CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using paper CRFs, designated investigator staff must record the information required by the protocol onto the Novartis CRFs that are printed on multi-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The harvested CRFs will be forwarded to the Medical Documents Reception Center of Novartis by field monitors or by the investigational site, with one copy being retained at the investigational site.

The Principal Investigator is responsible for assuring that the data recorded on CRFs is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

For studies using paper CRFs, data will be entered into a fully validated study database by Novartis Data Management personnel (or designated CRO). Following entry from the CRFs, the data are systematically checked by Novartis Data Management personnel (or designated CRO) using programmed checks and data review tools/reports. Data Query Forms (DQF) are created for discrepancies or missing values and sent to the investigational site for resolution. Original signed responses to the DQFs must be returned to Novartis Data Management (or designated CRO) so that resolutions can be entered into the database. Copies of the resolved DQFs are kept with the CRFs at the investigator site.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

10 Statistical methods and data analysis

No statistical analysis is planned for this extension study. In this study, safety data will be descriptively summarized, and all data collected will be listed. Detailed methods of presenting data will be specified in the study RAP (or SAP).

Categorical data will be presented as frequencies and percentages.

10.1 Analysis sets

As the primary objective of this extension study is to assess the safety of the two treatments, only safety data will be collected besides demographics and treatment information.

10.1.1 Safety Set

The Safety Set includes all patients who received at least one dose of study medication. Patients will be analyzed according to the study treatment they actually received.

10.2 Patient demographics/other baseline characteristics

Demographic data at the enrollment will be listed for all patients.

10.3 Treatments (study treatment, concomitant therapies, compliance)

Usage of concomitant medications/therapies will not be collected in this study. Data of study treatment will be listed.

10.4 Primary objective

The primary objective of this extension study is to assess safety of nilotinib and imatinib in newly diagnosed Ph+ CML-CP patients who derive benefit from the study treatment, in the opinion of the investigator at the end of study CAMN107ECN02.

10.4.1 Variable

All AEs recorded during the study will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of AE, and relation to the treatment. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE.

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by treatment they actually received.

10.4.2 Statistical hypothesis, model, and method of analysis

Not applicable

10.4.3 Handling of missing values/censoring/discontinuations

Not applicable

10.4.4 Supportive analyses

Not applicable

10.5 Secondary objectives

Not applicable

10.6 Exploratory objectives

Not applicable.

10.7 Interim analysis

No interim analysis is planned for this study.

10.8 Sample size calculation

The size of this study depends on the number of patients who complete the study of CAMN107ECN02 and their eligibility to this extension. There are 234 patients currently on treatment in CAMN107ECN02, so the sample size of this extension study will not be larger than this number.

10.9 Power for analysis of key secondary variables

Not applicable

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.

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.

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.

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 but not later than 10 working days.

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14 Appendix

14.1 Appendix 1 List of CYP3A4 inducers and inhibitors

These lists are compiled based on the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated 30 August 2010) for update or more details.

Table 14-1 List of medications metabolized by CYP3A4, strong, moderate and weak inhibitors of CYP3A4 to be used with caution

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

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

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

Note:

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

Table 14-2 Medications that can inhibit CYP3A4

Strong inducers	Moderate inducers	Weak inducers	Unclassified inducers
avasimibe	bosentan	amprenavir	topiramate
carbamazepine	efavirenz	aprepitant	
dexamethasone*	etravirine	armodafinil (R-modafinil)	
phenobarbital	modafinil	echinacea	
phenytoin	nafcillin	garlic	
rifabutin	ritonavir	gingko	
rifampin	talviraline	glycyrrhizin	
rifapentin*	tipranavir	methylprednisolone	
St. John's wort		nevirapine	
		oxcarbazepine	
		pioglitazone	
		prednisone	
		pleconaril	
		rufinamide	
		troglitazone	

* Discrepancies on the level of induction of these drugs exist in the literature; however, they are listed in the “strong inducers” group in order to be consistent with the Tasigna Labeling.

Note:

- Inducer classification:
  - Strong inducers may result in a substrate AUC decreased by ≥ 80%.
  - Moderate inducers may result in a substrate AUC decreased by 50-80%.
  - Weak inducers may result in a substrate AUC decreased by 20-50%.